25TH EDITION

Williams OBSTETRICS

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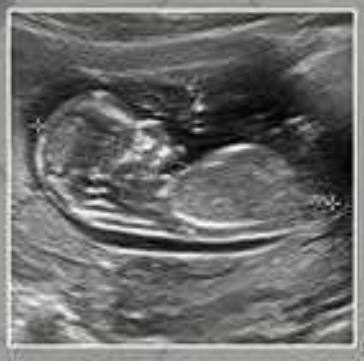


Mc Graw Hill Education

CHAPTER 1: Overview of Obstetrics

> *In the following pages I have attempted to set forth, as briefly as seemed to be consistent with thoroughness, the scientific basis for and the practical application of the obstetrical art. At the same time, I have endeavored to present the more practical aspects of obstetrics in such a manner as to be of direct service to the obstetrician at the bedside.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

So reads the introduction to Williams' first edition of this textbook, *Obstetrics—A Text-Book for the Use of Students and Practitioners.* In this 25th edition, we strive to follow the tenets described by Williams. And, each chapter begins with a quote from his original textbook.

The science and clinical practice of obstetrics is concerned with human reproduction. Through quality perinatal care, the specialty promotes the health and well-being of the pregnant woman and her fetus. Such care entails appropriate recognition and treatment of complications, supervision of labor and delivery, initial care of the newborn, and management of the puerperium. Postpartum care promotes health and provides family planning options.

The importance of obstetrics is reflected by the use of maternal and neonatal outcomes as an index of the quality of health and life among nations. Intuitively, indices that reflect poor obstetrical and perinatal outcomes would lead to the assumption that medical care for the entire population is lacking. With those thoughts, we now provide a synopsis of the current state of maternal and newborn health in the United States as it relates to obstetrics.

VITAL STATISTICS

The National Vital Statistics System of the United States is the oldest and most successful example of intergovernmental data sharing in public health. This agency collects statistics through vital registration systems that operate in various jurisdictions. These systems are legally responsible for registration of births, fetal deaths, deaths, marriages, and divorces. Legal authority resides individually with the 50 states; two regions—the District of Columbia and New York City; and five territories—American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, and the Virgin Islands.

The standard birth certificate was revised in 1989 to include more information on medical and lifestyle risk factors and obstetrical practices. In 2003, an extensively revised Standard Certificate of Live Birth was implemented in the United States. The enhanced data categories and specific examples of each are summarized in Table 1-1. By 2013, 35 states had implemented the revised birth certificate representing 76 percent of all births (MacDorman, 2015). Importantly, the 2003 version of the population death certificate contains a pregnancy checkbox to eventually be implemented by all states (Joseph, 2017).

TABLE 1-1

General Categories of New Information Added to the 2003 Revision of the Birth Certificate

Risk factors in pregnancy—Examples: prior preterm birth, prior eclampsia
Obstetrical procedures—Examples: tocolysis, cerclage, external cephalic version
Labor—Examples: noncephalic presentation, glucocorticoids for fetal lung maturation, antibiotics during labor
Delivery—Examples: unsuccessful operative vaginal delivery, trial of labor with prior cesarean delivery
Newborn—Examples: assisted ventilation, surfactant therapy, congenital anomalies

Definitions

The uniform use of standard definitions is encouraged by the World Health Organization as well as the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017). Such uniformity allows data comparison not only between states or regions of the country but also between countries. Still, not all definitions are uniformly applied. For example, the American College of Obstetricians and Gynecologists recommends that reporting include all fetuses and neonates born weighing at minimum 500 g, whether alive or dead. But, not all states follow this recommendation. Specifically, 28 states stipulate that fetal deaths beginning at 20 weeks' gestation should be recorded as such; eight states report all products of conception as fetal deaths; and still others use a minimum birthweight of 350 g, 400 g, or 500 g to define fetal death. To further the confusion, the National Vital Statistics Reports tabulates fetal deaths from gestations that are 20 weeks or older (Centers for Disease Control and Prevention, 2016). This is problematic because the 50th percentile for fetal weight at 20 weeks approximates 325 to 350 g—considerably less than the 500-g definition. Indeed, a birthweight of 500 g corresponds closely with the 50th percentile for 22 weeks' gestation.

Definitions recommended by the National Center for Health Statistics and the Centers for Disease Control and Prevention are as follows:

Perinatal period. The interval between the birth of a neonate born after 20 weeks' gestation and the 28 completed days after that birth. When perinatal rates are based on birthweight, rather than gestational age, it is recommended that the perinatal period be defined as commencing at the birth of a 500-g neonate.

Birth. The complete expulsion or extraction from the mother of a fetus after 20 weeks' gestation. As described above, in the absence of accurate dating criteria, fetuses weighing <500 g are usually not considered as births but rather are termed *abortuses* for purposes of vital statistics.

Birthweight. The weight of a neonate determined immediately after delivery or as soon thereafter as feasible. It should be expressed to the nearest gram.

Birth rate. The number of live births per 1000 population.

Fertility rate. The number of live births per 1000 females aged 15 through 44 years.

Live birth. The term used to record a birth whenever the newborn at or sometime after birth breathes spontaneously or shows any other sign of life such as a heartbeat or definite spontaneous movement of voluntary muscles. Heartbeats are distinguished from transient cardiac contractions, and respirations are differentiated from fleeting respiratory efforts or gasps.

Stillbirth or fetal death. The absence of signs of life at or after birth.

Early neonatal death. Death of a liveborn neonate during the first 7 days after birth.

Late neonatal death. Death after 7 days but before 29 days.

Stillbirth rate or fetal death rate. The number of stillborn neonates per 1000 neonates born, including live births and stillbirths.

Neonatal mortality rate. The number of neonatal deaths per 1000 live births.

Perinatal mortality rate. The number of stillbirths plus neonatal deaths per 1000 total births.

Infant death. All deaths of liveborn infants from birth through 12 months of age.

Infant mortality rate. The number of infant deaths per 1000 live births.

Low birthweight. A newborn whose weight is <2500 g.

Very low birthweight. A newborn whose weight is <1500 g.

Extremely low birthweight. A newborn whose weight is <1000 g.

Term neonate. A neonate born any time after 37 completed weeks of gestation and up until 42 completed weeks of gestation (260 to 294 days). The American College of Obstetricians and Gynecologists (2016b) and Society for Maternal– Fetal Medicine endorse and encourage specific gestational age designations. *Early term* refers to neonates born at 37 completed weeks up to $38^{6/7}$ weeks. *Full term* denotes those born at 39 completed weeks up to $40^{6/7}$ weeks. Last, *late term* describes neonates born at 41 completed weeks up to $41^{6/7}$ weeks.

Preterm neonate. A neonate born before 37 completed weeks (the 259th day). A neonate born before 34 completed weeks is early preterm, whereas a neonate born between 34 and 36 completed weeks is late preterm.

Postterm neonate. A neonate born anytime after completion of the 42nd week, beginning with day 295.

Abortus. A fetus or embryo removed or expelled from the uterus during the first half of gestation—20 weeks or less, or in the absence of accurate dating criteria, born weighing <500 g.

Induced termination of pregnancy. The purposeful interruption of an intrauterine pregnancy that has the intention other than to produce a liveborn neonate and that does not result in a live birth. This definition excludes retention of products of conception following fetal death.

Direct maternal death. The death of the mother that results from obstetrical complications of pregnancy, labor, or the puerperium and from interventions, omissions, incorrect treatment, or a chain of events resulting from any of these factors. An example is maternal death from exsanguination after uterine rupture.

Indirect maternal death. A maternal death that is not directly due to an obstetrical cause. Death results from previously existing disease or a disease developing during pregnancy, labor, or the puerperium that was aggravated by maternal physiological adaptation to pregnancy. An example is maternal death from complications of mitral valve stenosis.

Nonmaternal death. Death of the mother that results from accidental or incidental causes not related to pregnancy. An example is death from an automobile accident or concurrent malignancy.

Maternal mortality ratio. The number of maternal deaths that result from the reproductive process per 100,000 live births. Used more commonly, but less accurately, are the terms *maternal mortality rate* or *maternal death rate.* The term *ratio* is more accurate because it includes in the numerator the number of deaths regardless of pregnancy outcome—for example, live births, stillbirths, and ectopic pregnancies—whereas the denominator includes the number of live births.

Pregnancy-associated death. The death of a woman, from any cause, while pregnant or within 1 calendar year of termination of pregnancy, regardless of the duration and the site of pregnancy.

Pregnancy-related death. A pregnancy-associated death that results from: (1) complications of pregnancy itself, (2) the chain of events initiated by pregnancy that led to death, or (3) aggravation of an unrelated condition by the physiological or pharmacological effects of pregnancy and that subsequently caused death.

PREGNANCY RATES IN THE UNITED STATES

According to the Centers for Disease Control and Prevention (CDC), the fertility rate of women aged 15 to 44 years in the United States in 2015 was 62.5 live births per 1000 women (Martin, 2017). This rate began slowly trending downward in 1990 and has now dropped below that for replacement births. This indicates a

population decline (Hamilton, 2012). There were 3.98 million births in 2015, and this constituted the lowest birth rate ever recorded for the United States—12.3 per 1000 population. The birth rate decreased for all major ethnic and racial groups, for adolescents and unmarried women, and for those aged 20 to 24 years. For women older than 30 years, the birth rate rose slightly. Almost half of newborns in 2010 in the United States were minorities: Hispanic—25 percent, African-American—14 percent, and Asian—4 percent (Frey, 2011).

The total number of pregnancies and their outcomes in 2015 are shown in Table 1-2. According to the Guttmacher Institute (2016b), 45 percent of births in the United States are unintended at the time of conception. Importantly, the overall proportion of unintended births has declined only slightly since 2001. Unmarried women, black women, and women with less education or income are more likely to have unplanned pregnancies.

TABLE 1-2

Total Pregnancies and Outcomes in the United States in 2015

Outcome	Number or Percent
Births	3,988,076
Cesarean deliveries	32.2%
Preterm births (<37 weeks)	9.5%
Low birthweight (<2500 g)	8.0%
Induced abortions	664,435
Total pregnancies[a]	4,652,511

[a]Excludes spontaneous abortions and ectopic pregnancies.

Data from Martin, 2017.

In Table 1-2, induced abortion information derives from CDC abortion surveillance data from 45 states combined with Guttmacher Institute data on induced abortion. These data have been collected beginning in 1976. Since *Roe v. Wade* legalization of abortion, more than 46 million American women have chosen legalized abortions. As discussed later, this provides a compelling argument for easily accessible family planning.

MEASURES OF OBSTETRICAL CARE

Perinatal Mortality

Several indices are used to assess obstetrical and perinatal outcomes as measures of medical care quality. As noted, the perinatal mortality rate includes the numbers of stillbirths and neonatal deaths per 1000 total births. In 2013, the perinatal mortality rate was 9.98 per 1000 births (Fig. 1-1) (MacDorman, 2015). There were 25,972 fetal deaths at gestational ages of 20 weeks or older. Fetal deaths at 28 weeks or more have been declining since 1990, whereas rates for those between 20 and 27 weeks are static (Fig. 1-2). By way of comparison, there were a total of 19,041 neonatal deaths in 2006—meaning that nearly 60 percent of the perinatal deaths in the United States were fetal.

FIGURE 1-1

Perinatal mortality rates: United States, 2000–2013. (Reproduced with permission from MacDorman MF, Gregory EC: Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep. 2015 Jul 23;64(8):1–24.)

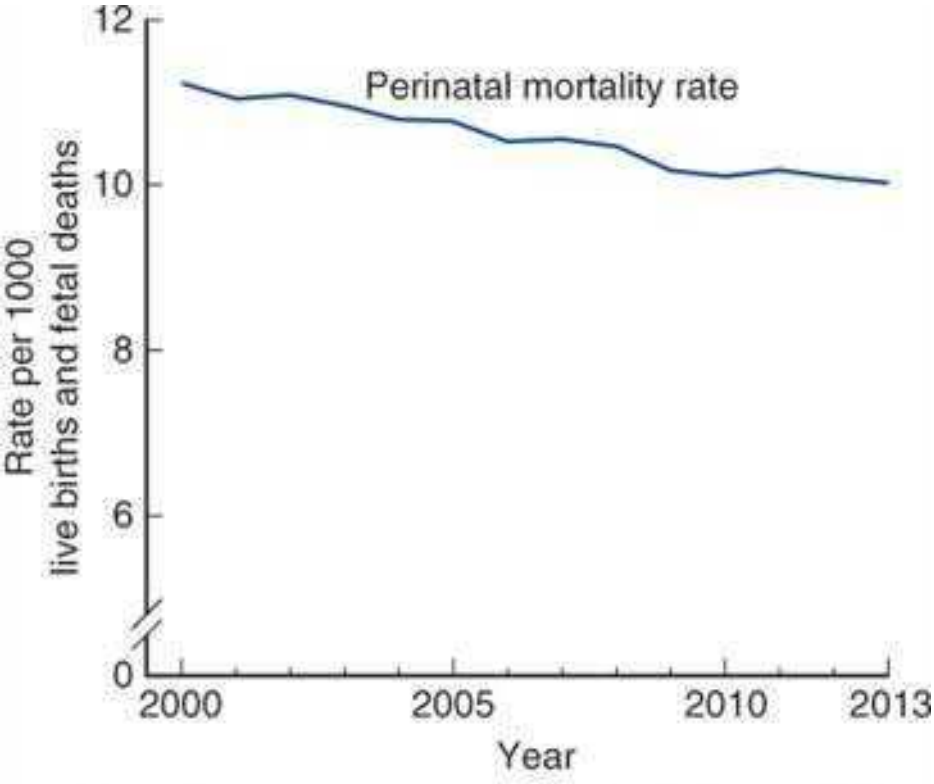
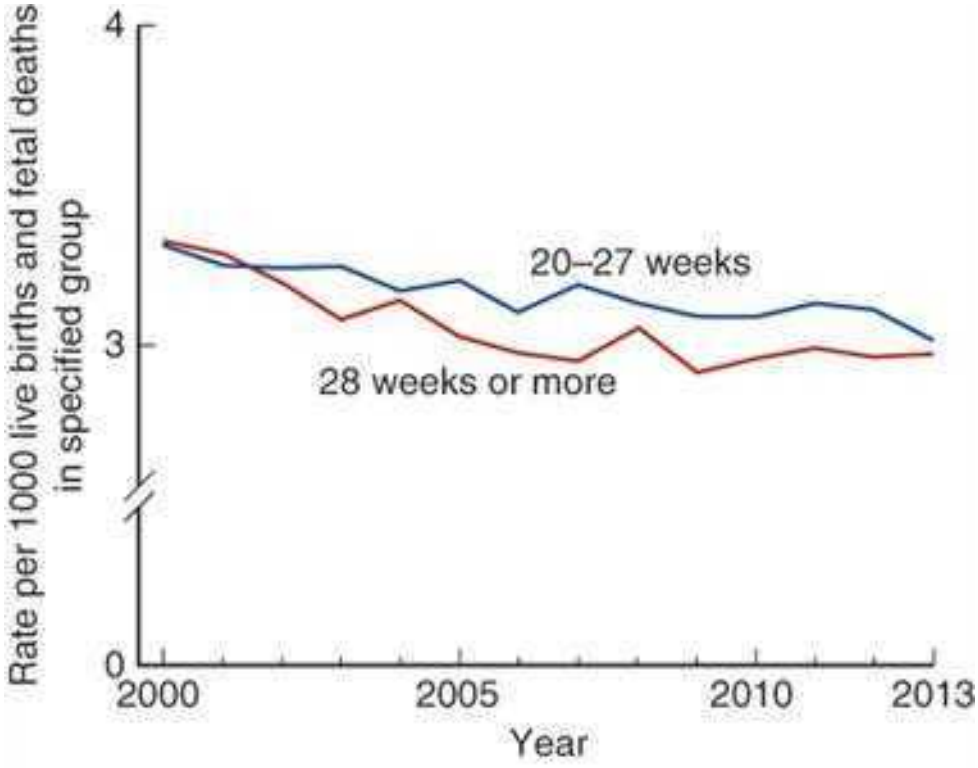


FIGURE 1-2

Fetal and neonatal deaths: United States, 2000–2013. (Modified with permission from MacDorman MF, Gregory EC: Fetal and perinatal mortality: United States, 2013. Natl Vital Stat Rep. 2015 Jul 23;64(8):1–24.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Infant Deaths

There were 6.1 infant deaths per 1000 live births in 2013 compared with 6.8 in 2001 (MacDorman, 2015). The three leading causes of infant death—congenital malformations, low birthweight, and sudden infant death syndrome—accounted for almost half of all deaths (Heron, 2015). Infants born at the lowest gestational ages and birthweights add substantively to these mortality rates. For example, more than half of all infant deaths in 2005 were in the 2 percent of infants born before 32 weeks' gestation. Indeed, the percentage of infant deaths related to preterm birth increased from 34.6 percent in 2000 to 36.5 percent in 2005. When analyzed by birthweight, two thirds of infant deaths were in low-birthweight neonates. Of particular interest are infants with birthweights <500 g, for whom neonatal intensive care can now be offered.

Maternal Mortality

As shown in Figure 1-3, maternal mortality rates dropped precipitously in the United States during the 20th century. Pregnancy-related deaths are so uncommon as to be measured per 100,000 births. The CDC (2017a) has maintained data on pregnancy-related deaths since 1986 in its Pregnancy Mortality Surveillance System. In the latest report, Creanga and coworkers (2017) described 2009 pregnancy-related deaths during the period from 2011 to 2013. Approximately 5 percent were early-pregnancy deaths due to ectopic gestation or abortive outcomes. The deadly obstetrical triad of hemorrhage, preeclampsia, and infection has accounted for a third of all deaths (Fig. 1-4). Thromboembolism, cardiomyopathy, and other cardiovascular disease together accounted for another third. Other significant contributors were amnionic fluid embolism (5.3 percent) and cerebrovascular accidents (6.2 percent). Anesthesia-related deaths were at an all-time low—

only 0.7 percent. Similar causes were reported for selected cohorts for years 2008 to 2009 and 2013 to 2014 (MacDorman, 2017).

FIGURE 1-3

Maternal mortality rates for the United States, 1950–2003. (Data from Berg, 2010; Hoyert, 2007.)

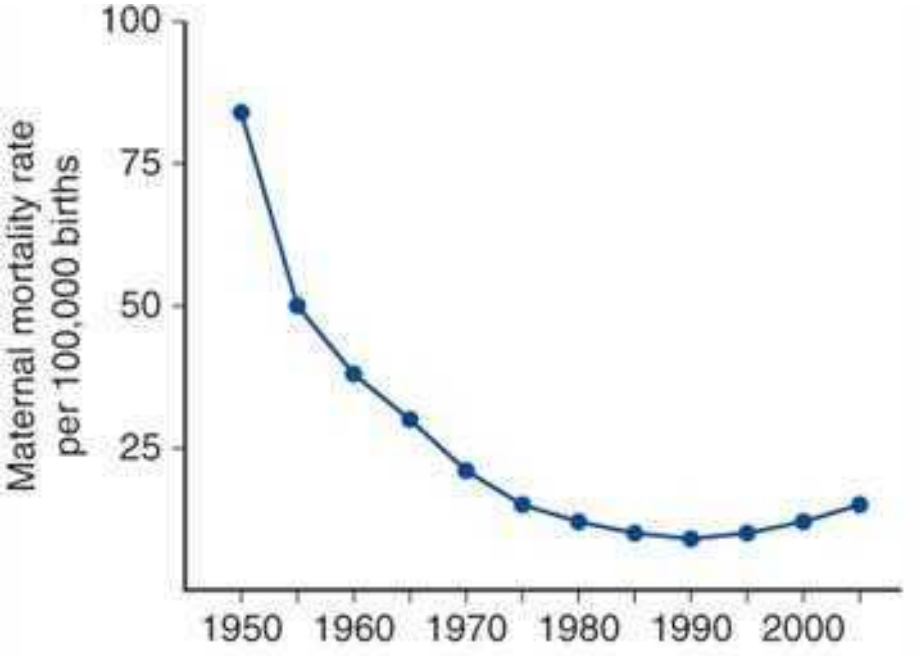
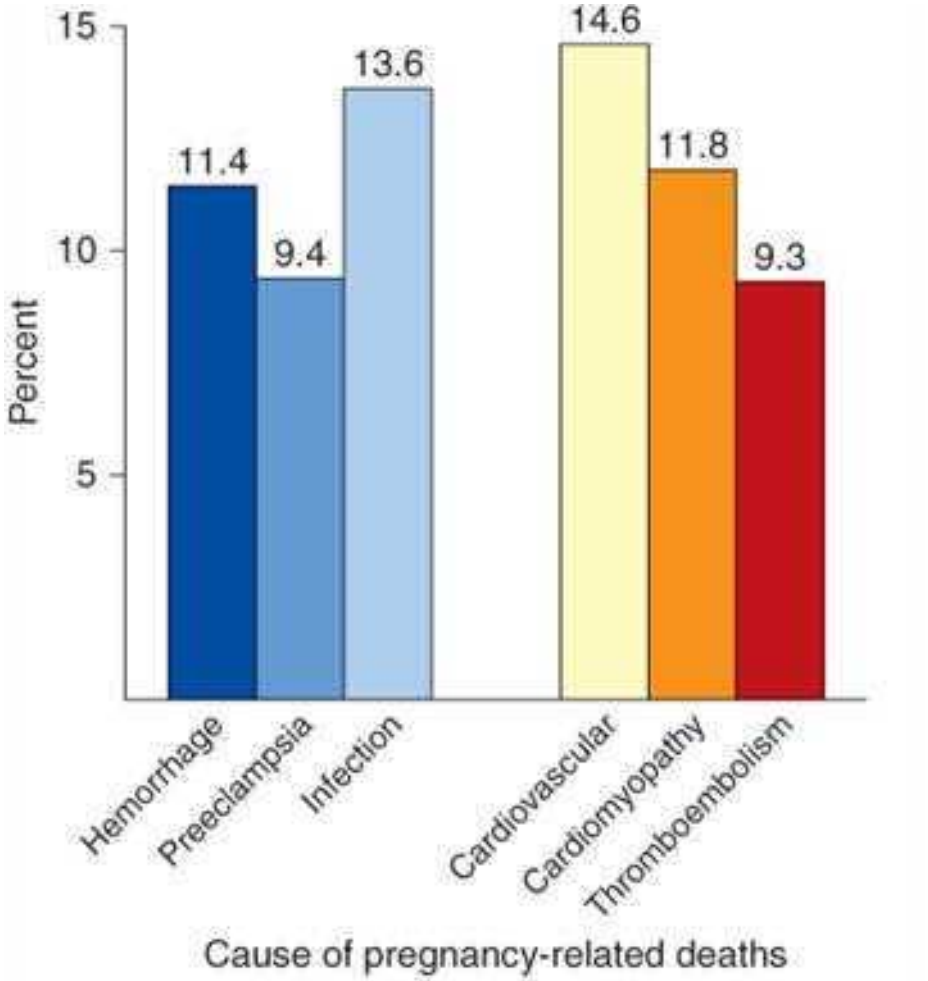


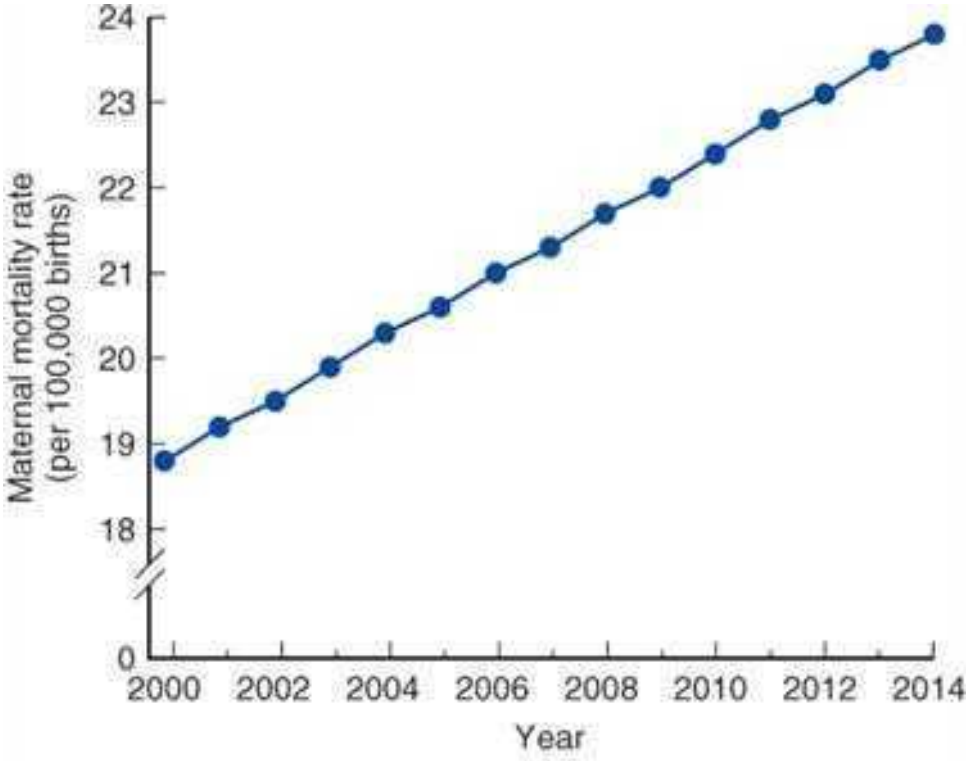
FIGURE 1-4

Six common causes of pregnancy–related deaths for the United States, 2006–2010. (Data from Creanga, 2015.)



Shown in Figure 1-5, the pregnancy-related mortality ratio of 23.8 per 100,000 live births in 2014 is the highest during the previous 40 years. And, according to the Institute of Health Metrics, it was 28 per 100,000 in 2013 (Tavernise, 2016). This rise simply may be that more women are dying, however, other factors explain this doubling of the rate from 1990 to 2013 (Joseph, 2017). The first is an artificial elevation caused by the International Statistical Classification of Diseases, 10th Revision (ICD-10), implemented in 1999. Second, improved reporting definitely contributes to the rise (MacDorman, 2016b, 2017). In the past, maternal deaths were notoriously underreported (Koonin, 1997). Third, and related to the second explanation, the rate of rise is at least partially due to the revised death certificate and its pregnancy checkbox described earlier (Main, 2015). Fourth, the number of pregnant women with severe chronic health conditions, which place women at higher risk, is greater (Centers for Disease Control and Prevention, 2017a). Finally, the increased proportion of births to women older than 40 years contribute to higher mortality rates (MacDorman, 2017).

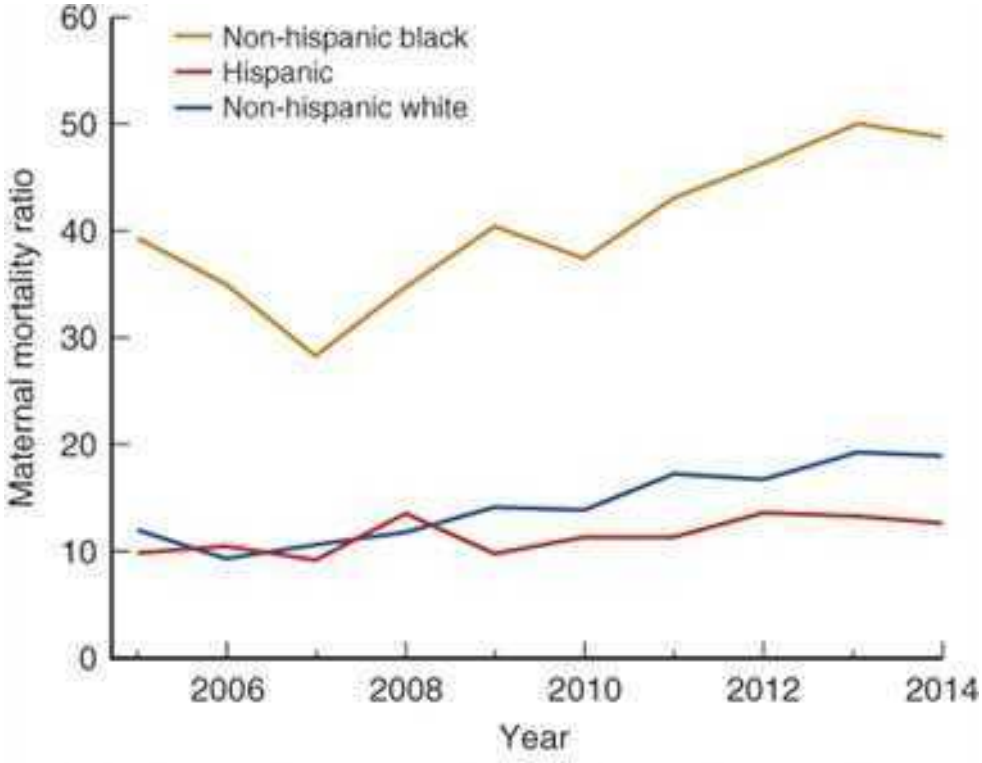
FIGURE 1-5
Estimated maternal mortality rates in 48 states and the District of Columbia. (Data from MacDorman, 2016.)



Whatever the cause, the apparent sharp rise of the maternal mortality rates has galvanized the obstetrical community to action (Chescheir, 2015). According to Barbieri (2015), the Joint Commission has recommended that birthing centers establish standardized protocols and implement simulation efforts. D'Alton and colleagues (2016) described efforts of a working group to lower morbidity and mortality rates.

Another consideration is the obvious disparity of higher mortality rates among black, Hispanic, and white women as shown in Figure 1-6. Racial disparities translate to health care availability, access, or utilization (Howell, 2016; Moaddab, 2016). And, maternal mortality is disparately high in rural compared with metropolitan areas (Maron, 2017).

FIGURE 1-6
Trends in maternal mortality ratio (per 100,000 live births) by race: United States, 2005–2014. (Data from Moaddab, 2016.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Importantly, many of the reported maternal deaths are considered preventable. Berg and colleagues (2005) estimated that this may be up to a third of pregnancy-related deaths in white women and up to half of those in black women. In one evaluation of an insured cohort, 28 percent of 98 maternal deaths were judged preventable (Clark, 2008). Thus, although significant progress has been made, further efforts are imperative for obstetrics in the 21st century.

Severe Maternal Morbidity

This serves as another measure to guide prevention efforts. Lowering medical error rates serves to diminish risks for maternal mortality or severe maternal morbidity. The terms *near misses* or *close calls* were introduced and defined as unplanned events caused by error that do not result in patient injury but have the potential to do so (Institute for Safe Medication Practices, 2009). These are much more common than injury events, but for obvious reasons, they are more difficult to identify and quantify. Systems designed to encourage reporting have been installed in various institutions and allow focused safety efforts (Clark, 2012; Main, 2017; Shields, 2017). The American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine (2016f) have provided lists of suggested screening topics for this purpose.

Several data systems now measure indicators of unplanned events caused by errors that have injurious potential. This evolution followed inadequacies in the ability of hospitalization coding to reflect the severity of maternal complications. Thus, coding indicators or modifiers are used to allow analysis of serious adverse clinical events (Clark, 2012; King, 2012). Such a system was implemented by the World Health Organization. It has been validated in Brazil and accurately reflects maternal death rates (Souza, 2012). Similar systems are in

use in Britain as the *UK Obstetric Surveillance System—UKOSS* (Knight, 2005, 2008). In the United States, one example is the National Partnership for Maternal Safety (D'Alton, 2016; Main, 2015).

To study severe morbidity, the CDC analyzed more than 50 million maternity records from the Nationwide Inpatient Sample from 1998 to 2009 (Callaghan, 2012). They used ICD-9-CM codes and reported that 129 per 10,000 of these gravidas had at least one indicator for severe morbidity (Table 1-3). Thus, for every maternal death, approximately 200 women experience severe morbidity. The CDC (2017b) estimates that 65,000 women per year have such maternal morbidity. These numbers are greatest in smaller hospitals with <1000 deliveries annually (Hehir, 2017). Finally, as with mortality rates, there are serious racial and ethnic disparities for severe maternal morbidity, and black women are disproportionately affected (Creanga, 2014).

TABLE 1-3

Severe Maternal Morbidity Indicators

Acute myocardial infarction
Acute renal failure
Adult respiratory distress syndrome
Amnionic fluid embolism
Cardiac arrest/ventricular fibrillation
Disseminated intravascular coagulation
Eclampsia
Heart failure during procedure
Injuries of thorax, abdomen, and pelvis
Intracranial injuries
Puerperal cerebrovascular disorders
Pulmonary edema
Severe anesthesia complications
Sepsis
Shock
Sickle-cell crisis
Thrombotic embolism
Cardiac monitoring
Conversion of cardiac rhythm
Hysterectomy

Cardiac surgery
Tracheostomy
Ventilation

Summarized from the Centers for Disease Control and Prevention, 2017b.

TIMELY TOPICS IN OBSTETRICS

Various topics have been in the forefront for obstetrical providers in the 4 years since the last edition of this textbook. In the following, we discuss several of these topics.

U.S. Health Care in Crisis

Obamacare and Medicaid

In a 2016 issue of the *Journal of the American Medical Association (JAMA),* then-President Barack Obama presented a summary of the Affordable Care Act (ACA), so-called Obamacare. He described the successes, the challenges ahead, and the policy implications of the policy (Bauchner, 2016). He summarized three lessons from his experiences with the ACA. First, change is especially difficult in the face of hyperpartisanship. Second, special interests pose a continued obstacle to change. Third, he stressed the importance of pragmatism. Here, he was referring to the pragmatism necessary when the ACA did not work effectively on day 1 of implementation.

At this same time, draconian cuts to Medicaid were being proposed, and President Obama ended his JAMA report with a quotation from John Kasich, the Republican governor of Ohio. “For those that live in the shadows of life, those who are the least among us, I will not accept the fact that the most vulnerable in our state should be ignored. We can help them.”

These potential effects to Medicaid ripple into the specialty of obstetrics. In 2010, it was estimated that Medicaid insured 48 percent of the births in the United States (Markus, 2013). Importantly, Medicaid covered a disproportionate number of complicated births. Specifically, Medicaid insured more than half of all hospital stays for preterm and low-birthweight infants and approximately 45 percent of infant hospital stays due to birth defects.

Repeal and Replace

The young, healthy Americans who were expected to financially bolster the ACA ultimately enrolled in insufficient numbers to ensure long-term ACA sustainability. Thus, long-term options included repair or repeal of the ACA. Throughout Donald Trump’s campaign for the presidency of the United States, he made repeal of the ACA a focus of his candidacy. As of this writing, both the United States House of Representatives and the Senate have grappled with “repeal and replace” for 6 months. According to the Congressional

Budget Office, this action would result in 23 million Americans losing health care insurance and cuts in Medicaid dollars (Fiedler, 2017). The latter was to be accomplished by transferring funding of Medicaid from the Federal government to the states. These potential outcomes have prompted considerable debate among voters, and "repeal and replace" has become politically charged. Currently, the Senate has been unable to recruit sufficient Republican votes for Senate passage of such a bill. We suggest that the health care crisis should be reframed and redirected instead to a critical analysis of health care costs and resource utilization.

Maternal and Infant Health Care Costs

The Centers for Medicare and Medicaid Services estimated that spending on health care in the United States in 2015 accounted for 17.8 percent of the gross domestic product—GDP (Voelker, 2010). The total amount of health-care spending—$3.2 trillion—equated to an estimated $10,000 per person. Moreover, compared with 12 other high-income countries, health-care spending in the United States as a proportion of GDP was approximately 50 percent more than the next highest country. Yet, health-care outcomes, which included infant mortality rates, were worse in the United States. And, approximately two thirds of U.S. infant deaths result from complications stemming from preterm births (Matthews, 2015). Indeed, in its 2010 annual global Premature Birth Report Card, the United States garnered a grade of "D" from the March of Dimes for its recognition and prevention of preterm labor in the more than 540,000 neonates born annually before 37 weeks' gestation.

Causes for the excessive health care costs in the United States are attributed, in part, to greater use of medical technology and excessive prices (Squires, 2017). Two recent studies demonstrate the detrimental effect of obstetrics on health care costs. The first report by Nelson and coworkers (2017) described the ineffectiveness of 17-alpha hydroxyprogesterone caproate (17-OHP-C) to prevent recurrent preterm birth. Methodology for this trial is presented in Chapter 42 (Progesterone Use without Prior Preterm Birth). Several lessons can be learned from this investigation. First, use of 17-OHP-C was legitimized in the United States by a national consensus committee using expert opinion. These opinions were promulgated, despite FDA reservations that the evidence was lacking in several important respects. However, once approved, 17-OHP-C was sold by one pharmaceutical company for $1500 for a single, 250-mg injectable dose. Remarkably, this same dose could be compounded and purchased for $25 from local pharmacies. In the subsequent price-gouging controversy, members of the United States Congress intervened to permit continued use of the less expensive 17-OHP-C.

The second study is a multisite prospective trial of the effectiveness of transvaginal sonography to screen for cervical-length shortening to predict preterm birth (Esplin, 2017). A total of 9410 nulliparous women were studied. The Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists (2016d) both legitimized *universal* cervical-length screening in their joint Committee Opinion (Bloom, 2017). And, by 2015, one survey of 78 Maternal-Fetal Medicine fellowship programs showed that 68 percent were using universal cervical-length screening to predict preterm birth (Khalifeh, 2017). It was estimated that a modest Medicaid rate of $237 per cervical-length ultrasound would result in approximately $350 million in added health care costs. But, Esplin and associates (2017) found that *routine* screening for a short cervix was not beneficial. That is, a widely used intervention was actually ineffective. This is a clear example of how unproven technology can seep into widespread practice.

These two reports highlight a substantial problem in U.S. health care, namely, ineffective yet expensive interventions introduced into broad use without robust evidence. These two reports also speak to a demand for robust scientific evidence. Scrutiny of other ingredients in the health-care paradigm such as prices for hospitalization, prices for surgical procedures, and prices charged by health insurance companies may illuminate similar contributions to the health care fiscal crisis.

Cesarean Delivery Rate

In past editions of this textbook, the rising cesarean delivery rate was considered problematic. This rate has leveled, but there are still imperatives in progress to help lower this rate. One collateral source of cesarean delivery morbidity is from the growing incidence of morbidly adherent placentas encountered in women with a prior hysterotomy incision, discussed in Chapters 31 and 41.

Genomic Technology

Breakthroughs in fetal testing and diagnosis continue to stun. By 2012, prenatal gene microarray techniques were used for clinical management (Dugoff, 2012). The advantages of these techniques are outlined in Chapters 13 and 14. Wapner and coworkers (2012) compared chromosomal microarray analysis of maternal blood with karyotyping for chromosomal anomalies. Reddy and associates (2012) applied this technology to stillbirth evaluation and reported it to be superior to karyotyping. Another report by Talkowski and colleagues (2012) described whole-genome sequencing of a fetus using maternal blood.

Screening for fetal aneuploidy using cell-free DNA (cfDNA) was first introduced in 2011. The technique is described in Chapter 14 (Cell-Free DNA Screening), and it is based on isolation of free fetal (placental) DNA in maternal blood. In a landmark study, Norton and associates (2015) found that cfDNA had a higher sensitivity and specificity compared with standard prenatal screening for trisomy 21 fetuses. Still, invasive testing is currently necessary to confirm a positive cfDNA test result (Chitty, 2015; Snyder, 2015).

The Ob/Gyn Hospitalist

The term “hospitalist” was coined in the 1990s and referred to physicians whose primary professional focus was generalized care of hospitalized patients. From this concept came the obstetrical and gynecological hospitalist whose primary role was to care for hospitalized obstetrical patients and to help manage their emergencies. These physicians could also provide urgent gynecological care and emergency department consultation. Alternative terms include “obstetrical hospitalist” or “laborist,” but the preferred standardized term by the American College of Obstetricians and Gynecologists (2016e) is “Ob/Gyn hospitalist.”

Although not a recognized subspecialty of obstetrics and gynecology, the Ob/Gyn hospitalist movement has gained momentum. The Society of Ob-Gyn Hospitalists had 528 members in 2017 (Burkard, 2017). Various practice models are described to fit the needs of a wide spectrum of obstetrical volumes (McCue, 2016). In addition to providing lifestyle modifications, Ob/Gyn hospitalists are used by some hospitals to improve the quality and safety of their women’s services and to reduce adverse events. Aside from a possible lowering of

the labor induction rate, studies are needed to demonstrate improved outcomes with these providers (American College of Obstetricians and Gynecologists, 2016e; Srinivas, 2016).

Medical Liability

The American College of Obstetricians and Gynecologists periodically surveys its fellows concerning the effect of liability on their practice. The 2015 Survey on Professional Liability is the 12th such report since 1983 (Carpentieri, 2015). From this survey, it appears that there is still a "liability crisis," and the reasons for it are complex. Because it is largely driven by money and politics, a consensus seems unlikely. Although some interests are diametrically opposite, other factors contribute to the problem's complexity. For example, each state has its own laws and opinions on tort reform. In some states, annual premiums for obstetricians approach $300,000—expenses that at least partially are borne by the patient and certainly by the entire health-care system. In 2011, all tort costs in the United States totaled nearly $265 billion. This is an astounding 1.8 percent of the gross domestic product and averages to a cost of $838 per citizen (Towers Watson, 2015).

The American College of Obstetricians and Gynecologists (2016a,c) has taken a lead in adopting a fair system for malpractice litigation—or *maloccurrence litigation*. And nationally, there is the possibility of federal tort reform under the Trump administration (Lockwood, 2017; Mello, 2017).

Home Births

Following a slight decline from 1990 through 2004, the percentage of out-of-hospital births in the United States increased from 0.86 to 1.5 percent—almost 75 percent—through 2014 (MacDorman, 2016a). Of these home births, only a third are attended by nurse midwives certified by the American Midwife Certification Board (Grünebaum, 2015; Snowden, 2015).

Proponents of home births cite successes derived from laudatory observational data from England and The Netherlands (de Jonge, 2015; Van der Kooy, 2011). Data from the United States, however, are less convincing and indicate a higher incidence of perinatal morbidity and mortality (Grünebaum, 2014, 2015; Snowden, 2015; Wasden, 2014; Wax, 2010). These latter findings have led Chervenak and coworkers (2013, 2015) to question the ethics of participation in planned home births. Greene and Ecker (2015) take a broader view. Given data from these more recently cited studies, they are of the view that these data empower women to make a rational decision regarding home delivery. The American College of Obstetricians and Gynecologists (2017b) believes that hospitals and accredited birth centers offer the safest settings, but that each woman has the right to make a medically informed decision regarding delivery.

Family Planning Services

Politics and religion over the years have led to various governmental interferences with the reproductive rights of women. These intrusions have disparately affected indigent women and adolescents. This is despite all reports of the overwhelming success of such programs. One example is the exclusion of Planned

Parenthood affiliates from the Texas Medicaid fee-for-service family planning program. In some groups of women served, there was discontinuation of contraception and an increased rate of Medicaid births (Stevenson, 2016).

According to the Guttmacher Institute (2016a), publicly funded family planning services are needed by 20 million American women. In 2014, such services prevented nearly 2 million unintended pregnancies and 700,000 abortions in the United States. The fate of family planning services is not fully determined, while waiting for decisions regarding provisions within the 2017 American Health Care Act (AHCA), or "Trumpcare." In his response to news that the AHCA may dismantle contraceptive coverage, American College of Obstetricians and Gynecologists President Dr. Haywood Brown (2017) called this a deep disregard for women's health.

Opioid Abuse in Pregnancy

According to the CDC (2014), there were 259 million prescriptions written in 2012 for opioid medications. In 2013, more than a third of American adults reported prescription opioid use (Han, 2017). These freely available—albeit requiring a prescription—addictive drugs are associated with *opioid use disorders*. It remains uncertain if opioid use is teratogenic (Lind, 2017). Still, their abuse by pregnant women has caused an unprecedented rise in the *neonatal abstinence syndrome,* described further in Chapters 12 (Cocaine) and 33 (Neonatal Abstinence Syndrome). Treatment of opioid abuse in pregnancy and its sequelae result in $1.5 billion annually in hospital charges.

For obstetrical providers to better deal with opioid-addicted pregnant women and their fetus–newborns, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a workshop in 2016 to study many aspects of the problem (Reddy, 2017). The Workshop was cosponsored by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Society for Maternal–Fetal Medicine, the CDC, and the March of Dimes. Several topics were addressed, and hopefully implementation of these findings will help improve maternal treatment and neonatal outcomes (American College of Obstetricians and Gynecologists, 2017a).

Brave New World

The bold new concept of in-vitro fertilization (IVF) produced the first IVF baby in Britain in 1978. This was soon followed in 1981 with an American success. After four decades, the Society for Assisted Reproductive Technology (SART) reports that more than 1 million babies have been born in the United States using assisted reproductive technologies (ART) offered by 440 clinics (Fox, 2017).

After 15 years of experimental preparation, the promise of a successful human uterine transplant was finally realized with an IVF-conceived liveborn neonate in Sweden (Brännström, 2015). During pregnancy, the mother was treated with tacrolimus, azathioprine, and corticosteroids and underwent cesarean delivery at 32 weeks for preeclampsia and abnormal fetal heart rate testing. This was followed by uterine transplantation programs at the Cleveland Clinic and Baylor Medical Center in Dallas (Flyckt, 2016, 2017;

Testa, 2017). In 2017, the Swedish team had completed a nine-patient trial, in which seven women had become pregnant and five had successful deliveries (Kuehn, 2017). Also, in Dallas, the first such newborn in the United States was born (Rice, 2017).

Meanwhile, researchers at Children's Hospital of Philadelphia pursued a 20-year goal in search of an artificial womb (Yuko, 2017). Using incubator technology, the team devised an artificial amnionic sac. Through this, the umbilical vessels were perfused and drained, and the blood was returned to systems that performed extracorporeal membrane oxygenation and dialysis. To date, lamb fetuses have been kept alive for as long as 1 month. Adverse effects of cerebrovascular hypotension and hypoxemia are conjectural but highly worrisome.

The ethical and legal challenges of these new technologies are daunting. Of those that arose from IVF, most are settled. For the other two endeavors, there are likely many years of ethical and legal milestones ahead.

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CHAPTER 2: Maternal Anatomy

As the mechanism of labour is essentially a process of accommodation between the foetus and the passage through which it must pass, it is apparent that obstetrics lacked a scientific foundation until the anatomy of the bony pelvis and of the soft parts connected with it was clearly understood.

—J. Whitridge Williams (1903)

ANTERIOR ABDOMINAL WALL

Skin, Subcutaneous Layer, and Fascia

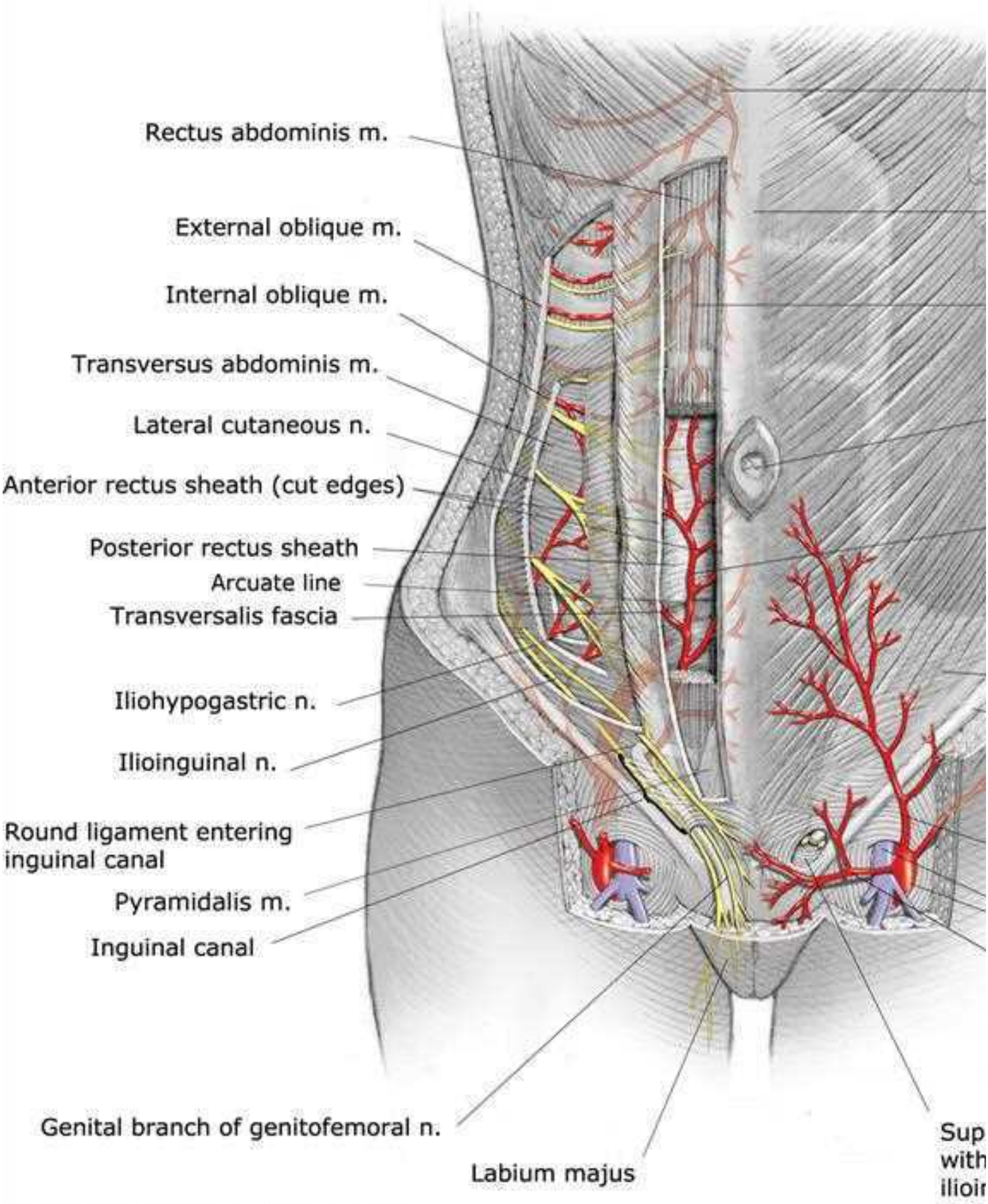
The anterior abdominal wall confines abdominal viscera, stretches to accommodate the expanding uterus, and provides surgical access to the internal reproductive organs. Thus, a comprehensive knowledge of its layered structure is required to surgically enter the peritoneal cavity.

Langer lines describe the orientation of dermal fibers within the skin. In the anterior abdominal wall, they are arranged transversely. As a result, vertical skin incisions sustain greater lateral tension and thus, in general, develop wider scars. In contrast, low transverse incisions, such as the Pfannenstiel, follow Langer lines and lead to superior cosmetic results.

The subcutaneous layer can be separated into a superficial, predominantly fatty layer—Camper fascia, and a deeper membranous layer—Scarpa fascia. Camper fascia continues onto the perineum to provide fatty substance to the mons pubis and labia majora and then to blend with the fat of the ischioanal fossa. Scarpa fascia continues inferiorly onto the perineum as Colles fascia, described in Perineum.

Beneath the subcutaneous layer, the anterior abdominal wall muscles consist of the midline rectus abdominis and pyramidalis muscles as well as the external oblique, internal oblique, and transversus abdominis muscles, which extend across the entire wall (Fig. 2-1). The fibrous aponeuroses of these three latter muscles form the primary fascia of the anterior abdominal wall. These fuse in the midline at the linea alba, which normally measures 10 to 15 mm wide below the umbilicus (Beer, 2009). An abnormally wide separation may reflect diastasis recti or hernia.

FIGURE 2-1
Anterior abdominal wall anatomy. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



These three aponeuroses also invest the rectus abdominis muscle as the rectus sheath. The construction of this sheath varies above and below a boundary, termed the arcuate line (see Fig. 2-1). Cephalad to this border, the aponeuroses invest the rectus abdominis bellies on both dorsal and ventral surfaces. Caudal to this line,

all aponeuroses lie ventral or superficial to the rectus abdominis muscle, and only the thin transversalis fascia and peritoneum lie beneath the rectus (Loukas, 2008). This transition of rectus sheath composition can be seen best in the upper third of a midline vertical abdominal incision.

The paired small triangular pyramidalis muscles originate from the pubic crest and insert into the linea alba. These muscles lie atop the rectus abdominis muscle but beneath the anterior rectus sheath.

Blood Supply

The superficial epigastric, superficial circumflex iliac, and superficial external pudendal arteries arise from the femoral artery just below the inguinal ligament within the femoral triangle (see Fig. 2-1). These vessels supply the skin and subcutaneous layers of the anterior abdominal wall and mons pubis. Of these three, the superficial epigastric vessels are surgically important to the obstetrician and course diagonally from their origin toward the umbilicus. With a low transverse skin incision, these vessels can usually be identified at a depth halfway between the skin and the anterior rectus sheath. They lie above Scarpa fascia and several centimeters from the midline. Ideally, these vessels are identified and surgically occluded.

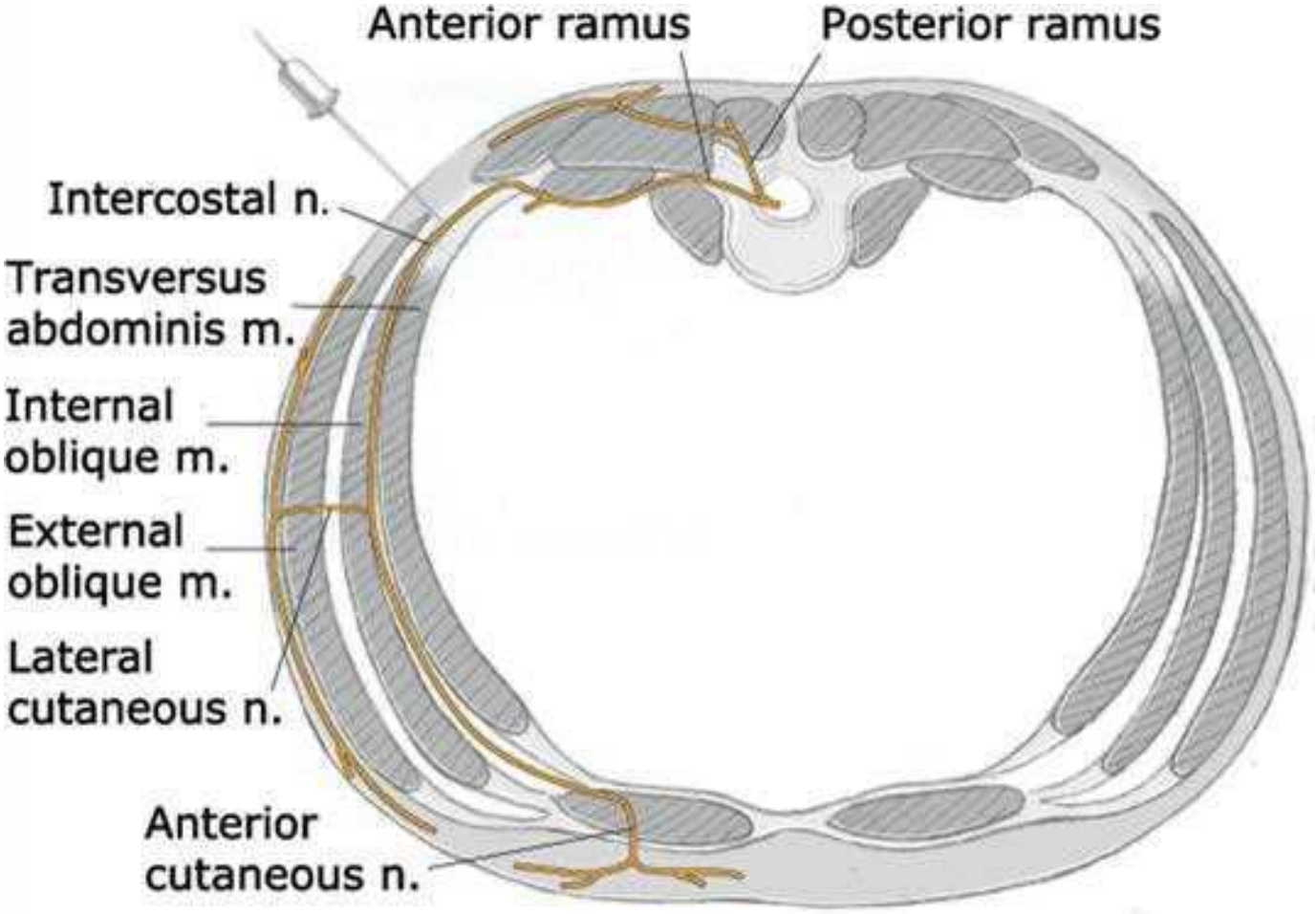
In contrast, the inferior “deep” epigastric vessels are branches of the external iliac vessels and supply anterior abdominal wall muscles and fascia. Of surgical relevance, the inferior epigastric vessels initially course lateral to, then posterior to the rectus abdominis muscles, which they supply. Above the arcuate line, these vessels course ventral to the posterior rectus sheath and lie between this sheath and the posterior surface of the rectus muscles. Near the umbilicus, the inferior epigastric vessels anastomose with the superior epigastric artery and vein, which are branches of the internal thoracic vessels. Clinically, when a Maylard incision is used for cesarean delivery, the inferior epigastric vessels may be lacerated lateral to the rectus belly during muscle transection. Preventively, identification and surgical occlusion are preferable. These vessels rarely may rupture following abdominal trauma and create a rectus sheath hematoma (Tolcher, 2010; Wai, 2015).

On each side of the lower anterior abdominal wall, Hesselbach triangle is the region bounded laterally by the inferior epigastric vessels, inferiorly by the inguinal ligament, and medially by the lateral border of the rectus abdominis muscle. Hernias that protrude through the abdominal wall in Hesselbach triangle are termed direct inguinal hernias. In contrast, indirect inguinal hernias do so through the deep inguinal ring, which lies lateral to this triangle, and then may exit out the superficial inguinal ring.

Innervation

The entire anterior abdominal wall is innervated by intercostal nerves ($T_{7–11}$), the subcostal nerve (T_{12}), and the iliohypogastric and the ilioinguinal nerves (L_1). Of these, the intercostal and subcostal nerves are anterior rami of the thoracic spinal nerves and run along the lateral and then anterior abdominal wall between the transversus abdominis and internal oblique muscles (Fig. 2-2). This space, termed the transversus abdominis plane, can be used for postcesarean analgesia blockade (Chap. 25, Postpartum Analgesia) (Fusco, 2015; Tawfik, 2017). Others report rectus sheath or ilioinguinal-iliohypogastric nerve blocks to decrease postoperative pain (Mei, 2011; Wolfson, 2012).

FIGURE 2-2
Intercostal and subcostal nerves are the anterior rami of spinal nerves. In this figure, an intercostal nerve extends ventrally between the transversus abdominis and internal oblique muscles. During this path, the nerve gives rise to lateral and anterior cutaneous branches, which innervate the anterior abdominal wall. As shown by the inserted needle, the transversus abdominis plane (TAP) block takes advantage of this anatomy. (Modified with permission from Hawkins JL: Anesthesia for the pregnant woman. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstraps’s Operative Obstetrics, 3rd ed. New York, McGraw Hill Education, 2017.)



Near the rectus abdominis lateral borders, anterior branches of the intercostal and subcostal nerves pierce the posterior sheath, rectus muscle, and then anterior sheath to reach the skin. Thus, these nerve branches may be severed during a Pfannenstiel incision creation during the step in which the overlying anterior rectus sheath is separated from the rectus abdominis muscle.

In contrast, the iliohypogastric and ilioinguinal nerves originate from the anterior ramus of the first lumbar spinal nerve. They emerge lateral to the psoas muscle and travel retroperitoneally across the quadratus lumborum inferomedially toward the iliac crest. Near this crest, both nerves pierce the transversus abdominis muscle and course ventromedially. At a site 2 to 3 cm medial to the anterior superior iliac spine, the nerves then pierce the internal oblique muscle and course superficial to it toward the midline (Whiteside, 2003). The iliohypogastric nerve perforates the external oblique aponeurosis near the lateral rectus border to provide sensation to the skin over the suprapubic area (see Fig. 2-1). The ilioinguinal nerve in its course medially travels through the inguinal canal and exits through the superficial inguinal ring, which forms by splitting of external abdominal oblique aponeurosis fibers. This nerve supplies the skin of the mons pubis, upper labia majora, and medial upper thigh.

The ilioinguinal and iliohypogastric nerves can be severed during a low transverse incision or entrapped during closure, especially if incisions extend beyond the lateral borders of the rectus abdominis muscle (Rahn, 2010). These nerves carry sensory information only, and injury leads to loss of sensation within the areas supplied. Rarely, chronic pain may develop (Whiteside, 2005).

The T_{10} dermatome approximates the level of the umbilicus. Analgesia to this level is suitable for labor and vaginal birth. Regional analgesia for cesarean delivery or for puerperal sterilization ideally extends to T_4.

EXTERNAL GENERATIVE ORGANS

Vulva

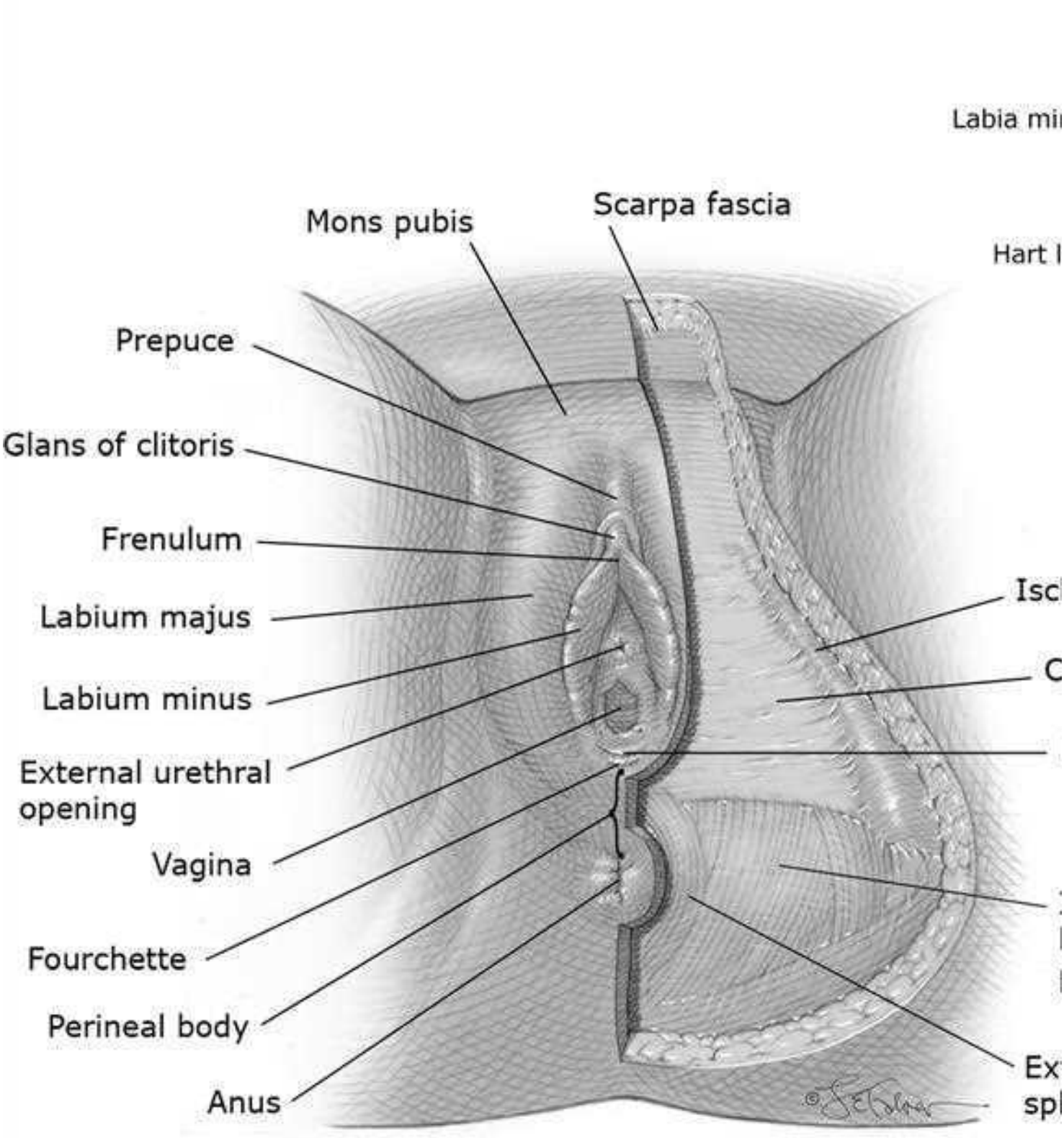
Mons Pubis, Labia, and Clitoris

The pudenda—commonly designated the vulva—includes all structures visible externally from the symphysis pubis to the perineal body. This includes the mons pubis, labia majora and minora, clitoris, hymen, vestibule, urethral opening, greater vestibular or Bartholin glands, minor vestibular glands, and paraurethral glands (Fig. 2-3). The vulva receives innervations and vascular support from the pudendal nerve (Pudendal Nerve).

FIGURE 2-3

Vulvar structures and subcutaneous layer of the anterior perineal triangle. Note the continuity of Colles and Scarpa fasciae. Inset: Vestibule boundaries and openings onto vestibule. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New

York, McGraw-Hill Education, 2016.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

The mons pubis is a fat-filled cushion overlying the symphysis pubis. After puberty, the mons pubis skin is covered by curly hair that forms the triangular escutcheon, whose base aligns with the upper margin of the symphysis pubis. In men and some hirsute women, the escutcheon extends farther onto the anterior abdominal wall toward the umbilicus.

Labia majora usually are 7 to 8 cm long, 2 to 3 cm wide, and 1 to 1.5 cm thick. They are continuous directly with the mons pubis superiorly, and the round ligaments terminate at their upper borders. Hair covers the labia majora, and apocrine, eccrine, and sebaceous glands are abundant. Beneath the skin, a dense connective tissue layer is nearly void of muscular elements but is rich in elastic fibers and fat. This fat mass provides bulk to the labia majora and is supplied with a rich venous

plexus. During pregnancy, this vasculature may develop varicosities, especially in multiparas, from increased venous pressure created by the enlarging uterus. They appear as engorged tortuous veins or as small grapelike clusters, but they are typically asymptomatic and require no treatment.

Each labium minus is a thin tissue fold that lies medial to each labium majus. The labia minora extend superiorly, where each divides into two lamellae. From each side, the lower lamellae fuse to form the frenulum of the clitoris, and the upper lamellae merge to form the prepuce (see Fig. 2-3). Inferiorly, the labia minora extend to approach the midline as low ridges of tissue that join to form the fourchette. The labia minora dimensions vary greatly among individuals, with lengths from 2 to 10 cm and widths from 1 to 5 cm (Lloyd, 2005).

Structurally, the labia minora are composed of connective tissue with numerous vessels, elastin fibers, and very few smooth muscle fibers. They are supplied with many nerve endings and are extremely sensitive (Ginger, 2011a; Schober, 2015). The epithelia of the labia minora differ with location. Thinly keratinized stratified squamous epithelium covers the outer surface of each labium. On their inner surface, the lateral portion is covered by this same epithelium up to a demarcating line, termed Hart line. Medial to this line, each labium is covered by squamous epithelium that is nonkeratinized. The labia minora lack hair follicles, eccrine glands, and apocrine glands. However, sebaceous glands are numerous (Wilkinson, 2011).

The clitoris is the principal female erogenous organ. It is located beneath the prepuce, above the frenulum and urethra, and projects downward and inward toward the vaginal opening. The clitoris rarely exceeds 2 cm in length and is composed of a glans, a corpus or body, and two crura (Verkauf, 1992). The glans is usually less than 0.5 cm in diameter, is covered by stratified squamous epithelium, and is richly innervated. The clitoral body contains two corpora cavernosa. Extending from the clitoral body, each corpus cavernosum diverges laterally to form a long, narrow crus. Each crus lies along the inferior surface of its respective ischiopubic ramus and deep to the ischiocavernosus muscle. The clitoral blood supply stems from branches of the internal pudendal artery. Specifically, the deep artery of the clitoris supplies the clitoral body, whereas the dorsal artery of the clitoris supplies the glans and prepuce.

Vestibule

In adult women, the vestibule is an almond-shaped area that is enclosed by Hart line laterally, the external surface of the hymen medially, the clitoral frenulum anteriorly, and the fourchette posteriorly (see Fig. 2-3). The vestibule is usually perforated by six openings: the urethra, the vagina, two Bartholin gland ducts, and two ducts of the largest paraurethral glands—the Skene glands. The posterior portion of the vestibule between the fourchette and the vaginal opening is called the fossa navicularis. It is usually observed only in nulliparas.

The bilateral Bartholin glands, also termed greater vestibular glands, measure 0.5 to 1 cm in diameter. On their respective side, each lies inferior to the vestibular bulb and deep to the inferior end of the bulbospongiosus muscle (former bulbocavernosus muscle). A duct extends medially from each gland, measures 1.5 to 2 cm long, and opens distal to the hymeneal ring—one at 5 and the other at 7 o'clock on the vestibule. Following trauma or infection, either duct may swell and obstruct to form a cyst or, if infected, an abscess. In contrast, the minor vestibular glands are shallow glands lined by simple mucin-secreting epithelium and open along Hart line.

The paraurethral glands are a collective arborization of glands whose numerous small ducts open predominantly along the entire inferior aspect of the urethra. The two largest are called Skene glands, and their ducts typically lie distally and near the urethral meatus. Clinically, inflammation and duct obstruction of any of the paraurethral glands can lead to urethral diverticulum formation. The urethral opening or meatus is in the midline of the vestibule, 1 to 1.5 cm below the pubic arch, and a short distance above the vaginal opening.

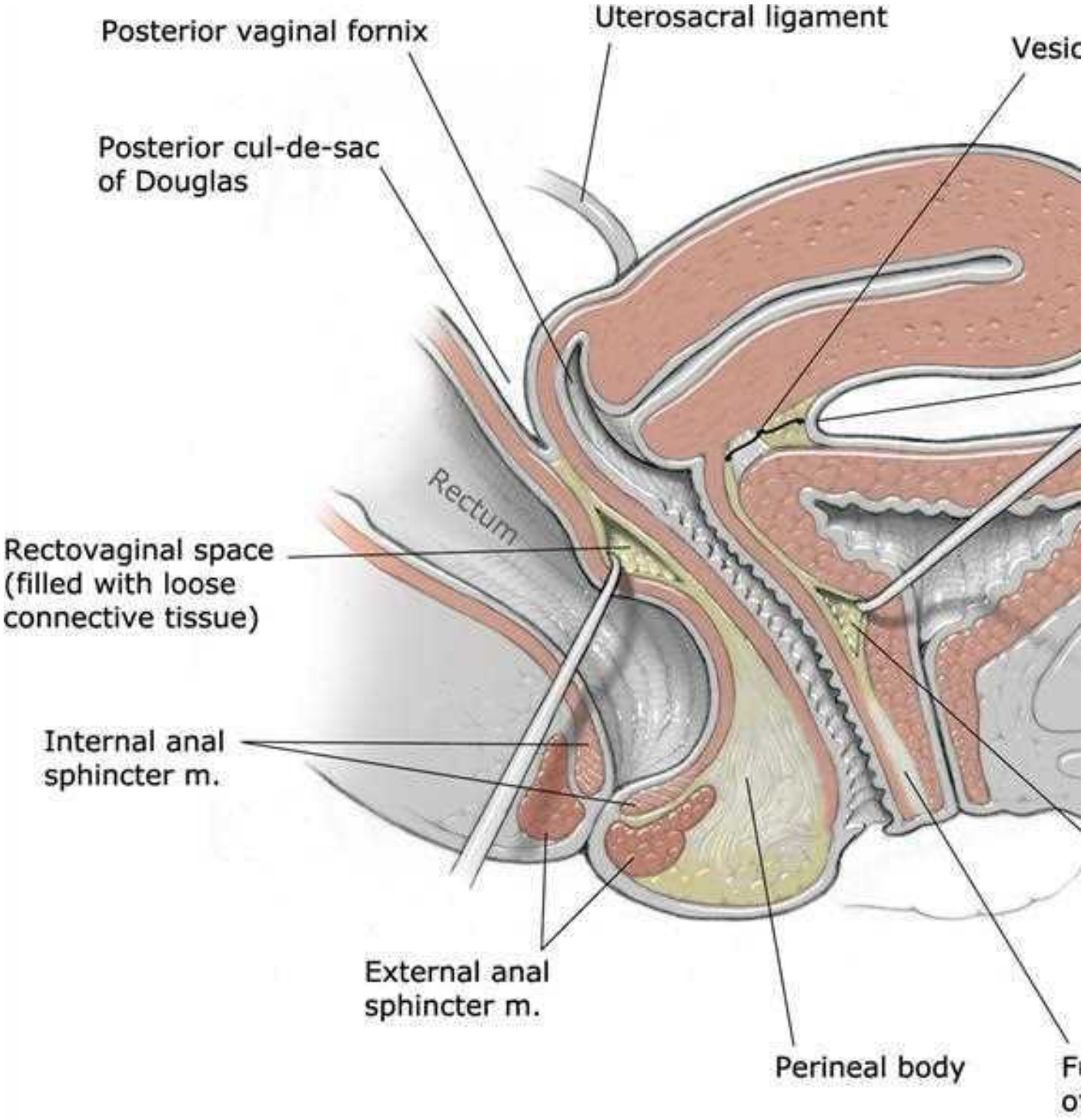
Vagina and Hymen

In adult women, the hymen is a membrane of varying thickness that surrounds the vaginal opening more or less completely. It is composed mainly of elastic and collagenous connective tissue, and both outer and inner surfaces are covered by nonkeratinized stratified squamous epithelium. The aperture of the intact hymen ranges in diameter from pinpoint to one that admits one or even two fingertips. As a rule, the hymen is torn at several sites during first coitus. However, identical tears may form by other penetration, for example, by tampons used during menstruation. The edges of the torn tissue soon reepithelialize. In pregnant women, the hymeneal epithelium is thick and rich in glycogen. Changes produced in the hymen by childbirth are usually readily recognizable. For example, over time, the hymen transforms into several nodules of various sizes, termed hymeneal or myrtiform caruncles.

Proximal to the hymen, the vagina is a musculomembranous tube that extends to the uterus and is interposed lengthwise between the bladder and the rectum (Fig. 2-4). Anteriorly, the vagina is separated from the bladder and urethra by connective tissue—the vesicovaginal septum. Posteriorly, between the lower portion of the vagina and the rectum, similar tissues together form the rectovaginal septum. The upper fourth of the vagina is separated from the rectum by the rectouterine pouch, also called the cul-de-sac or pouch of Douglas.

FIGURE 2-4

Vagina and surrounding anatomy. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Normally, the anterior and posterior walls of the vaginal lumen lie in contact, with only a slight space intervening at the lateral margins. Vaginal length varies considerably, but commonly, the anterior wall measures 6 to 8 cm, whereas the posterior vaginal wall is 7 to 10 cm. The upper end of the vaginal vault is subdivided by the cervix into anterior, posterior, and two lateral fornices. Clinically, the internal pelvic organs usually can be palpated through the thin walls of these fornices.

The vaginal lining is composed of nonkeratinized stratified squamous epithelium and underlying lamina propria. In premenopausal women, this lining is thrown into numerous thin transverse ridges, known as rugae, which line the anterior and posterior vaginal walls along their length. Deep to this, a muscular layer contains smooth muscle, collagen, and elastin. Beneath this muscularis lies an adventitial layer consisting of collagen and elastin (Weber, 1997).

The vagina lacks glands. Instead, it is lubricated by a transudate that originates from the vaginal subepithelial capillary plexus and crosses the permeable epithelium (Kim, 2011). Due to increased vascularity during pregnancy, vaginal secretions are notably increased. At times, this may be confused with amnionic fluid leakage, and clinical differentiation of these two is described in Chapter 22 (Identification of Labor).

After birth-related epithelial trauma and healing, fragments of stratified epithelium occasionally are embedded beneath the vaginal surface. Similar to its native tissue, this buried epithelium continues to shed degenerated cells and keratin. As a result, epidermal inclusion cysts, which are filled with keratin debris, may form. These are a common vaginal cyst.

The vagina has an abundant vascular supply. The proximal portion is supplied by the cervical branch of the uterine artery and by the vaginal artery. The latter may variably arise from the uterine or inferior vesical artery or directly from the internal iliac artery. The middle rectal artery contributes supply to the posterior vaginal wall, whereas the distal walls receive contributions from the internal pudendal artery. At each level, vessels supplying each side of the vagina course medially across the anterior or posterior vaginal wall and form midline anastomoses.

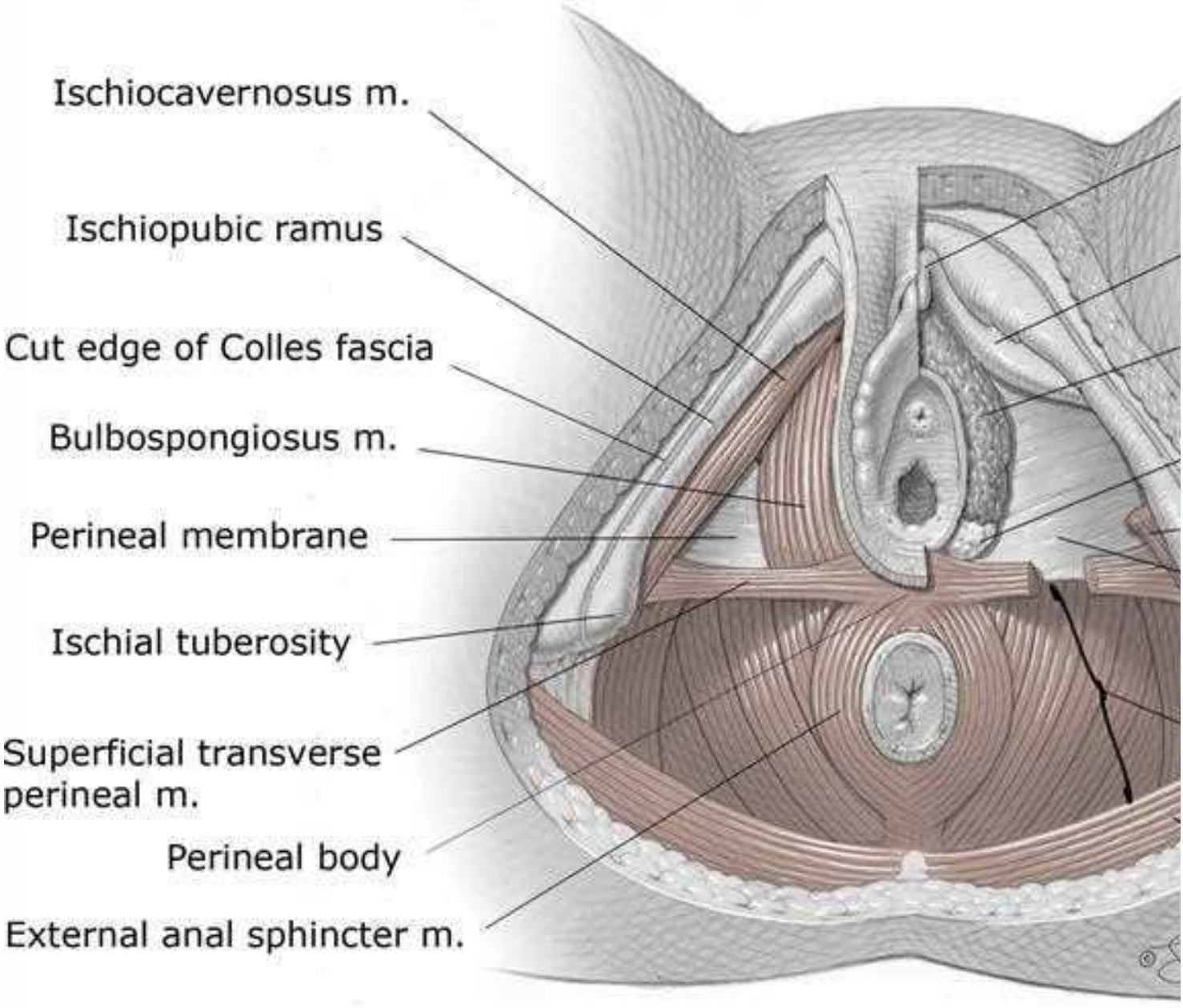
An extensive venous plexus also surrounds the vagina and follows the course of the arteries. Lymphatics from the lower third, along with those of the vulva, drain primarily into the inguinal lymph nodes. Those from the middle third drain into the internal iliac nodes, and those from the upper third drain into the external, internal, and common iliac nodes.

Perineum

This diamond-shaped area between the thighs has boundaries that mirror those of the bony pelvic outlet: the pubic symphysis anteriorly, ischiopubic rami and ischial tuberosities anterolaterally, sacrotuberous ligaments posterolaterally, and coccyx posteriorly. An arbitrary line joining the ischial tuberosities divides the perineum into an anterior triangle, also called the urogenital triangle, and a posterior triangle, termed the anal triangle.

The perineal body is a fibromuscular pyramidal mass found in the midline at the junction between these anterior and posterior triangles (Fig. 2-5). Also called the central tendon of the perineum, the perineal body sonographically measures 8 mm tall and 14 mm wide and thick (Santoro, 2016). It serves as the junction for several structures and provides significant perineal support (Shafik, 2007). Superficially, the bulbospongiosus, superficial transverse perineal, and external anal sphincter muscles converge on the perineal body. More deeply, the perineal membrane, portions of the pubococcygeus muscle, and internal anal sphincter contribute (Larson, 2010). The perineal body is incised by an episiotomy incision and is torn with second-, third-, and fourth-degree lacerations.

FIGURE 2-5
Superficial space of the anterior perineal triangle and posterior perineal triangle. Structures on the left side of the image can be seen after removal of Colles fascia. Those on the right side are noted after removal of the superficial muscles of the anterior triangle. (Modified with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Superficial Space of the Anterior Triangle

This triangle is bounded by the pubic rami superiorly, the ischial tuberosities laterally, and the superficial transverse perineal muscles posteriorly. It is divided into superficial and deep spaces by the perineal membrane. This membranous partition is a dense fibrous sheet that was previously known as the inferior fascia of the urogenital diaphragm. The perineal membrane attaches laterally to the ischiopubic rami, medially to the distal third of the urethra and vagina, posteriorly to the perineal body, and anteriorly to the arcuate ligament of the pubis (see Fig. 2-5).

The superficial space of the anterior triangle is bounded deeply by the perineal membrane and superficially by Colles fascia. As noted earlier, Colles fascia is the continuation of Scarpa fascia onto the perineum. On the perineum, Colles fascia securely attaches laterally to the pubic rami and fascia lata of the thigh, inferiorly to the superficial transverse perineal muscle and inferior border of the perineal membrane, and medially to the urethra, clitoris, and vagina. As such, the superficial space of the anterior triangle is a relatively closed compartment.

This superficial pouch contains several important structures, which include the Bartholin glands, vestibular bulbs, clitoral body and crura, branches of the pudendal vessels and nerve, and the ischiocavernosus, bulbospongiosus, and superficial transverse perineal muscles. Of these muscles, the ischiocavernosus muscles each attach on their respective side to the medial aspect of the ischial tuberosity inferiorly and the ischiopubic ramus laterally. Anteriorly, each attaches to a clitoral crus and may help maintain clitoral erection by compressing the crus to obstruct venous drainage. The bilateral bulbospongiosus muscles overlie the vestibular bulbs and Bartholin glands. They attach to the body of the clitoris anteriorly and the perineal body posteriorly. The muscles constrict the vaginal lumen and aid release of secretions from the Bartholin glands. They also may contribute to clitoral erection by compressing the deep dorsal vein of the clitoris. The bulbospongiosus and ischiocavernosus muscles also pull the clitoris downward. Last, the superficial transverse perineal muscles are narrow strips that attach to the ischial tuberosities laterally and the perineal body medially. They may be attenuated or even absent, but when present, they contribute to the perineal body (Corton, 2016).

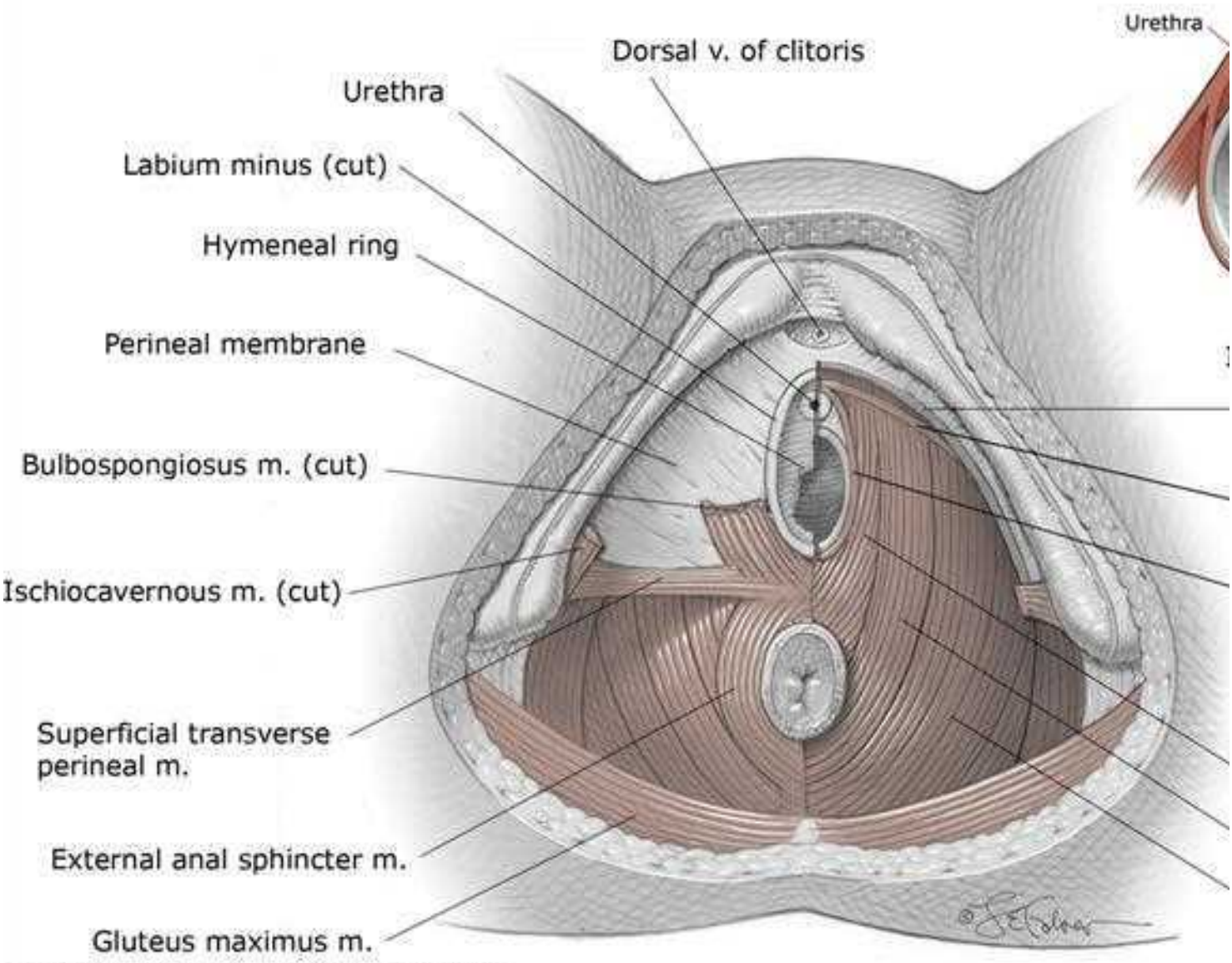
The vestibular bulbs are almond-shaped aggregations of veins that lie beneath the bulbospongiosus muscle on either side of the vestibule. They measure 3 to 4 cm long, 1 to 2 cm wide, and 0.5 to 1 cm thick. The bulbs terminate inferiorly at approximately the middle of the vaginal opening and extend upward toward the clitoris. Their anterior extensions merge in the midline, below the clitoral body. During childbirth, veins in the vestibular bulbs may be lacerated or even rupture to create a vulvar hematoma enclosed within the superficial space of the anterior triangle (Fig. 41-11).

Deep Space of the Anterior Triangle

This space lies deep to the perineal membrane and extends up into the pelvis (Mirilas, 2004). In contrast to the superficial perineal space, the deep space is continuous superiorly with the pelvic cavity (Corton, 2005). It contains portions of urethra and vagina, certain portions of internal pudendal artery branches, and muscles of the striated urogenital sphincter complex (Fig. 2-6).

FIGURE 2-6

Deep space of anterior triangle of the perineum. Structures on the right side of the image can be seen after removal of the perineal membrane. Also shown are structures that attach to the perineal body: bulbospongiosus, superficial transverse perineal, external anal sphincter, and puboperinealis muscles as well as perineal membrane. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Urethra

The female urethra measures 3 to 4 cm and originates within the bladder trigone (Ovaries). The distal two thirds of the urethra are fused with the anterior vaginal wall. The epithelial lining of the urethra changes from transitional epithelium proximally to nonkeratinized stratified squamous epithelium distally. The walls of the urethra consist of two layers of smooth muscle, an inner longitudinal and an outer circular. This is in turn surrounded by a circular layer of skeletal muscle referred to

as the *sphincter urethrae* or *rhabdosphincter* (see Fig. 2-6). Approximately at the junction of the middle and lower third of the urethra, and just above or deep to the perineal membrane, two strap skeletal muscles called the *urethrovaginal sphincter* and *compressor urethrae* are found. Together with the sphincter urethrae, these constitute the *striated urogenital sphincter complex.* This complex supplies constant tonus and provides emergency reflex contraction to sustain continence.

Distal to the level of the perineal membrane, the walls of the urethra consist of fibrous tissue, serving as the nozzle that directs the urine stream. Here, the urethra has a prominent submucosal layer that is lined by hormonally sensitive stratified squamous epithelium. Within the submucosal layer on the dorsal (vaginal) surface of the urethra lie the paraurethral glands, described earlier (Vagina and Hymen).

The urethra receives its blood supply from branches of the inferior vesical, vaginal, or internal pudendal arteries. Although still controversial, the pudendal nerve is believed to innervate the most distal part of the striated urogenital sphincter complex. Somatic efferent branches from S_2–S_4 that course along the inferior hypogastric plexus variably innervate the sphincter urethrae.

Pelvic Diaphragm

Found deep to the anterior and posterior triangles, this broad muscular sling provides substantial support to the pelvic viscera. The pelvic diaphragm is composed of the levator ani and the coccygeus muscles. The levator ani, in turn, contains the pubococcygeus, puborectalis, and iliococcygeus muscles. The pubococcygeus muscle is also termed the pubovisceral muscle and is subdivided based on points of insertion and function. These include the pubovaginalis, puboperinealis, and puboanalis muscles, which insert into the vagina, perineal body, and anus, respectively (Kearney, 2004).

Vaginal birth conveys significant risk for damage to the levator ani or to its innervation (DeLancey, 2003; Weidner, 2006). Evidence supports that levator ani avulsion may predispose women to greater risk of pelvic organ prolapse (Dietz, 2008; Schwertner-Tiepelmann, 2012). For this reason, current research efforts are aimed at minimizing these injuries.

Posterior Triangle

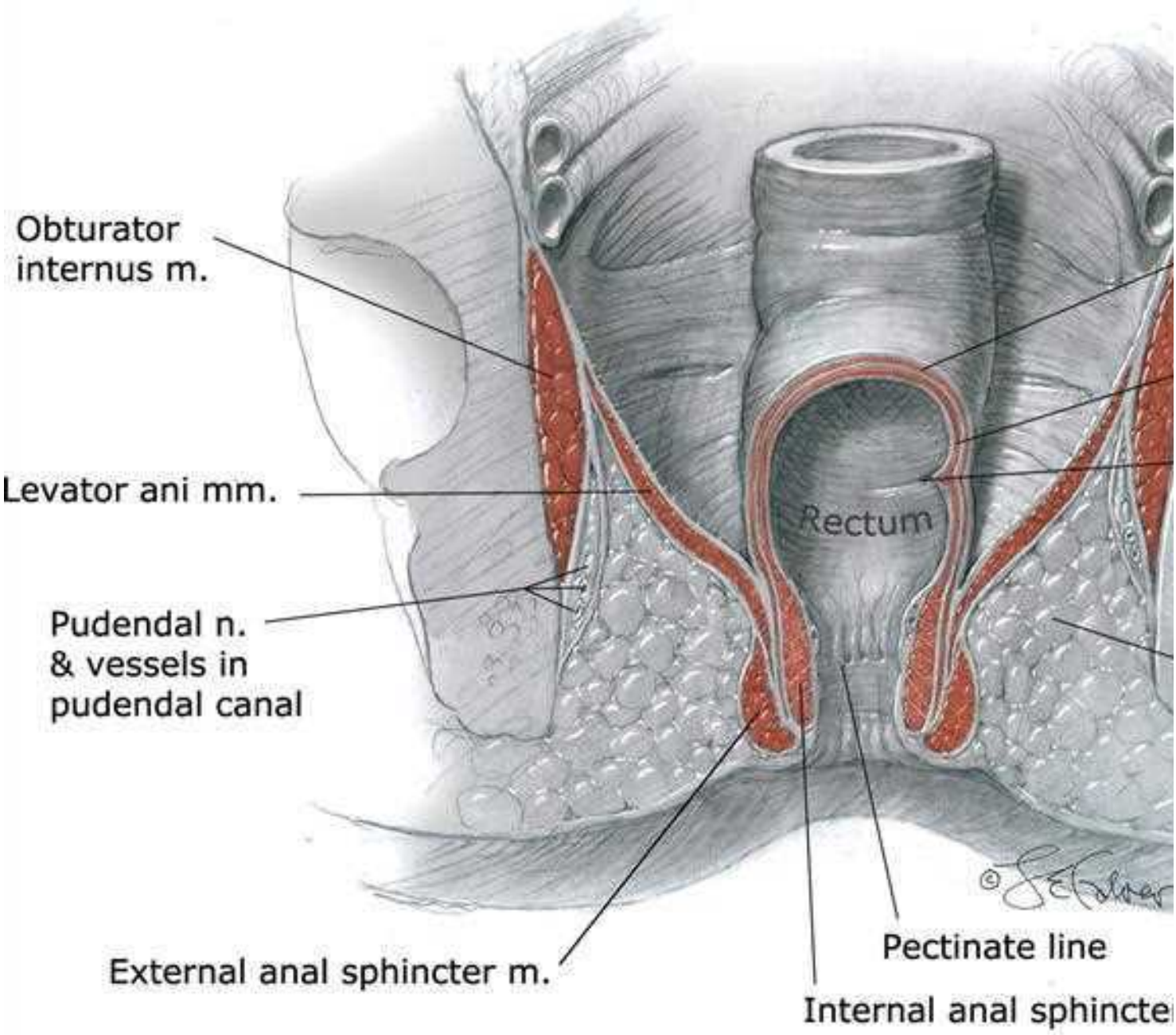
This triangle contains the ischioanal fossae, anal canal, and anal sphincter complex, which consists of the internal anal sphincter, external anal sphincter, and puborectalis muscle. Branches of the pudendal nerve and internal pudendal vessels are also found within this triangle.

Ischioanal Fossae

Also known as ischiorectal fossae, these two fat-filled wedge-shaped spaces are found on either side of the anal canal and comprise the bulk of the posterior triangle (Fig. 2-7). Each fossa has skin as its superficial base, whereas its deep apex is formed by the junction of the levator ani and obturator internus muscles. Other borders include: laterally, the obturator internus muscle fascia and ischial tuberosity; inferomedially, the anal canal and sphincter complex; superomedially, the inferior fascia of the downwardly sloping levator ani; posteriorly, the gluteus maximus muscle and sacrotuberous ligament; and anteriorly, the inferior border of the anterior triangle.

FIGURE 2-7

Anal canal and ischioanal fossa. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



The fat found within each fossa provides support to surrounding organs yet allows rectal distention during defecation and vaginal stretching during delivery. Clinically, injury to vessels in the posterior triangle can lead to hematoma formation in the ischioanal fossa, and the potential for large accumulation in these easily distensible spaces. Moreover, the two fossae communicate dorsally, behind the anal canal. This can be especially important because an episiotomy infection or hematoma may extend from one fossa into the other.

Anal Canal

This distal continuation of the rectum begins at the level of levator ani attachment to the rectum and ends at the anal skin. Along this 4- to 5-cm length, the mucosa consists of columnar epithelium in the uppermost portion. However, at the pectinate line, also termed dentate line, simple stratified squamous epithelium begins and continues to the anal verge. At the verge, keratin and skin adnexa join the squamous epithelium.

The anal canal has several tissue layers (see Fig. 2-7). Inner layers include the anal mucosa, the internal anal sphincter, and an intersphincteric space that contains continuation of the rectum's longitudinal smooth muscle layer. An outer layer contains the puborectalis muscle as its cephalad component and the external anal sphincter caudally.

Within the anal canal, three highly vascularized submucosal arteriovenous plexuses, termed anal cushions, aid complete closure of the canal and fecal continence when apposed. Increasing uterine size, excessive straining, and hard stool create increased pressure that ultimately leads to degeneration and subsequent laxity of the cushion's supportive connective tissue base. These cushions then protrude into and downward through the anal canal. This leads to venous engorgement within the cushions—now termed hemorrhoids. Venous stasis results in inflammation, erosion of the cushion's epithelium, and then bleeding.

External hemorrhoids are those that arise distal to the pectinate line. They are covered by stratified squamous epithelium and receive sensory innervation from the inferior rectal nerve. Accordingly, pain and a palpable mass are typical complaints. Following resolution, a hemorrhoidal tag may remain and is composed of redundant anal skin and fibrotic tissue. In contrast, internal hemorrhoids are those that form above the pectinate line and are covered by insensitive anorectal mucosa. These may prolapse or bleed but rarely become painful unless they undergo thrombosis or necrosis.

Anal Sphincter Complex

Two sphincters surround the anal canal to provide fecal continence—the external and internal anal sphincters. Both lie near the vagina and may be torn during vaginal delivery. The internal anal sphincter (IAS) is a distal continuation of the rectal circular smooth muscle layer. It receives predominantly parasympathetic fibers, which pass through the pelvic splanchnic nerves. Along its length, this sphincter is supplied by the superior, middle, and inferior rectal arteries. The IAS contributes the bulk of anal canal resting pressure for fecal continence and relaxes prior to defecation. The IAS measures 3 to 4 cm in length, and at its distal margin, it overlaps the external sphincter for 1 to 2 cm (DeLancey, 1997). The distal site at which this overlap ends, called the intersphincteric groove, is palpable on digital examination.

In contrast, the external anal sphincter (EAS) is a striated muscle ring that anteriorly attaches to the perineal body and posteriorly connects to the coccyx via the anococcygeal ligament. The EAS maintains a constant resting contraction to aid continence, provides additional squeeze pressure when continence is threatened, yet relaxes for defecation. The external sphincter receives blood supply from the inferior rectal artery, which is a branch of the internal pudendal artery. Somatic motor fibers from the inferior rectal branch of the pudendal nerve supply innervation. Clinically, the IAS and EAS may be involved in third- and fourth-degree lacerations during vaginal delivery, and reunion of these rings is integral to defect repair (Chap. 27, Laceration and Episiotomy Repairs).

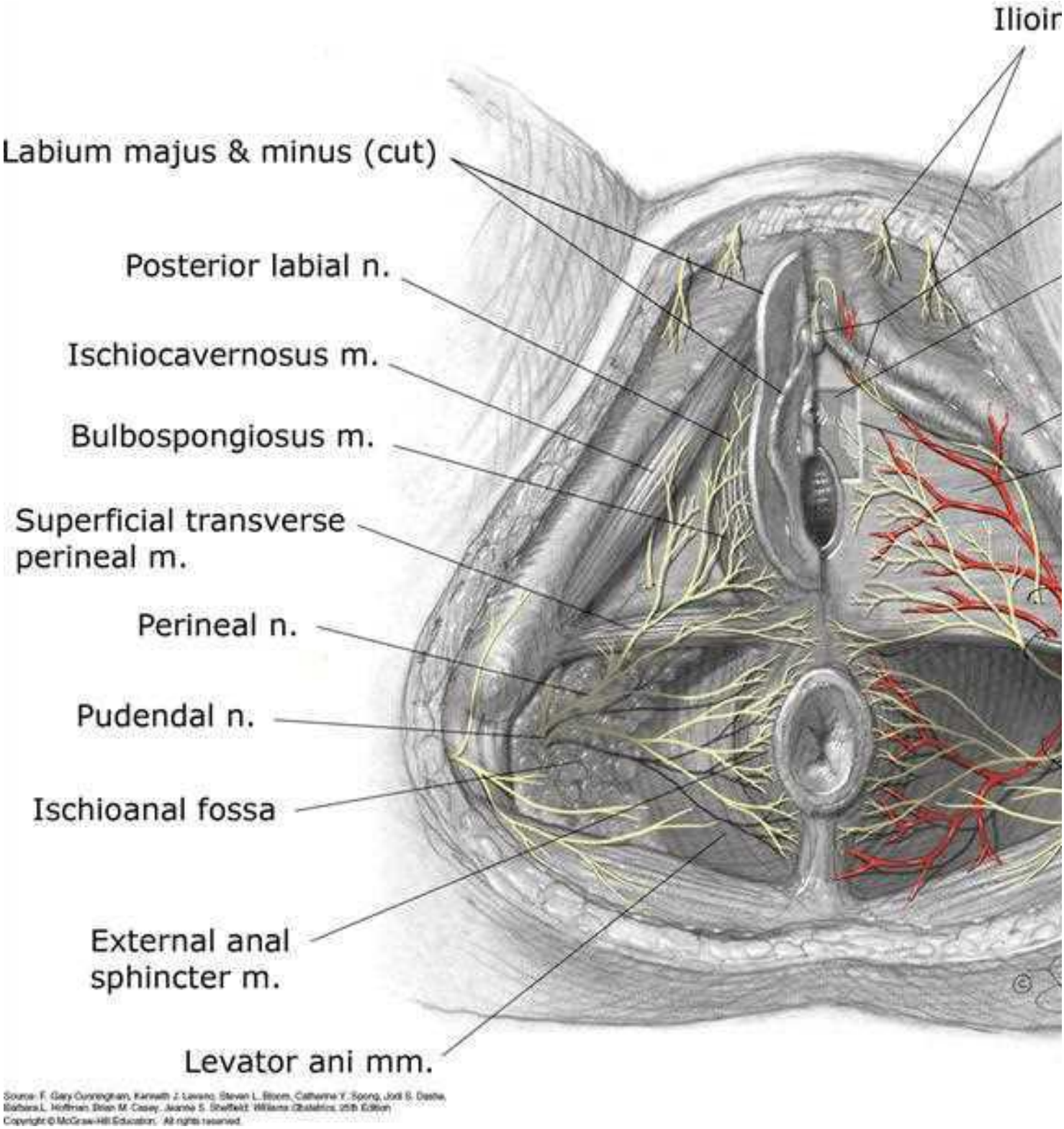
Pudendal Nerve

This is formed from the anterior rami of S_{2-4} spinal nerves. It courses between the piriformis and coccygeus muscles and exits through the greater sciatic foramen at a location posterior to the sacrospinous ligament and just medial to the ischial spine (Barber, 2002; Maldonado, 2015). Thus, when injecting local anesthetic for a pudendal nerve block, the ischial spine serves an identifiable landmark (Chap. 25, Central Nervous System Toxicity). The pudendal nerve then runs beneath the sacrospinous ligament and above the sacrotuberous ligament as it reenters the lesser sciatic foramen to course along the obturator internus muscle. Atop this muscle, the nerve lies within the pudendal canal, also known as Alcock canal, which is formed by splitting of the obturator internus investing fascia (Shafik, 1999). In general, the pudendal nerve is relatively fixed as it courses behind the sacrospinous ligament and within the pudendal canal. Accordingly, it may be at risk of stretch injury during downward displacement of the pelvic floor during childbirth (Lien, 2005).

The pudendal nerve leaves this canal to enter the perineum and divides into three terminal branches (Fig. 2-8). The first of these, the dorsal nerve of the clitoris, runs between the ischiocavernosus muscle and perineal membrane to supply the clitoral glans (Ginger, 2011b). Second, the perineal nerve runs superficial to the perineal membrane (Montoya, 2011). It divides into posterior labial branches and muscular branches, which serve the labial skin and the anterior perineal triangle muscles, respectively. Last, the inferior rectal branch runs through the ischioanal fossa to supply the external anal sphincter, the anal mucosa, and the perianal skin (Mahakkanukrauh, 2005). The major blood supply to the perineum is via the internal pudendal artery, and its branches mirror the divisions of the pudendal nerve.

FIGURE 2-8

Pudendal nerve and vessels. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



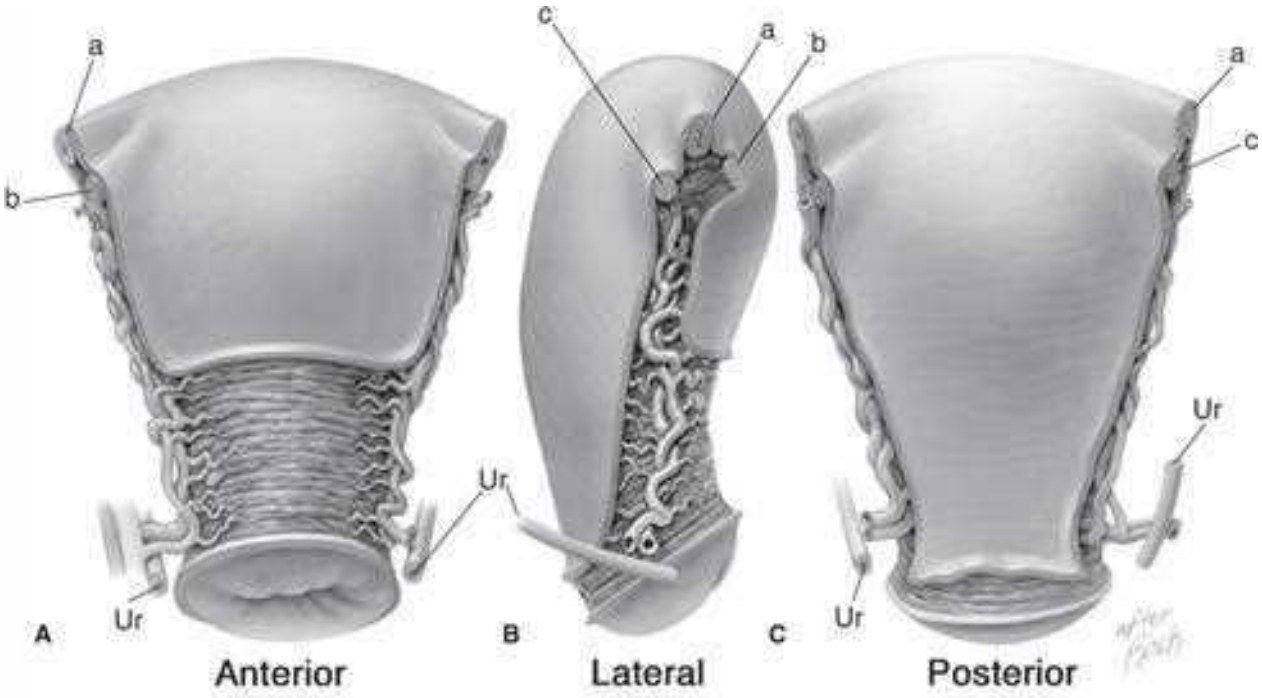
INTERNAL GENERATIVE ORGANS

Uterus

The nonpregnant uterus lies in the pelvic cavity between the bladder anteriorly and the rectum posteriorly. Almost the entire posterior wall of the uterus is covered by serosa, that is, visceral peritoneum (Fig. 2-9). The lower portion of this peritoneum forms the anterior boundary of the rectouterine cul-de-sac, or pouch of Douglas. Only the upper portion of the anterior uterine wall is covered by visceral peritoneum. At the caudal border of this portion, the peritoneum reflects forward onto the bladder dome to create the vesicouterine pouch. As a result, the lower portion of the anterior uterine wall is separated from the posterior wall of the bladder only by a well-defined loose connective tissue layer—the vesicouterine space. Clinically, during cesarean delivery, the peritoneum of the vesicouterine pouch is sharply incised, and the vesicouterine space is entered. Dissection caudally within this space lifts the bladder safely off the lower uterine segment for hysterotomy and delivery (Chap. 30, Hysterotomy).

FIGURE 2-9

Anterior **(A)**, right lateral **(B)**, and posterior **(C)** views of the uterus of an adult woman. a = oviduct; b = round ligament; c = ovarian ligament; Ur = ureter.



The uterus is pear shaped and consists of two major but unequal parts. The upper, larger portion is the body or corpus, whereas the lower smaller cervix projects into the vagina. The isthmus is the union site of these two. It is of special obstetrical significance because it forms the lower uterine segment during pregnancy. At each superolateral margin of the body is a uterine cornu, from which a fallopian tube emerges. This area also contains the origins of the round and ovarian ligaments. Between the points of fallopian tube insertion is the convex upper uterine segment termed the fundus.

The bulk of the uterine body, but not the cervix, is muscle. The inner surfaces of the anterior and posterior walls lie almost in contact, and the cavity between these walls forms a mere slit. The nulligravid uterus measures 6 to 8 cm in length compared with 9 to 10 cm in multiparas. The uterus averages 60 g and typically weighs more in parous women (Langlois, 1970; Sheikhazadi, 2010).

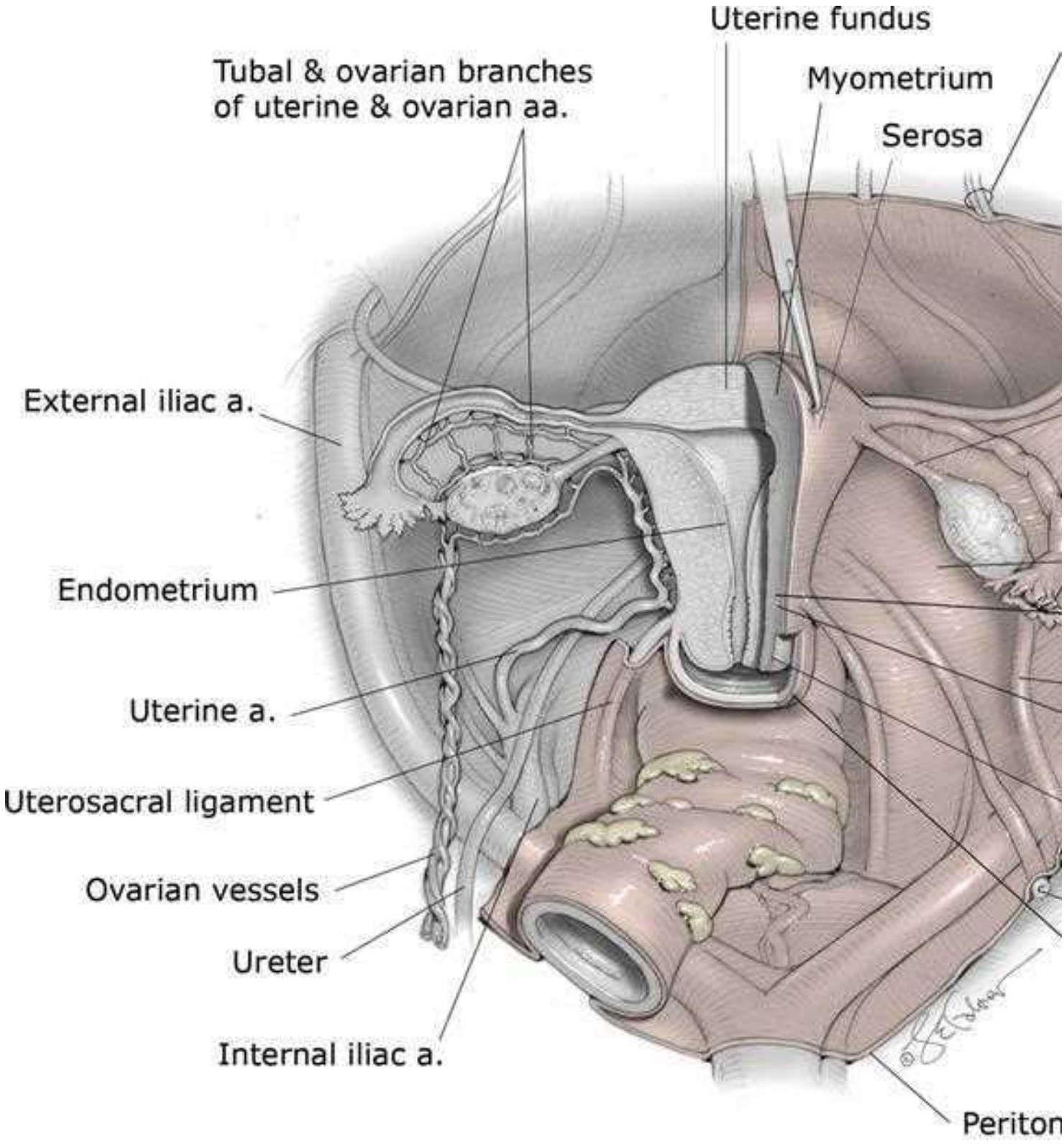
Pregnancy stimulates remarkable uterine growth due to muscle fiber hypertrophy. The uterine fundus, a previously flattened convexity between tubal insertions, now becomes dome shaped. Moreover, the round ligaments appear to insert at the junction of the middle and upper thirds of the organ. The fallopian tubes elongate, but the ovaries grossly appear unchanged.

Cervix

This portion of the uterus is cylindrical and has small apertures at each end—the internal and external cervical ora. The endocervical canal runs through the cervix and connects these ora. The cervix is divided into upper and lower portions by the vagina's attachment to its outer surface. The upper portion—the portio supravaginalis—begins at the internal os, which corresponds to the level at which the peritoneum is reflected up onto the bladder (Fig. 2-10). The lower cervical portion protrudes into the vagina as the portio vaginalis.

FIGURE 2-10

Uterus, adnexa, and associated anatomy. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Before childbirth, the external cervical os is a small, regular, oval opening. After labor, especially vaginal childbirth, the orifice is converted into a transverse slit that is divided such that there are the so-called anterior and posterior cervical lips. If torn deeply during labor or delivery, the cervix may heal in such a manner that it appears irregular, nodular, or stellate (Fig. 36-1).

The cervical surface that radially surrounds the external os is called the ectocervix and is lined predominantly by nonkeratinized stratified squamous epithelium. In contrast, the endocervical canal is covered by a single layer of mucin-secreting columnar epithelium, which creates deep cleftlike infoldings or “glands.” Commonly during pregnancy, the endocervical epithelium moves out and onto the ectocervix in a physiological process termed eversion (Chap. 4, Cervix).

The cervical stroma is composed mainly of collagen, elastin, and proteoglycans, but very little smooth muscle. As described in Chapter 21 (Cervical Ripening), changes in the amount, composition, and orientation of these components lead to cervical ripening prior to labor onset. In early pregnancy, increased vascularity within the cervix stroma beneath the epithelium creates an ectocervical blue tint that is characteristic of Chadwick sign. Cervical edema leads to softening—Goodell sign, whereas isthmic softening is Hegar sign.

Myometrium and Endometrium

Most of the uterus is composed of myometrium, which contains smooth muscle bundles united by connective tissue with many elastic fibers. Interlacing myometrial fibers surround myometrial vessels and contract to compress these. This anatomy allows hemostasis at the placental site during the third stage of labor.

The number of myometrial muscle fibers varies by location (Schwalm, 1966). Levels progressively diminish caudally such that, in the cervix, muscle makes up only 10 percent of the tissue mass. The uterine body's inner wall has relatively more muscle than its outer layers. And, in the anterior and posterior walls, the muscle content is greater than in the lateral walls. During pregnancy, the upper myometrium undergoes marked hypertrophy, but cervical muscle content does not change significantly.

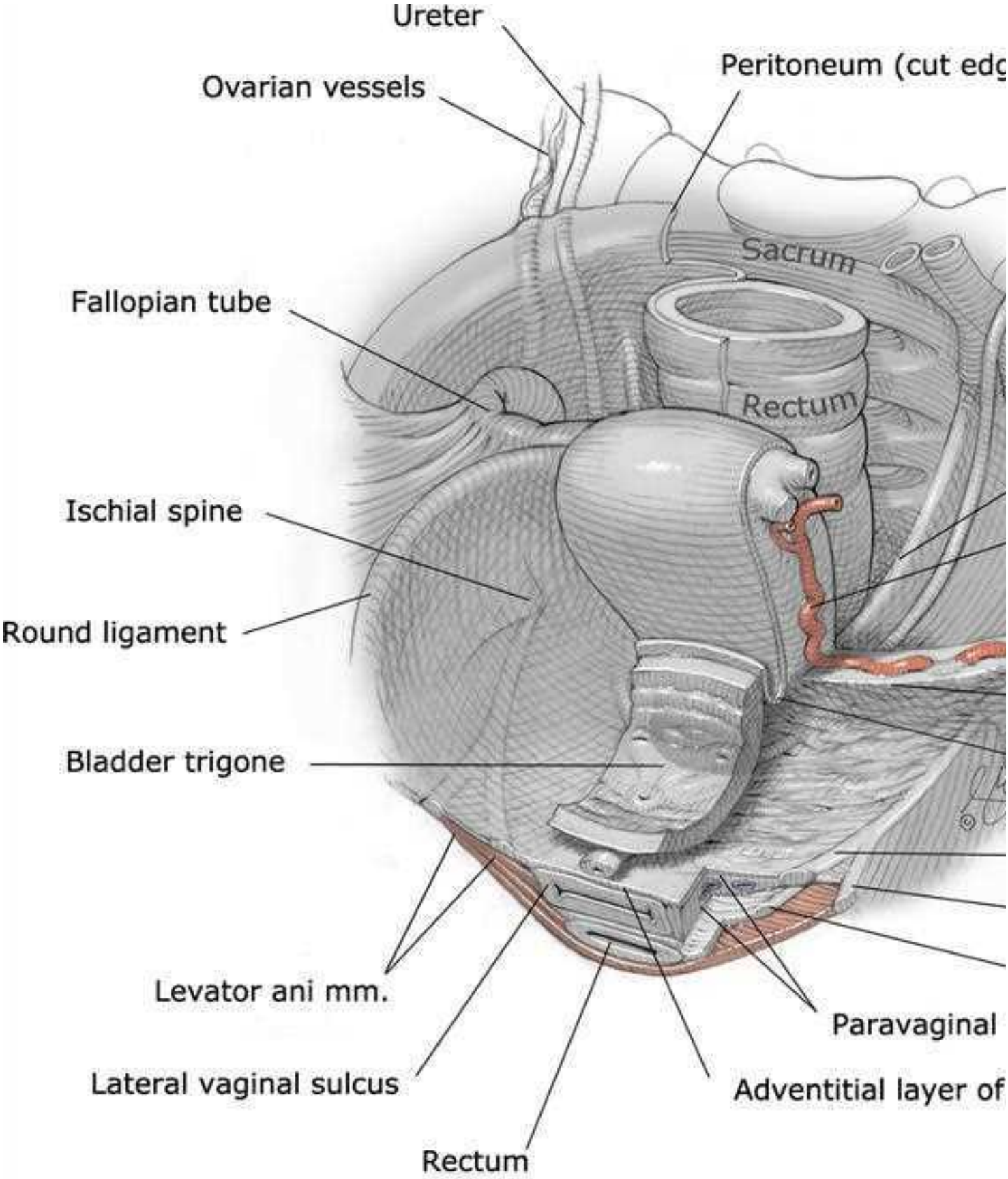
The uterine cavity is lined with endometrium, which is composed of an overlying epithelium, invaginating glands, and a supportive, vascular stroma. As discussed in Chapter 5 (Estrogen and Progesterone Action), the endometrium varies greatly throughout the menstrual cycle. This layer is divided into a functionalis layer, which is sloughed with menses, and a basalis layer, which serves to regenerate the functionalis layer following each menses. During pregnancy, the endometrium is termed decidua and undergoes dramatic hormonally driven alterations.

Ligaments

Several ligaments extend from the uterine surface toward the pelvic sidewalls and include the round, broad, cardinal, and uterosacral ligaments (Figs. 2-10 and 2-11). Despite their appellation, the round and broad ligaments provide no substantial uterine support, which contrasts with the cardinal and uterosacral ligaments.

FIGURE 2-11

Pelvic viscera and their connective tissue support. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

The round ligament originates somewhat below and anterior to the origin of the fallopian tubes. Clinically, this orientation can aid fallopian tube identification during puerperal sterilization. This is important if pelvic adhesions limit tubal mobility and thus, hinder fimbria visualization and tubal confirmation prior to ligation. Each round ligament extends laterally and down into the inguinal canal, through which it passes, to terminate in the upper portion of the ipsilateral labium majus. Sampson artery, a branch of the uterine artery, runs within this ligament. In nonpregnant women, the round ligament varies from 3 to 5 mm in diameter and is

composed of smooth muscle bundles separated by fibrous tissue septa (Mahran, 1965). During pregnancy, these ligaments undergo considerable hypertrophy and increase appreciably in both length and diameter.

The broad ligaments are two winglike structures that extend from the lateral uterine margins to the pelvic sidewalls. Each broad ligament consists of a double-layer drape of peritoneum. The anterior and posterior layers of this drape are termed the anterior and posterior leaves, respectively. In forming the broad ligament, this peritoneum folds over structures extending from each cornu. Peritoneum that folds over the fallopian tube is termed the mesosalpinx, that around the round ligament is the mesoteres, and that over the ovarian ligament is the mesovarium. Peritoneum that extends beneath the fimbriated end of the fallopian tube toward the pelvic wall forms the suspensory ligament or the infundibulopelvic ligament of the ovary. This contains nerves and the ovarian vessels, and during pregnancy, these vessels, especially the venous plexuses, are dramatically enlarged. Specifically, the diameter of the ovarian vascular pedicle increases from 0.9 cm to reach 2.6 cm at term (Hodgkinson, 1953).

The cardinal ligament—also called the transverse cervical ligament or Mackenrodt ligament—anchors medially to the uterus and upper vagina. The cardinal ligament is the thick base of the broad ligament. As such, during cesarean hysterectomy, sturdy clamps and suture are required for its transection and ligation.

Each uterosacral ligament originates with a posterolateral attachment to the supravaginal portion of the cervix and inserts into the fascia over the sacrum, with some variations (Ramanah, 2012; Umek, 2004). These ligaments are composed of connective tissue, small bundles of vessels and nerves, and some smooth muscle. Covered by peritoneum, these ligaments form the lateral boundaries of the pouch of Douglas.

The term parametrium is used to describe the connective tissues adjacent and lateral to the uterus within the broad ligament. Paracervical tissues are those adjacent to the cervix, whereas paracolpium is that tissue lateral to the vaginal walls.

Pelvic Blood Supply

During pregnancy, there is marked hypertrophy of the uterine vasculature, which is supplied principally from the uterine and ovarian arteries (see Fig. 2-10). The uterine artery, a main branch of the internal iliac artery—previously called the hypogastric artery—enters the base of the broad ligament. The uterine artery courses medially to the lateral side of the uterus. Approximately 2 cm lateral to the cervix, the uterine artery crosses over the ureter. This proximity is of great surgical significance, as the ureter may be injured or ligated during hysterectomy when the uterine vessels are clamped and ligated.

Once the uterine artery has reached the supravaginal portion of the cervix, it divides. The smaller cervicovaginal artery supplies blood to the lower cervix and upper vagina. The main uterine artery branch turns abruptly upward and travels cephalad along the lateral margin of the uterus. Along its path, this main artery provides a branch of considerable size to the upper cervix and then numerous other medial branches serially penetrate the body of the uterus to form the arcuate arteries. As indicated by the name, each branch arches across the organ by coursing within the myometrium just beneath the serosal surface. Arcuate vessels from each side anastomose at the uterine midline. Radial artery branches originate at right angles from the arcuate arteries and travel inward through the myometrium, enter the endometrium/decidua, and branch there to become either basal arteries or coiled spiral arteries. The spiral arteries supply the functionalis layer. Also called the straight arteries, the basal arteries extend only into the basalis layer.

As the uterine artery courses cephalad, it gives rise to Sampson artery of the round ligament. Just before the main uterine artery vessel reaches the fallopian tube, it divides into three terminal branches. The ovarian branch of the uterine artery forms an anastomosis with the terminal branch of the ovarian artery; the tubal branch makes its way through the mesosalpinx and supplies part of the fallopian tube; and the fundal branch penetrates the uppermost uterus.

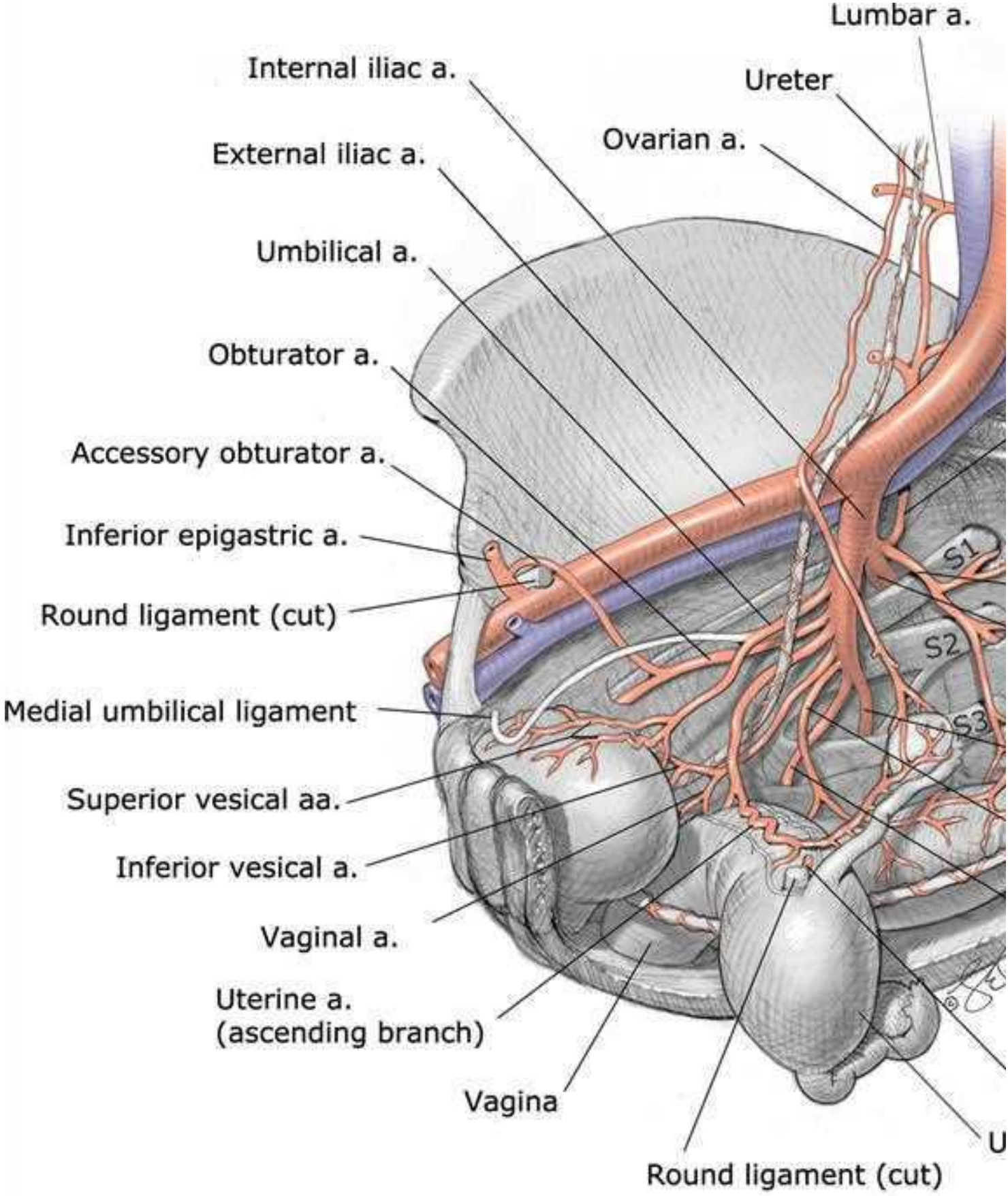
In addition to the uterine artery, the uterus receives blood supply from the ovarian artery (see Fig. 2-10). This artery is a direct branch of the aorta and enters the broad ligament through the infundibulopelvic ligament. At the ovarian hilum, it divides into smaller branches that enter the ovary. As the ovarian artery runs along the hilum, it also sends several branches through the mesosalpinx to supply the fallopian tubes. Its main stem, however, traverses the entire length of the broad ligament toward the uterine cornu. Here, it forms an anastomosis with the ovarian branch of the uterine artery. This dual uterine blood supply creates a vascular reserve to prevent uterine ischemia if ligation of the uterine or internal iliac artery is performed to control postpartum hemorrhage.

Uterine veins accompany their respective arteries. As such, the arcuate veins unite to form the uterine vein, which empties into the internal iliac vein and then the common iliac vein. Some of the blood from the upper uterus, the ovary, and the upper part of the broad ligament is collected by several veins. Within the broad ligament, these veins form the large pampiniform plexus that terminates in the ovarian vein. From here, the right ovarian vein empties into the vena cava, whereas the left ovarian vein empties into the left renal vein.

Blood supply to the pelvis is predominantly provided by branches of the internal iliac artery (Fig. 2-12). These branches are organized into anterior and posterior divisions, and subsequent branches are highly variable between individuals. The anterior division provides blood supply to the pelvic organs and perineum and includes the inferior gluteal, internal pudendal, middle rectal, vaginal, uterine, and obturator arteries, as well as the umbilical artery and its continuation as the superior vesical artery. The posterior division branches extend to the buttock and thigh and include the superior gluteal, lateral sacral, and iliolumbar arteries. For this reason, during internal iliac artery ligation, many advocate ligation distal to the posterior division to avoid compromised blood flow to the areas supplied by this division (Bleich, 2007).

FIGURE 2-12

Pelvic arteries. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Pelvic Lymphatics

The lymphatics from the uterine corpus are distributed to two groups of nodes. One set of vessels drains into the internal iliac nodes. The other set, after joining lymphatics from the ovarian region, terminates in the paraaortic lymph nodes. Lymphatics from the cervix terminate mainly in the internal iliac nodes, which are situated near the bifurcation of the common iliac vessels.

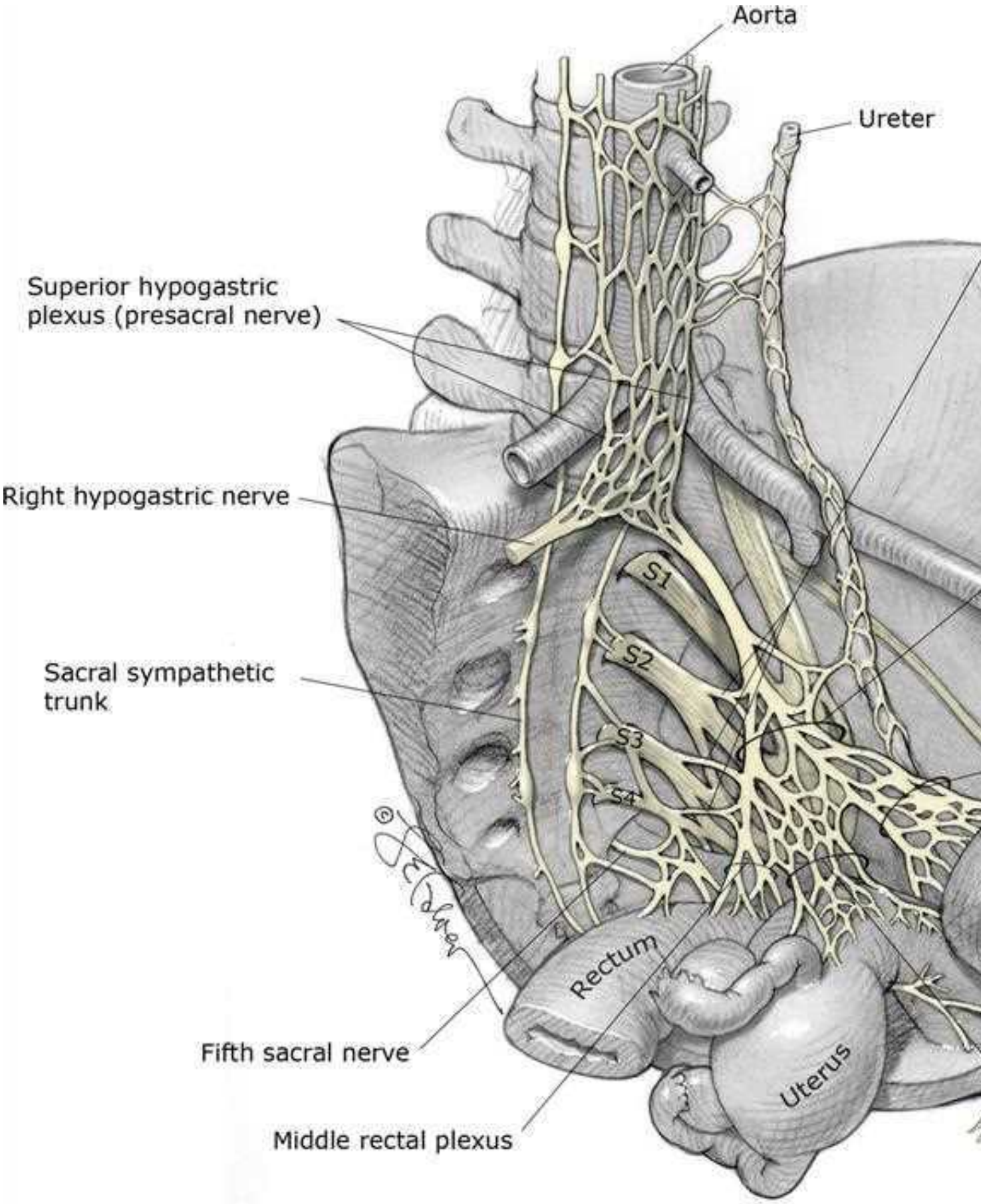
Pelvic Innervation

As a brief review, the peripheral nervous system is divided into a somatic division, which innervates skeletal muscle, and an autonomic division, which innervates smooth muscle, cardiac muscle, and glands. Pelvic visceral innervation is predominantly autonomic, which is further divided into sympathetic and parasympathetic components.

Sympathetic innervation to pelvic viscera begins with the superior hypogastric plexus, also termed the presacral nerve (Fig. 2-13). Beginning below the aortic bifurcation and extending downward retroperitoneally, this plexus is formed by sympathetic fibers arising from spinal levels T_{10} through L_2. At the level of the sacral promontory, this superior hypogastric plexus divides into a right and a left hypogastric nerve, which run downward along the pelvis sidewalls (Ripperda, 2015).

FIGURE 2-13

Pelvic innervation. (Reproduced with permission from Corton MM: Anatomy. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



In contrast, parasympathetic innervation to the pelvic viscera derives from neurons at spinal levels S_2 through S_4. Their axons exit as part of the anterior rami of the spinal nerves for those levels. These combine on each side to form the pelvic splanchnic nerves, also termed nervi erigentes.

Blending of the two hypogastric nerves (sympathetic) and the two pelvic splanchnic nerves (parasympathetic) gives rise to the inferior hypogastric plexus, also termed the pelvic plexus. This retroperitoneal plaque of nerves lies at the S_4 and S_5 level (Spackman, 2007). From here, fibers of this plexus accompany internal iliac artery branches to their respective pelvic viscera. Thus, the inferior hypogastric plexus divides into three plexuses. The vesical plexus innervates the bladder, and the middle rectal plexus travels to the rectum. The uterovaginal plexus, also termed Frankenhäuser plexus, reaches the proximal fallopian tubes, uterus, and upper vagina. Extensions of the inferior hypogastric plexus also reach the perineum along the vagina and urethra to innervate the clitoris and vestibular bulbs (Montoya, 2011). Of these, the uterovaginal plexus is composed of variably sized ganglia, but particularly of a large ganglionic plate that is situated on either side of the cervix, proximate to the uterosacral and cardinal ligaments (Ramanah, 2012).

For the uterus, most of its afferent sensory fibers ascend through the inferior hypogastric plexus and enter the spinal cord via T_{10} through T_{12} and L_1 spinal nerves. These transmit the painful stimuli of contractions to the central nervous system. For the cervix and upper part of the birth canal, sensory nerves pass through the pelvic splanchnic nerves to the second, third, and fourth sacral nerves. Last, those from the lower portion of the birth canal pass primarily through the pudendal nerve. Anesthetic blocks used during delivery target these levels of innervation.

Ovaries

Along the pelvic sidewall, each ovary usually rests in the ovarian fossa of Waldeyer, which is a slight depression between the external and internal iliac vessels. During childbearing years, ovaries variably measure 2.5 to 5 cm in length, 1.5 to 3 cm in width, and 0.6 to 1.5 cm in thickness.

The ovarian ligament, also called the uteroovarian ligament, originates from the upper posterolateral portion of the uterus, just beneath the tubal insertion level, and extends to the uterine pole of the ovary (see Fig. 2-10). Measuring a few centimeters long and 3 to 4 mm in diameter, this ligament is made up of muscle and connective tissue and is covered by peritoneum—the mesovarium. Blood supply reaches the ovary through this double-layered mesovarium to enter the ovarian hilum.

The ovary consists of an outer cortex and inner medulla. In young women, the cortex is smooth, has a dull white surface, and is lined by single layer of cuboidal epithelium, the germinal epithelium of Waldeyer. This epithelium is supported by a connective tissue condensation, the tunica albuginea. Beneath this, the ovarian cortex contains oocytes and developing follicles. The medulla is composed of loose connective tissue, numerous arteries and veins, and a small amount of smooth muscle fibers.

The ovaries are supplied with both sympathetic and parasympathetic nerves. The sympathetic nerves are derived primarily from the ovarian plexus that accompanies the ovarian vessels and originates in the renal plexus. Others are derived from the plexus that surrounds the ovarian branch of the uterine artery. Parasympathetic input is from the vagus nerve. Sensory afferents follow the ovarian artery and enter at T_{10} spinal cord level.

Fallopian Tubes

Also called oviducts, these serpentine tubes extend laterally 8 to 14 cm from the uterine cornua. They are anatomically classified along their length as an interstitial portion, isthmus, ampulla, and infundibulum (Fig. 2-14). Most proximal, the interstitial portion is embodied within the uterine muscular wall. Next, the narrow 2- to 3-mm wide isthmus widens gradually into the 5- to 8-mm wide ampulla. Last, the infundibulum is the funnel-shaped fimbriated distal extremity of the tube, which opens into the abdominal cavity. These latter three extrauterine portions are covered by the mesosalpinx at the superior margin of the broad ligament.

FIGURE 2-14
The fallopian tube of an adult woman with cross-sectioned illustrations of the gross structure in several portions: **(A)** isthmus, **(B)** ampulla, and **(C)** infundibulum. Below these are photographs of corresponding histological sections. (Used with permission from Dr. Kelley S. Carrick.)

In cross section, the extrauterine fallopian tube contains a mesosalpinx, myosalpinx, and endosalpinx. The outer of these, the mesosalpinx, is a single-cell mesothelial layer functioning as visceral peritoneum. In the myosalpinx, smooth muscle is arranged in an inner circular and an outer longitudinal layer. The tubal musculature undergoes rhythmic contractions constantly, the rate of which varies with cyclical ovarian hormonal changes.

The tubal mucosa or endosalpinx is a single layer of columnar epithelium composed of ciliated, secretory, and intercalary cells resting on a sparse lamina propria. Clinically, its close proximity to the underlying myosalpinx contributes to easy invasion by ectopic trophoblast. The tubal mucosa is arranged in longitudinal folds that become progressively more complex toward the fimbria. In the ampulla, the lumen is occupied almost completely by the arborescent mucosa. The current produced by the tubal cilia is such that the direction of flow is toward the uterine cavity. Tubal peristalsis created by cilia and muscular layer contraction is believed to be an important factor in ovum transport (Croxatto, 2002).

The tubes are supplied richly with elastic tissue, blood vessels, and lymphatics. Their sympathetic innervation is extensive, in contrast to their parasympathetic innervation. This nerve supply derives partly from the ovarian plexus and partly from the uterovaginal plexus. Sensory afferent fibers ascend to T_{10} spinal cord levels.

LOWER URINARY TRACT STRUCTURES

Bladder

Anteriorly, the bladder rests against the inner surface of the pubic bones and then, as it fills, also against the anterior abdominal wall. Posteriorly, it rests against the vagina and cervix. The bladder is divided into a dome and a base approximately at the level of the ureteral orifices. The dome is thin walled and distensible, whereas the base is thicker and undergoes less distention during filling. The vesical trigone lies in the bladder base and contains both ureteral orifices and the internal urinary meatus (see Fig. 2-11). The urethral lumen begins at this meatus and then courses through the bladder base for less than 1 cm. This region where the urethral lumen traverses the bladder base is called the bladder neck.

The bladder wall consists of coarse bundles of smooth muscle known as the detrusor muscle, which extends into the proximal part of the urethra. A submucosal layer intervenes between this detrusor muscle and the mucosa. The bladder mucosa consists of transitional epithelium and underlying lamina propria.

The blood supply to the bladder arises from the superior vesical arteries, which are branches of the patent portion of the umbilical artery, and from the middle and inferior vesical arteries, which, when present, often arise from either the internal pudendal or the vaginal arteries (see Fig. 2-12). The nerve supply to the bladder arises from the vesical plexus, a component of the inferior hypogastric plexus (see Fig. 2-13).

Ureter

As the ureter enters the pelvis, it crosses over the bifurcation of the common iliac artery and passes just medial to the ovarian vessels (see Fig. 2-10). As the ureter descends into the pelvis, it lies medial to the internal iliac branches and anterolateral to the uterosacral ligaments. The ureter then traverses through the cardinal ligament approximately 1 to 2 cm lateral to the cervix. Near the level of the uterine isthmus, it courses below the uterine artery and travels anteromedially toward the bladder base. In this path, it runs close to the upper third of the anterior vaginal wall (Rahn, 2007). Finally, the ureter enters the bladder and travels obliquely for approximately 1.5 cm before opening at the ureteral orifices.

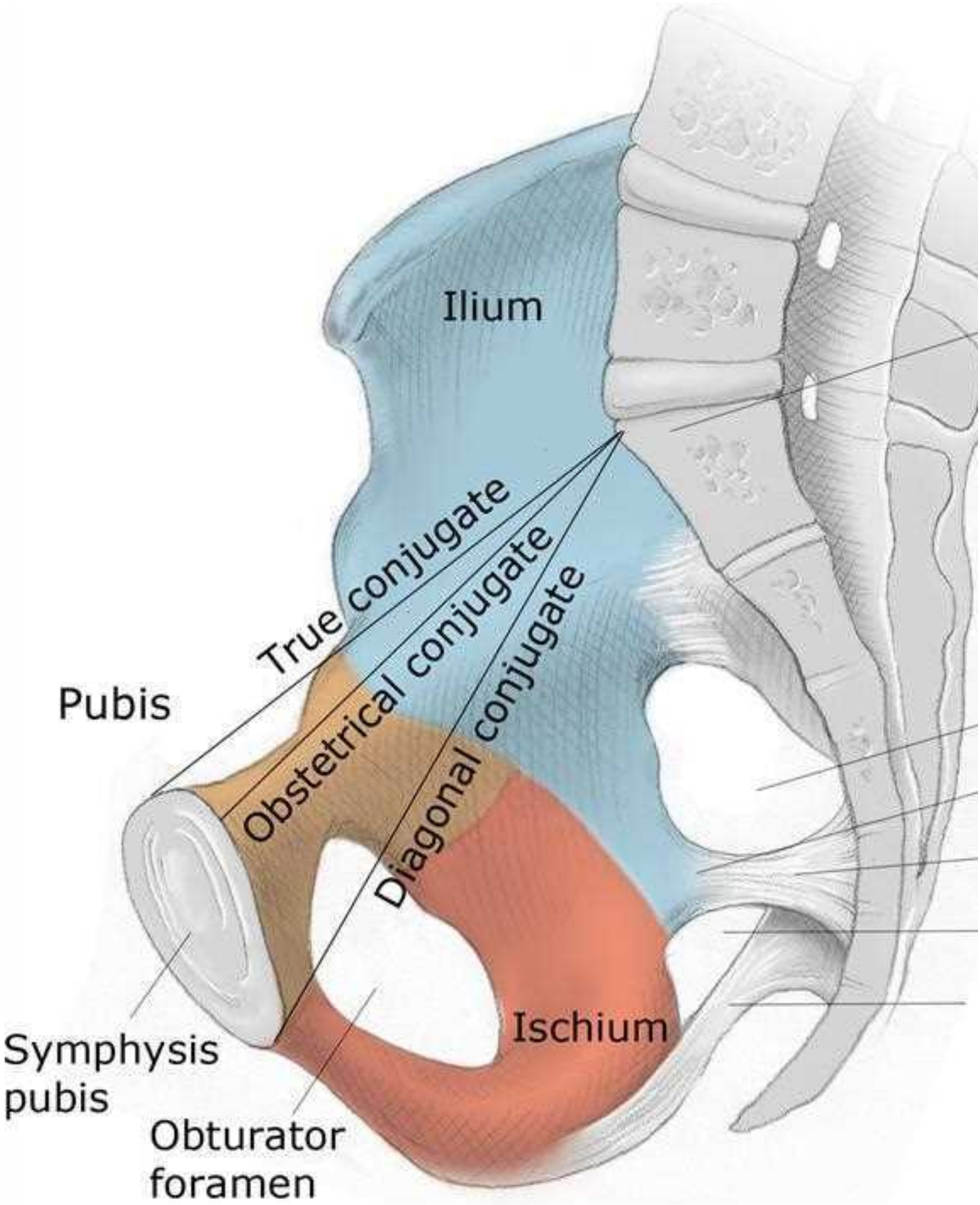
The pelvic ureter receives blood supply from the vessels it passes: the common iliac, internal iliac, uterine, and superior vesical vessels. The ureter's course runs medial to these vessels, and thus its blood supply reaches the ureter from lateral sources. This is important during ureteral isolation. Vascular anastomoses on the connective tissue sheath enveloping the ureter form a longitudinal network of vessels.

MUSCULOSKELETAL PELVIC ANATOMY

Pelvic Bones

The pelvis is composed of four bones—the sacrum, coccyx, and two innominate bones. Each innominate bone is formed by the fusion of three bones—the ilium, ischium, and pubis (Fig. 2-15). Both innominate bones are joined to the sacrum at the sacroiliac synchondroses and to one another at the symphysis pubis.

FIGURE 2-15
The innominate bone is composed of the pubis (*brown*), ischium (*red*), and ilium (*blue*). Of the three anteroposterior diameters of the pelvic inlet, only the diagonal conjugate can be measured clinically. The important obstetrical conjugate is derived by subtracting 1.5 cm from the diagonal conjugate.



Pelvic Joints

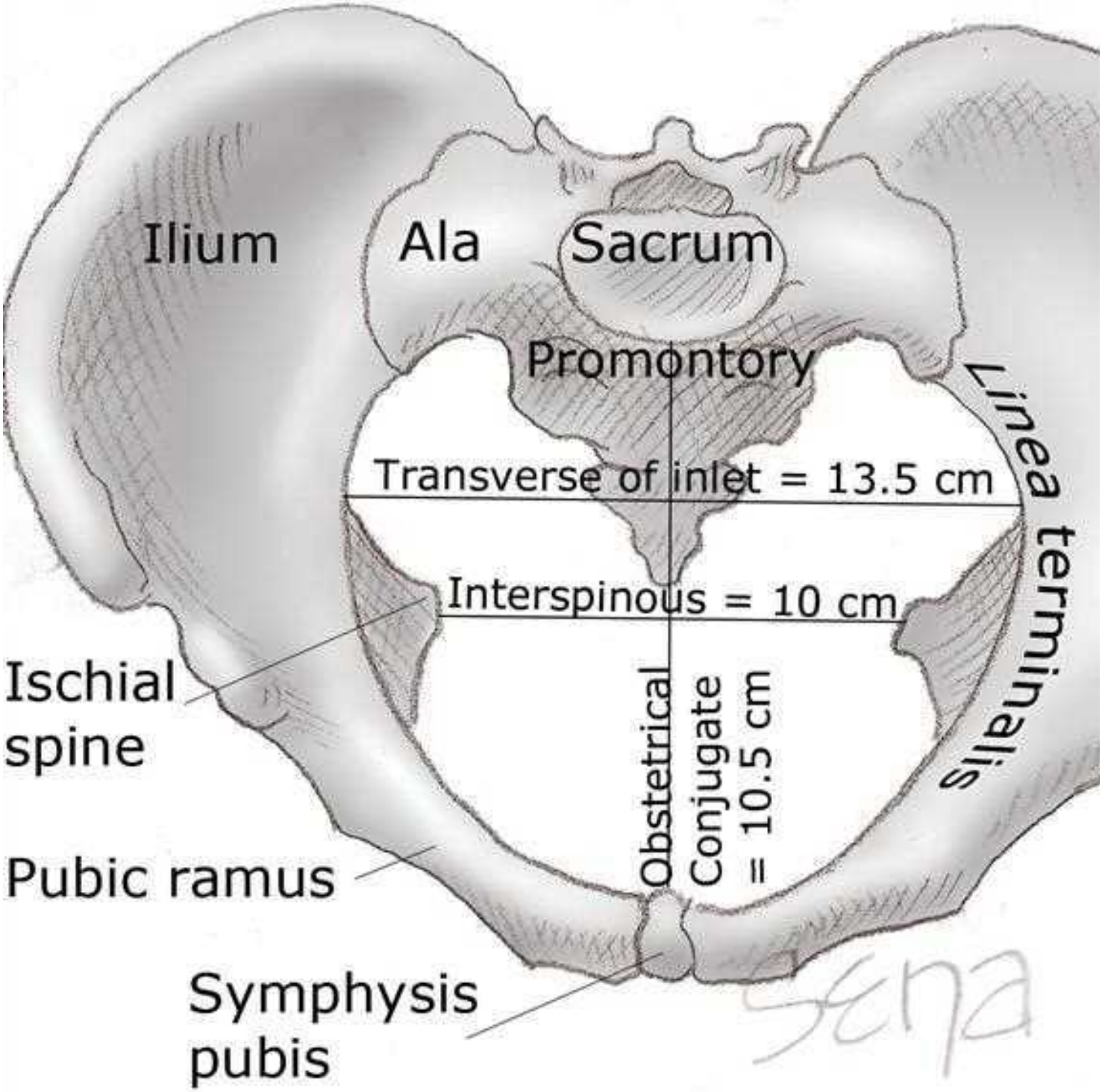
Anteriorly, the pelvic bones are joined together by the symphysis pubis. This structure consists of fibrocartilage and the superior and inferior pubic ligaments. The latter ligament is frequently designated the arcuate ligament of the pubis. Posteriorly, the pelvic bones are joined by articulations between the sacrum and the iliac portion of the innominate bones to form the sacroiliac joints.

The pelvic joints in general have a limited degree of mobility. However, during pregnancy, these joints relax remarkably at term. As one result, upward gliding of the sacroiliac joint, which is greatest in the dorsal lithotomy position, may increase the diameter of the outlet by 1.5 to 2.0 cm for delivery (Borell, 1957). Sacroiliac joint mobility also likely aids the McRoberts maneuver to release an obstructed shoulder in cases of shoulder dystocia (Chap. 27, Management). These changes may also contribute to the success of the modified squatting position to hasten second-stage labor (Gardosi, 1989). The squatting position may increase the interspinous diameter and the pelvic outlet diameter (Russell, 1969, 1982).

Planes and Diameters of the Pelvis

The pelvis is conceptually divided into false and true components. The false pelvis lies above the linea terminalis, and the true pelvis is below this boundary (Fig. 2-16). The false pelvis is bounded posteriorly by the lumbar vertebra and laterally by the iliac fossa. In front, the boundary is formed by the lower portion of the anterior abdominal wall.

FIGURE 2-16
Axial view of a normal female pelvis. The clinically important obstetrical conjugate and transverse diameter of the pelvic inlet are illustrated. The interspinous diameter of the midpelvis is also marked.



The pelvis is described as having four imaginary planes:

1. The plane of the pelvic inlet—the superior strait.
2. The plane of the pelvic outlet—the inferior strait.
3. The plane of the midpelvis—the least pelvic dimensions.
4. The plane of greatest pelvic dimension—of no obstetrical significance.

Pelvic Inlet

The pelvic inlet, also called the superior strait, is the superior plane of the true pelvis. It is bounded posteriorly by the promontory and alae of the sacrum, laterally by the linea terminalis, and anteriorly by the horizontal pubic rami and the symphysis pubis. During labor, fetal head engagement is defined by the fetal head's biparietal diameter passing through this plane.

Four diameters of the pelvic inlet are usually described: anteroposterior, transverse, and two oblique diameters. Of these, distinct anteroposterior diameters have been described using specific landmarks. Most cephalad, the anteroposterior diameter, termed the true conjugate, extends from the uppermost margin of the symphysis pubis to the sacral promontory (see Fig. 2-15). The clinically important obstetrical conjugate is the shortest distance between the sacral promontory and the symphysis pubis. Normally, this measures 10 cm or more, but unfortunately, it cannot be measured directly with examining fingers. Thus, the obstetrical conjugate is estimated indirectly by subtracting 1.5 to 2 cm from the diagonal conjugate. To measure the diagonal conjugate, a hand with the palm oriented laterally extends its index finger to the promontory. The distance from the fingertip to the point at which the lowest margin of the symphysis strikes the same finger's base is the diagonal conjugate.

The transverse diameter is constructed at right angles to the obstetrical conjugate and represents the greatest distance between the linea terminalis on either side (see Fig. 2-16). It usually intersects the obstetrical conjugate at a point approximately 5 cm in front of the promontory and measures approximately 13 cm.

Midpelvis and Pelvic Outlet

The midpelvis is measured at the level of the ischial spines, also called the midplane or plane of least pelvic dimensions (see Fig. 2-16). During labor, the degree of fetal head descent into the true pelvis may be described by station, and the midpelvis and ischial spines serve to mark zero station. The interspinous diameter is 10 cm or slightly greater and is usually the smallest pelvic diameter. The anteroposterior diameter through the level of the ischial spines normally measures at least 11.5 cm.

The pelvic outlet consists of two approximately triangular areas whose boundaries mirror those of the perineal triangle described earlier (Perineum). They have a common base, which is a line drawn between the two ischial tuberosities. The apex of the posterior triangle is the tip of the sacrum, and the lateral boundaries are the sacrotuberous ligaments and the ischial tuberosities. The anterior triangle is formed by the descending inferior rami of the pubic bones. These rami unite at an angle of 90 to 100 degrees to form a rounded arch under which the fetal head must pass. Unless there is significant pelvic bony disease, the pelvic outlet seldom obstructs vaginal delivery.

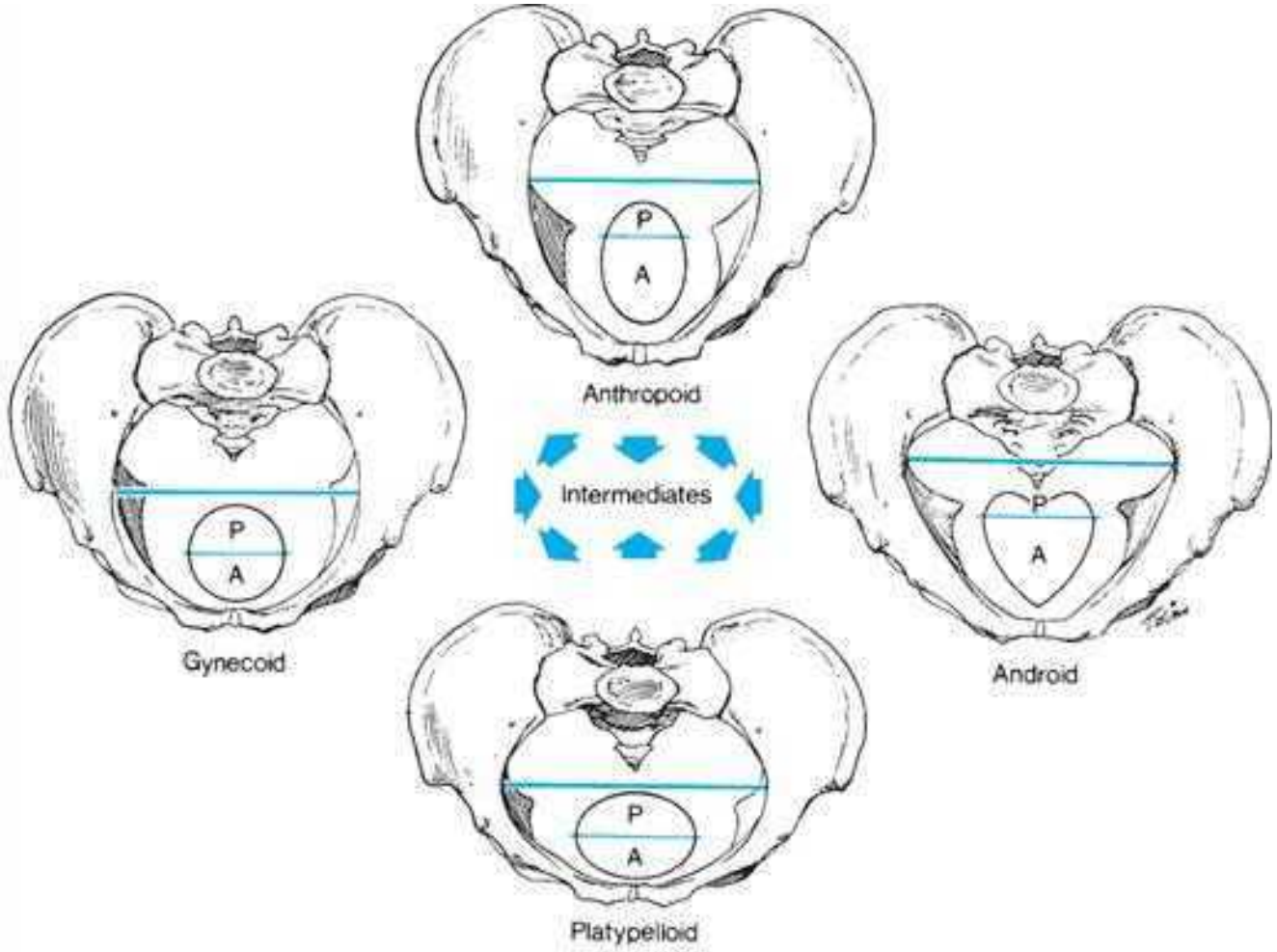
Pelvic Shapes

The Caldwell–Moloy (1933, 1934) anatomical classification of the pelvis is based on shape, and its concepts aid an understanding of labor mechanisms. Specifically, the greatest transverse diameter of the inlet and its division into anterior and posterior segments are used to classify the pelvis as gynecoid, anthropoid, android, or platypelloid. The posterior segment determines the type of pelvis, whereas the anterior segment determines the tendency. These are both determined because many pelves are not pure but are mixed types. For example, a gynecoid pelvis with an android tendency means that the posterior pelvis is gynecoid and the anterior pelvis is android shaped.

From viewing the four basic types in Figure 2-17, the configuration of the gynecoid pelvis would intuitively seem suited for delivery of most fetuses. Indeed, Caldwell (1939) reported that the gynecoid pelvis was found in almost half of women.

FIGURE 2-17

The four parent pelvic types of the Caldwell–Moloy classification. A line passing through the widest transverse diameter divides the inlets into posterior (P) and anterior (A) segments.



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CHAPTER 3: Congenital Genitourinary Abnormalities

Abnormalities in the development or fusion of one or both Müllerian ducts may result in malformations which sometimes possess an obstetrical significance. Pregnancy may be associated with any one of these malformations, provided an ovum be cast off from the ovaries and no serious obstacle be opposed to the upward passage of the spermatozoa and their subsequent union with it.

—J. Whitridge Williams (1903)

GENITOURINARY TRACT DEVELOPMENT

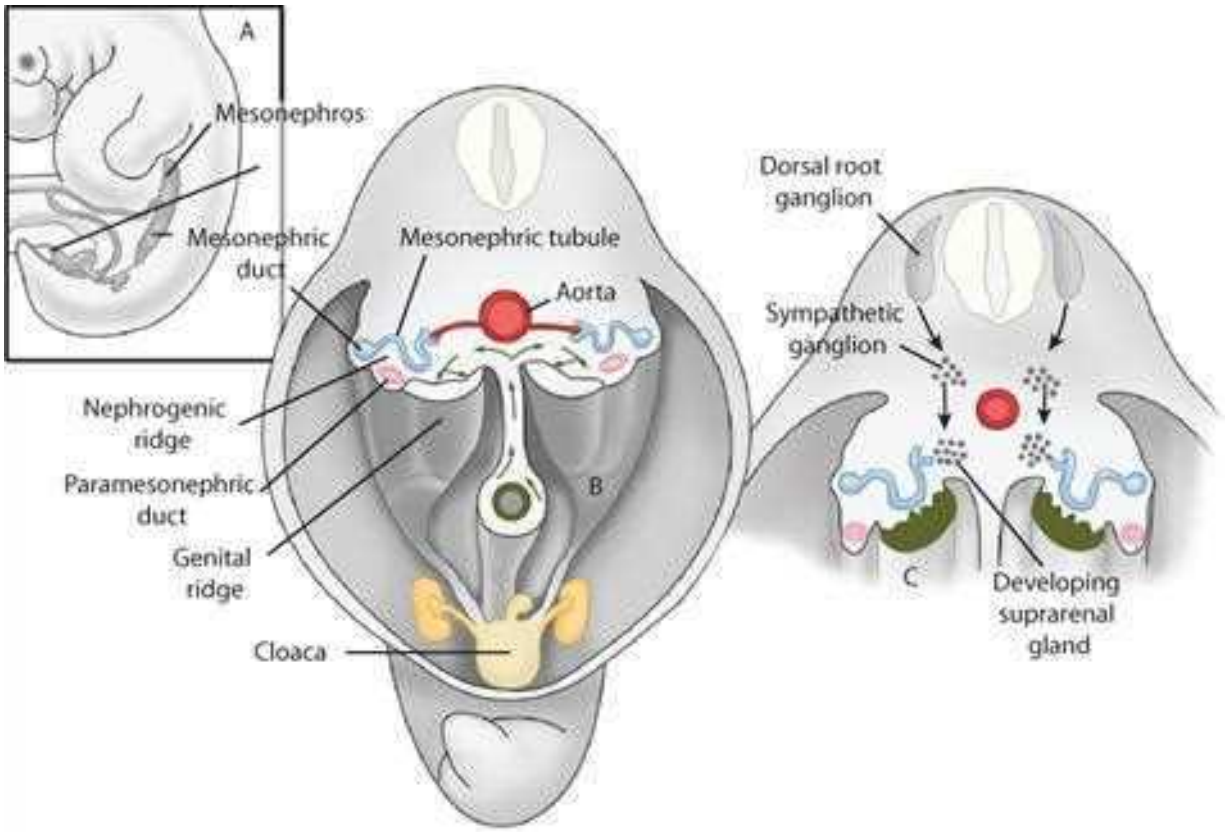
In females, the external genitalia, gonads, and müllerian ducts each derive from different primordia and in close association with the urinary tract and hindgut. Abnormal embryogenesis during this process is thought to be multifactorial and can create sporadic anomalies. Several of these can lead to infertility, subfertility, miscarriage, or preterm delivery. Thus, knowledge of genitourinary system development is essential.

Embryology of the Urinary System

Between the 3rd and 5th gestational weeks, an elevation of intermediate mesoderm on each side of the fetus—the urogenital ridge—begins development into the urogenital tract. Subsequently, the urogenital ridge divides into the genital ridge, destined to become the ovary, and into the nephrogenic ridge (Fig. 3-1). The nephrogenic ridges develop into the mesonephros (mesonephric kidney) and paired mesonephric ducts, also termed wolffian ducts, which connect to the cloaca.

FIGURE 3-1

A. Cross-section of an embryo at 4 to 6 weeks. **B.** Large ameboid primordial germ cells migrate (*arrows*) from the yolk sac to the area of germinal epithelium, within the genital ridge. **C.** Migration of sympathetic cells from the spinal ganglia to a region above the developing kidney.



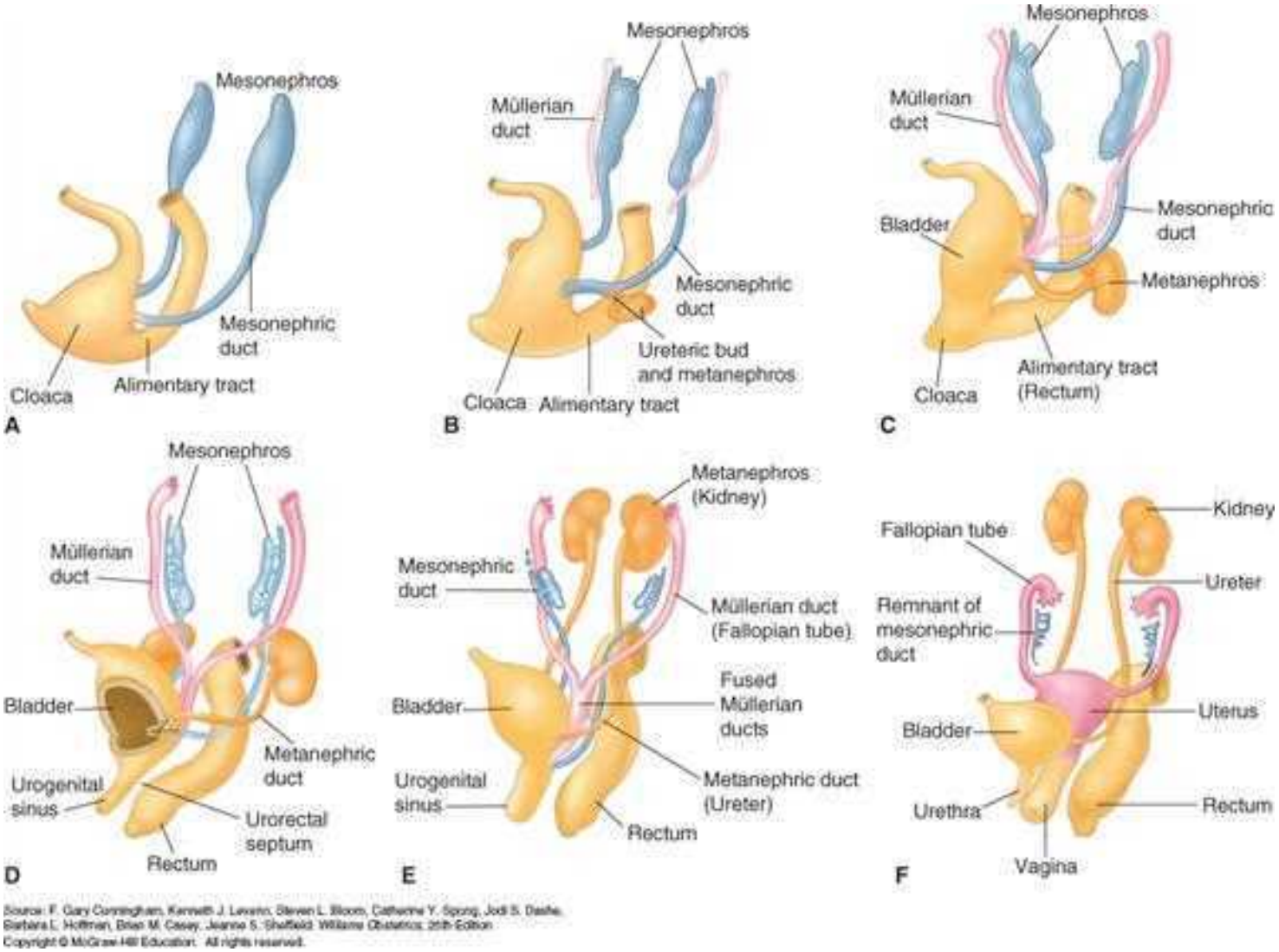
Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

The early urinary tract develops from the mesonephros and its mesonephric ducts (Fig. 3-2A). Recall that evolution of the renal system passes sequentially through the pronephric and mesonephric stages to reach the permanent metanephric system. Between the 4th and 5th weeks, each mesonephric duct gives rise to a ureteric bud, which grows cephalad toward its respective mesonephros (Fig. 3-2B). As each bud lengthens, it induces differentiation of the

metanephros, which will become the final kidney (Fig. 3-2C). Each mesonephros degenerates near the end of the first trimester, and without testosterone, the mesonephric ducts regress as well.

FIGURE 3-2

Embryonic development of the female genitourinary tract **(A-F)**. (Reproduced with permission from Shatzkes DR, Haller JO, Velcek FT: Imaging of uterovaginal anomalies in the pediatric patient, Urol Radiol 1991;13(1):58–66.)



The cloaca begins as a common opening for the embryonic urinary, genital, and alimentary tracts. By the 7th week it becomes divided by the urorectal septum to create the rectum and the urogenital sinus (Fig. 3-2D). The urogenital sinus is considered in three parts: (1) the cephalad or vesicle portion, which forms the urinary bladder; (2) the middle or pelvic portion, which creates the female urethra; and (3) the caudal or phallic part, which gives rise to the distal vagina and to the greater vestibular (Bartholin) and paraurethral glands.

Embryology of the Genital Tract

The fallopian tubes, uterus, and upper vagina derive from the müllerian ducts, also termed paramesonephric ducts, which form adjacent to each mesonephros (see Fig. 3-2B). These ducts extend downward and then turn medially to meet and fuse together in the midline. The uterus is formed by this union of the two müllerian ducts at approximately the 10th week (Fig. 3-2E). Fusion to create the uterus begins in the middle and then extends both caudally and cephalad. With cellular proliferation at the upper portion, a thick wedge of tissue creates the characteristic piriform uterine shape. At the same time, dissolution of cells at the lower pole forms the first uterine cavity (Fig. 3-2F). As the upper wedge-shaped septum is slowly reabsorbed, the final uterine cavity is usually formed by the 20th week. If the two müllerian ducts fail to fuse, then two separate uterine horns remain. In contrast, resorption failure of the common tissue between them results in various degrees of persistent uterine septum.

As the distal end of the fused müllerian ducts contacts the urogenital sinus, this induces endodermal outgrowths from the sinus termed the sinovaginal bulbs. These bulbs proliferate and fuse to form the vaginal plate, which later resorbs to form the vaginal lumen. This vaginal canalization is generally completed by the 20th week. However, the lumen remains separated from the urogenital sinus by the hymeneal membrane. This membrane further degenerates to leave only the hymeneal ring.

The close association of the mesonephric (wolffian) and paramesonephric (müllerian) ducts explains the simultaneous abnormalities in their end organs. Kenney and colleagues (1984) showed that up to half of females with uterovaginal malformations have associated urinary tract defects. Anomalies most frequently associated with renal defects are unicornuate uterus, uterine didelphys, and agenesis syndromes, whereas arcuate and bicornuate are less commonly linked (Reichman, 2010). When müllerian anomalies are identified, the urinary system can be evaluated with magnetic resonance (MR) imaging, sonography, or intravenous pyelography (Hall-Craggs, 2013). With müllerian anomalies, ovaries are functionally normal but have a higher incidence of anatomical maldescent into the pelvis (Allen, 2012; Dabirashrafi, 1994).

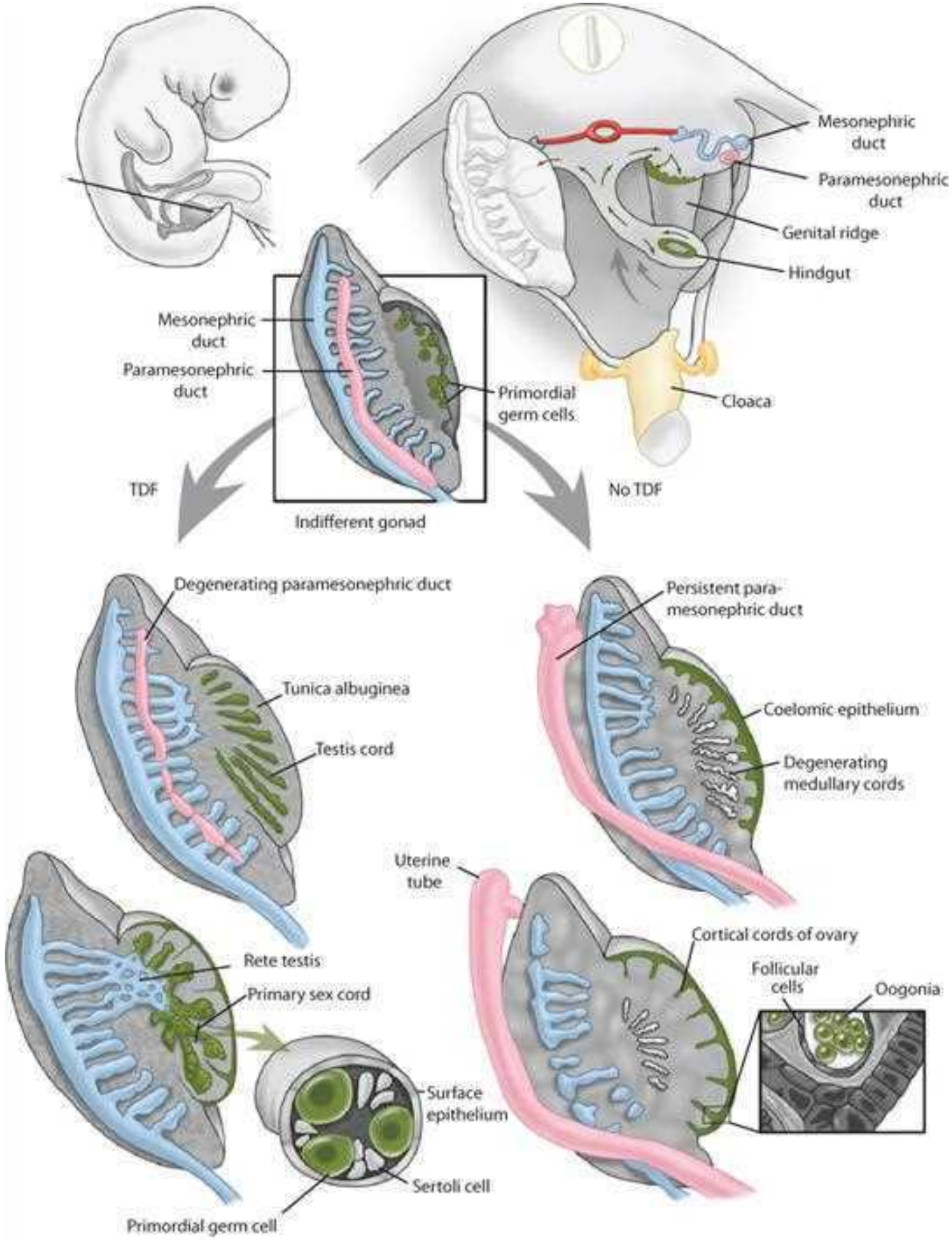
As discussed, the mesonephric ducts usually degenerate, however, persistent remnants may become clinically apparent. Mesonephric or wolffian vestiges can persist as Gartner duct cysts. These are typically located in the proximal anterolateral vaginal wall but may be found at other sites along the vaginal length. They can be further characterized by MR imaging, which provides excellent image resolution at soft tissue interfaces. Most cysts are asymptomatic and benign and usually do not require surgical excision.

Intraabdominal wolffian remnants in the female include a few blind tubules in the mesovarium—the epoöphoron—and similar ones adjacent to the uterus—paroöphoron (see Fig. 3-2F) (Moore, 2013). The epoöphoron or paroöphoron may develop into clinically identifiable cysts in the adult.

Embryology of the Gonads

At approximately 4 weeks, gonads derive from coelomic epithelium covering the medial and ventral surface of the nephrogenic cord at a site between the eighth thoracic and fourth lumbar segments. Because of this separate gonadal and müllerian derivation, women with müllerian defects typically have functionally normal ovaries and are phenotypic females. The coelomic epithelium thickens to form the genital ridge, also known as the gonadal ridge. Strands of these epithelial cells extend into the underlying mesenchyme as the primary sex cords. By the sixth week, primordial germ cells have migrated from the yolk sac to enter the genital ridge mesenchyme (Fig. 3-3). The primordial germ cells are then incorporated into the primary sex cords.

FIGURE 3-3
Embryonic gonad differentiation. TDF = testis-determining factor.



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In the seventh week, the sexes can be distinguished, and testes are recognized during microscopic sectioning by their well-defined radiating testis cords. These cords are separated from the coelomic epithelium by mesenchyme that is to become the tunica albuginea. The testis cords develop into the

seminiferous tubules and rete testis. The rete testis establishes connection with small tubes arising off the mesonephric duct. These small tubes become the efferent ducts that drain into the epididymis and then into the vas deferens, which are main mesonephric duct derivatives.

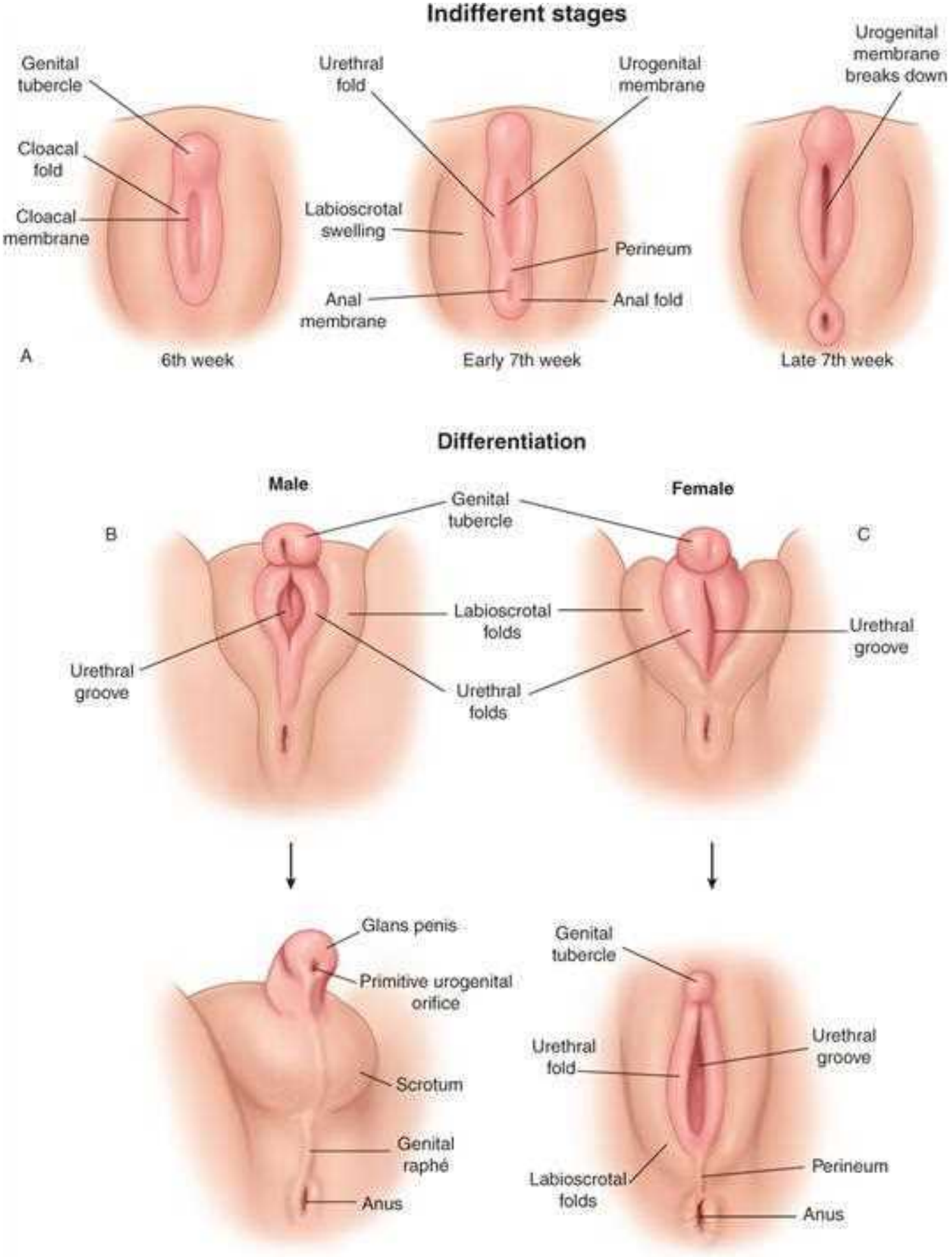
In the female embryo, the primary sex cords give rise to the medullary cords, which persist only for a short time. The coelomic epithelium again proliferates into the underlying mesenchyme, and these strands are the cortical cords. By the fourth month, the cortical cords begin to form isolated cell clusters called primordial follicles. These follicles contain the oogonia, which derive from primordial germ cells and are surrounded by a single layer of flattened follicular cells derived from the cortical cords. Follicular cells serve as supporting nutrient cells. By 8 months, the ovary has become a long, narrow, lobulated structure that is attached to the body wall by the mesovarium. The coelomic epithelium has been separated by a band of connective tissue—tunica albuginea—from the cortex. At this stage, the cortex contains follicles and is well defined from the inner medulla, which is composed of abundant blood vessels, lymphatic vessels, and nerve fibers.

Embryology of the External Genitalia

Early development of the external genitalia is similar in both sexes. By 6 weeks' gestation, three external protuberances have developed surrounding the cloacal membrane. These are the left and right cloacal folds, which meet ventrally to form the genital tubercle (Fig. 3-4). With division of the cloacal membrane into anal and urogenital membranes, the cloacal folds become the anal and urethral folds, respectively. Lateral to the urethral folds, genital swellings arise, and these become the labioscrotal folds. Between the urethral folds, the urogenital sinus extends onto the surface of the enlarging genital tubercle to form the urethral groove. By week 7, the urogenital membrane ruptures, exposing the cavity of the urogenital sinus to amnionic fluid.

FIGURE 3-4

Development of the external genitalia. **A.** Indifferent stage. **B.** Virilization of external genitalia. **C.** Feminization. (Reproduced with permission from Bradshaw KD: Anatomical disorders. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw Hill Education, 2016.)



The genital tubercle elongates to form the phallus in males and the clitoris in females. Still, it is not possible to visually differentiate between male and female external genitalia until week 12. In the male fetus, dihydrotestosterone (DHT) forms locally by the 5-α reduction of testosterone. DHT prompts the anogenital distance to lengthen, the phallus to enlarge, and the labioscrotal folds to fuse and form the scrotum.

In the female fetus, without DHT, the anogenital distance does not lengthen, and the labioscrotal and urethral folds do not fuse (Fig. 3-4C). The genital tubercle bends caudally to become the clitoris, and the urogenital sinus forms the vestibule of the vagina. The labioscrotal folds create the labia majora, whereas the urethral folds persist as the labia minora. Female external genital differentiation is complete by 11 weeks, whereas male external genital differentiation is complete by 14 weeks.

SEXUAL DIFFERENTIATION

Defining gender incorporates genetic gender, gonadal gender, and phenotypic gender. *Genetic gender*—XX or XY—is established at fertilization. However, for the first 6 weeks, development of male and female embryos is morphologically indistinguishable.

Gonadal gender is heralded by the differentiation of the primordial gonad into a testis or an ovary. If a Y chromosome is present, the gonad begins developing into a testis. Testis development is directed by a protein called the *testis-determining factor (TDF)*, which modulates the transcription of several genes involved in gonadal differentiation. TDF is encoded by the *sex-determining region (SRY) gene,* located on the short arm of the Y chromosome. But testis development is much more complex and requires other autosomal genes (Nistal, 2015a).

The importance of the *SRY* gene is demonstrated in several paradoxical conditions. First, 46,XX phenotypic males can result from translocation of the Y chromosome fragment containing *SRY* to the X chromosome during meiosis of male germ cells (Wu, 2014). Similarly, 46,XY individuals can appear phenotypically female if they carry a mutation in the *SRY* gene (Helszer, 2013).

Last, *phenotypic gender* begins at 8 weeks' gestation. Before this, urogenital tract development in both sexes is indistinguishable. Thereafter, differentiation of the internal and external genitalia to the male phenotype is dependent on testicular function. In the absence of a testis, female differentiation ensues irrespective of genetic gender (Table 3-1).

TABLE 3-1

Embryonic Urogenital Structures and Their Adult Homologues

Indifferent Structure	Female	Male
Genital ridge	Ovary	Testis
Primordial germ cells	Ova	Spermatozoa
Sex cords	Granulosa cells	Seminiferous tubules, Sertoli cells
Gubernaculum	Uteroovarian and round ligaments	Gubernaculum testis
Mesonephric tubules	Epoöphoron, paroöphoron	Efferent ductules, paradidymis
Mesonephric ducts	Gartner duct	Epididymis, ductus deferens, ejaculatory duct
Paramesonephric ducts	Uterus, fallopian tubes, upper vagina	Prostatic utricle, appendix of testis
Urogenital sinus	Bladder, urethra Vagina Paraurethral glands Greater (Bartholin) and lesser vestibular glands	Bladder, urethra Prostatic utricle Prostate glands Bulbourethral glands
Genital tubercle	Clitoris	Glans penis
Urogenital folds	Labia minora	Floor of penile urethra
Labioscrotal swellings	Labia majora	Scrotum

In males, the fetal testis secretes a protein called müllerian-inhibiting substance (MIS), also called antimüllerian hormone (AMH). It acts locally as a paracrine factor to cause müllerian duct regression. Thus, it prevents the development of uterus, fallopian tube, and upper vagina. AMH is produced by the Sertoli cells of the seminiferous tubules. Importantly, these tubules appear in fetal gonads and secrete AMH before differentiation of Leydig cells, which are the cellular

site of testosterone synthesis. AMH is secreted as early as 7 weeks, and müllerian duct regression is completed by 9 to 10 weeks. Because AMH acts locally near its site of formation, if a testis were absent on one side, the müllerian duct on that side would persist, and the uterus and fallopian tube would develop on that side.

Apparently through stimulation initially by human chorionic gonadotropin (hCG), and later by fetal pituitary luteinizing hormone (LH), the fetal testes secrete testosterone. This hormone acts directly on the wolffian duct to effect the development of the vas deferens, epididymis, and seminal vesicles. Testosterone also enters fetal blood and acts on the external genitalia anlage. In these tissues, testosterone is converted to 5α-DHT to cause virilization of the external genitalia.

DISORDERS OF SEX DEVELOPMENT

Definitions

As evident from the prior discussion, abnormal sex development may involve the gonads, internal duct system, or external genitalia. Rates vary and approximate 1 in every 1000 to 4500 births (Murphy, 2011; Ocal, 2011). The nomenclature used to describe disorders of sex development (DSDs) has evolved. Current classification of these disorders include: (1) sex chromosome DSDs, (2) 46,XY DSDs, and (3) 46,XX DSDs (Table 3-2) (Hughes, 2006).

TABLE 3-2

Disorders of Sex Development (DSD) Classification

Sex Chromosome DSD
45,X Turner[a]
47,XXY Klinefelter[a]
45,X/46,XY Mixed gonadal dysgenesis
46,XX/46,XY Ovotesticular DSD
46,XY DSD
Testicular development
Pure gonadal dysgenesis
Partial gonadal dysgenesis
Ovotesticular
Testis regression
Androgen production or action
Androgen synthesis
Androgen receptor
LH/hCG receptor
AMH
46,XX DSD
Ovary development
Ovotesticular
Testicular
Gonadal dysgenesis
Androgen excess
Fetal
Maternal
Placental

[a]And syndrome variants.

AMH = antimüllerian hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone.

Adapted with permission from Hughes IA, Houk C, Ahmed SF, et al: Consensus statement on management of intersex disorders. J Pediatr Urol 2:148, 2006.

Other important terms describe the abnormal phenotypic findings that can be found. First, some disorders of sexual development are associated with abnormal, underdeveloped gonads, that is, *gonadal dysgenesis*. With this, if a testis is poorly formed, it is called a *dysgenetic testis*, and if an ovary is poorly formed, it is called a *streak gonad*. In affected patients, the underdeveloped gonad ultimately fails, which is indicated by elevated gonadotropin levels. Another important clinical sequela is that patients bearing a Y chromosome are at high risk of developing a germ cell tumor in the dysgenetic gonad.

A second term, *ambiguous genitalia*, describes genitalia that do not appear clearly male or female. Abnormalities may include hypospadias, undescended testes, micropenis or enlarged clitoris, labial fusion, and labial mass.

Last, *ovotesticular* defines states characterized by ovarian and testicular tissue in the same individual. It was formerly termed true hermaphroditism. In these cases, different types of gonads can be paired. The types of gonads that may be paired include a normal testis, a normal ovary, a streak gonad, dysgenetic testis, or an ovotestis. In the latter, both ovarian and testicular elements are combined within the same gonad. With ovotesticular DSDs, the internal ductal system structure depends on the ipsilateral gonad and its degree of determination. Specifically, the amount of AMH and testosterone determines the degree to which the internal ductal system is masculinized or feminized. External genitalia are usually ambiguous and undermasculinized due to inadequate testosterone.

Sex Chromosome Disorders of Sex Development

Turner and Klinefelter Syndromes

Sex chromosome disorders of sexual development typically arise from an abnormal number of sex chromosomes. Of these, Turner and Klinefelter syndromes are most frequently encountered (Nielsen, 1990).

Turner syndrome is caused by de novo loss or severe structural abnormality of one X chromosome in a phenotypic female. Most affected fetuses are spontaneously aborted. However, in girls with Turner syndrome who survive, phenotype varies widely, but nearly all affected patients have short stature. Associated problems include cardiac anomalies (especially coarctation of the aorta), renal anomalies, hearing impairment, otitis media and mastoiditis, and an increased incidence of hypertension, achlorhydria, diabetes mellitus, and Hashimoto thyroiditis. It is the most common form of gonadal dysgenesis that leads to primary ovarian failure. In these cases, the uterus and vagina are normal and capable of responding to exogenous hormones (Matthews, 2017).

Another sex chromosome disorder is *Klinefelter syndrome* (47,XXY). These individuals tend to be tall, undervirilized males with gynecomastia and small, firm testes. They have significantly reduced fertility from hypogonadism due to gradual testicular cell failure. These men are at increased risk for germ cell tumors, osteoporosis, hypothyroidism, diabetes mellitus, breast cancer, cardiovascular abnormalities, and cognitive and psychosocial problems (Aksglaede, 2013; Calogero, 2017).

Chromosomal Ovotesticular DSD

Several karyotypes can create a coexistent ovary and testis, and thus ovotesticular DSD is found in all three DSD categories (see Table 3-2). In the sex chromosome group, ovotesticular DSD may arise from a 46,XX/46,XY karyotype. Here, an ovary, testis, or ovotestis may be paired. The phenotype in general mirrors that for ovotesticular disorders, which are described earlier on this page.

For others in the sex chromosome DSD group, ovotesticular disorder arises from a chromosomal mosaic such as 45,X/46,XY. With this karyotype, a picture of *mixed gonadal dysgenesis* shows a streak gonad on one side and a dysgenetic or normal testis on the other. The phenotypical appearance ranges from undervirilized male to ambiguous genitalia to Turner stigmata.

46,XY Disorders of Sex Development

Insufficient androgen exposure of a fetus destined to be a male leads to 46,XY DSD—formerly called male pseudohermaphroditism. The karyotype is 46,XY and testes are frequently present. The uterus is generally absent as a result of normal embryonic AMH production by Sertoli cells. These subjects are most often sterile from abnormal spermatogenesis and have a small phallus that is inadequate for sexual function. As seen in Table 3-2, etiology of 46,XY DSD may stem from abnormal testis development or from abnormal androgen production or action.

46,XY Gonadal Dysgenesis

This spectrum of abnormal gonad underdevelopment includes pure or complete, partial, or mixed 46,XY gonadal dysgenesis. These are defined by the amount of normal testicular tissue and by karyotype. Because of the potential for germ cell tumors in dysgenetic testes and intraabdominal testes, affected patients routinely have been advised to undergo gonadectomy (Jiang, 2016).

Of these, *pure gonadal dysgenesis* results from a mutation in the *SRY* gene or in other genes with testis-determining effects (Hutson, 2014). This leads to underdeveloped dysgenetic gonads that fail to produce androgens or AMH. Formerly named Swyer syndrome, the condition creates a normal prepubertal female phenotype and a normal müllerian system due to absent AMH.

Partial gonadal dysgenesis defines those with gonad development intermediate between normal and dysgenetic testes. Depending on the percentage of underdeveloped testis, wolffian and müllerian structures and genital ambiguity are variably expressed.

Mixed gonadal dysgenesis is one type of ovotesticular disorder of sexual differentiation. As discussed in Sex Chromosome Disorders of Sex Development, one gonad is streak, and the other is a normal or a dysgenetic testis. Of affected individuals, 15 percent have a 46,XY karyotype (Nistal, 2015b). The phenotype is wide ranging as with partial gonadal dysgenesis.

Last, *testicular regression* can follow initial testis development. A broad phenotypic spectrum is possible and depends on the timing of testis failure.

Abnormal Androgen Production or Action

In some cases, 46,XY disorders of sexual differentiation stem from abnormalities in: (1) testosterone biosynthesis, (2) LH receptor function, (3) AMH function, or (4) androgen receptor action. First, the sex steroid biosynthesis pathway can suffer enzymatic defects that block testosterone production. Depending on the timing and degree of blockade, undervirilized males or phenotypic females may result. In contrast to these central enzymatic defects, peripheral defects may be causative. Namely, abnormal 5-α reductase type 2 enzyme action leads to impaired conversion of testosterone to DHT and thus to undervirilization.

Second, hCG/LH receptor abnormalities within the testes can lead to Leydig cell aplasia/hypoplasia and impaired testosterone production. In contrast, disorders of AMH and AMH receptors result in persistent müllerian duct syndrome (PMDS). Affected patients appear as males but have a persistent uterus and fallopian tubes due to failed AMH action.

Last, the androgen receptor may be defective and result in androgen-insensitivity syndrome (AIS). Resistance to androgens may be incomplete and associated with varying degrees of virilization and genital ambiguity. Milder forms have been described in men with severe male factor infertility and poor virilization.

Females with complete androgen-insensitivity syndrome (CAIS) appear as phenotypically normal females at birth. They often present at puberty with primary amenorrhea. External genitalia appear normal; scant or absent pubic and axillary hair are noted; the vagina is shortened or blind ending; and the uterus and fallopian tubes are absent. However, these individuals develop breasts during pubertal maturation due to abundant androgen to estrogen conversion. Testes may be palpable in the labia or inguinal area or may be found intraabdominally. Surgical excision of the testes after puberty is recommended to decrease the associated risk of germ cell tumors, which may be as high as 20 to 30 percent.

46,XX Disorders of Sex Development

As seen in Table 3-2, etiology of 46,XX disorders of sexual differentiation may stem from abnormal ovarian development or from excess androgen exposure.

Abnormal Ovarian Development

Disorders of ovarian development of those with a 46,XX complement include: (1) gonadal dysgenesis, (2) testicular DSD, and (3) ovotesticular DSD.

With *46,XX gonadal dysgenesis*, similar to Turner syndrome, streak gonads develop. These lead to hypogonadism, prepubertal normal female genitalia, and normal müllerian structures, but other Turner stigmata are absent.

With *46,XX testicular DSD*, several possible genetic mutations lead to testis-like formation within the ovary—streak gonad, dysgenetic testis, or ovotestis. Defects may stem from *SRY* translocation onto one X chromosome. In individuals without *SRY* translocation, other genes with testis-determining effects are most likely activated. Regardless, production of AMH prompts müllerian system regression, and androgens promote wolffian system development and external genitalia masculinization. Spermatogenesis, however, is absent due to a lack of needed genes on the long arm of the Y chromosome. These individuals are not usually diagnosed until puberty or during infertility evaluation.

With *46,XX ovotesticular DSD*, individuals possess a unilateral ovotestis with a contralateral ovary or testis, or bilateral ovotestes. Phenotypic findings depend on the degree of androgen exposures and mirror those for other ovotesticular DSDs discussed in Sex Chromosome Disorders of Sex Development.

Androgen Excess

Discordance between gonadal sex (46,XX) and the phenotypic appearance of external genitalia (masculinized) may also result from excessive fetal androgen exposure. This was previously termed female pseudohermaphroditism. In affected individuals, the ovaries and female internal ductal structures such as the uterus, cervix, and upper vagina are present. Thus, patients are potentially fertile. The external genitalia, however, are virilized to a varying degree depending on the amount and timing of androgen exposure. The three embryonic structures that are commonly affected by elevated androgen levels or ovarian development disorders are the clitoris, labioscrotal folds, and urogenital sinus. As a result, virilization may range from modest clitoromegaly to posterior labial fusion and development of a phallus with a penile urethra. Degrees of virilization can be described by the Prader score, which ranges from 0 for a normal-appearing female to 5 for a normal, virilized male.

Fetal, placental, or maternal sources can provide the excessive androgen levels. Maternally derived androgen excess may come from virilizing ovarian tumors such as luteoma and Sertoli-Leydig cell tumor or from virilizing adrenal tumors. Fortunately, these neoplasms infrequently cause fetal effects because of the tremendous ability of placental syncytiotrophoblast to convert C_{19} steroids—androstenedione and testosterone—to estradiol via the enzyme aromatase (Chap. 5, Placental Estrogen Production). As another source, drugs such as testosterone, danazol, and other androgen derivatives may cause fetal virilization.

Of fetal sources, exposure can arise from fetal congenital adrenal hyperplasia (CAH). This stems from a fetal enzyme deficiency in the steroidogenic pathway that leads to androgen accumulation. The most common defect is 21-hydroxylase deficiency. CAH is a frequent cause of virilization and has an incidence approximating 1 in 10,000 to 20,000 live births (Speiser, 2010).

With CAH, phenotypes depend on the location of the enzyme defect in the steroidogenic pathway and on the severity of the resulting enzymatic deficiency (Miller, 2011). With severe enzymatic deficiency, affected newborns have life-threatening salt wasting and virilization. Other mutations may prompt virilization alone (Auchus, 2015). The mildest abnormalities present later and are described as "nonclassic," "late-onset," or "adult-onset" CAH. In these patients, activation of the adrenal axis at puberty increases steroidogenesis and unmasks a mild enzymatic deficiency. Excess androgen provides negative feedback to gonadotropin-releasing hormone (GnRH) receptors in the hypothalamus. These patients often present with hirsutism, acne, and anovulation. Thus, late-onset CAH may mimic polycystic ovarian syndrome (McCann-Crosby, 2014). In some instances, CAH can be diagnosed antenatally. Early maternal dexamethasone therapy can dampen androgen excess to minimize virilization (Chap. 16, Congenital Adrenal Hyperplasia).

Of rare placental sources, placental aromatase deficiency from a fetal *CYP19* gene mutation causes an accumulation of placental androgen and underproduction of placental estrogens (Chap. 5, Placental Estriol Synthesis) (Jones, 2007). Consequently, both the mother and the 46,XX fetus are virilized.

Gender Assignment

Delivery of a newborn with a disorder of sexual differentiation is a potential medical emergency and can create possible long-lasting psychosexual and social ramifications for the individual and family. Ideally, as soon as the affected neonate is stable, parents are encouraged to hold the child. The newborn is referred to as "your baby," and suggested terms include "phallus," "gonads," "folds," and "urogenital sinus" to reference underdeveloped structures. The obstetrician explains that the genitalia are incompletely formed and emphasizes the seriousness of the situation and the need for rapid consultation and laboratory testing.

Because similar or identical phenotypes may have several etiologies, identification of a specific DSD may require several diagnostic tools (McCann-Crosby, 2015). Relevant neonatal physical examination evaluates: (1) ability to palpate gonads in the labioscrotal or inguinal regions, (2) ability to palpate uterus during rectal examination, (3) phallus size, (4) genitalia pigmentation, and (5) presence of other syndromic features. The newborn metabolic condition is assessed, as hyperkalemia, hyponatremia, and hypoglycemia may indicate CAH. The mother is examined for signs of hyperandrogenism. Other neonatal tests include genetic studies, hormone measurements, imaging, and in some cases endoscopic, laparoscopic, and gonadal biopsy. Sonography shows the presence or absence of müllerian/wolffian structures, can locate the gonads, and can identify associated malformations such as renal anomalies.

BLADDER AND PERINEAL ABNORMALITIES

Very early during embryo formation, a bilaminar cloacal membrane lies at the caudal end of the germinal disc and forms the infraumbilical abdominal wall. Normally, an ingrowth of mesoderm between the ectodermal and endodermal layers of the cloacal membrane leads to formation of the lower abdominal musculature and pelvic bones. Without this reinforcement, the cloacal membrane may prematurely rupture, and depending on the extent of the infraumbilical defect, cloacal exstrophy, bladder exstrophy, or epispadias may result.

Of these, *cloacal exstrophy* is rare. It includes the triad of omphalocele, bladder exstrophy, and imperforate anus.

Bladder exstrophy is uncommon and is characterized by an exposed bladder lying outside the abdomen. Associated findings often include abnormal external genitalia and a widened symphysis pubis. At the same time, however, the uterus, fallopian tubes, and ovaries are typically normal except for occasional müllerian duct fusion defects. Pregnancy with bladder exstrophy is associated with greater risk for antepartum pyelonephritis, urinary retention, ureteral obstruction, pelvic organ prolapse, preterm birth, and breech presentation. The American Urological Association has published management guidelines for pregnancy (Eswara, 2016). Due to the extensive adhesions from prior repair and altered anatomy typically encountered, some recommend planned cesarean delivery at a tertiary center (Deans, 2012; Dy, 2015; Greenwell, 2003).

Epispadias without bladder exstrophy is rare and develops in association with other anomalies such as a widened, patulous urethra; absent or bifid clitoris; nonfused labial folds; and flattened mons pubis. Vertebral abnormalities and pubic symphysis diathesis are also common.

Clitoral anomalies are unusual. One is clitoral duplication or bifid clitoris, which is rare and usually develops in association with bladder exstrophy or epispadias. With female phallic urethra, the urethra opens at the clitoral tip. Last, clitoromegaly noted at birth suggests fetal exposure to excessive androgens (46,XX Disorders of Sex Development). In other cases, congenital clitoromegaly in females born extremely premature is a rare but well-recognized finding thought to be due to transient androgen levels in these neonates (Greaves, 2008).

As noted, the hymen marks the embryological boundary between structures derived from the müllerian and urogenital sinus. *Hymeneal anomalies* include imperforate, microperforate, cribriform (sievelike), navicular (boat-shaped), and septate hymens. They result from failure of the inferior end of the vaginal plate—the hymeneal membrane—to canalize. Their incidences approximate 1 in 1000 to 2000 females (American College of Obstetricians and Gynecologists, 2016). During the neonatal period, significant amounts of mucus can be secreted due to maternal estrogen stimulation. With an imperforate hymen, secretions collect to form a bulging, translucent yellow-gray mass, termed hydro- or mucocolpos, at the vaginal introitus. Most are asymptomatic and resolve as mucus is reabsorbed and estrogen levels decrease, but rarely can cause perinatal urinary retention from their mass effects (Johal, 2009).

MÜLLERIAN ABNORMALITIES

Four principal deformities arise from defective müllerian duct embryological steps: (1) agenesis of both ducts, either focally or along the entire duct length; (2) unilateral maturation of one müllerian duct with incomplete or absent development of the opposite side; (3) absent or faulty midline fusion of the ducts; or (4) defective canalization. Various classifications have been proposed, and Table 3-3 shows the one from the American Fertility Society (1988). It separates anomalies into groups with similar clinical characteristics, prognosis for pregnancy, and treatment. It also includes one for abnormalities associated with fetal exposure to diethylstilbestrol (DES). Several other classification systems have been crafted, but this one is the most widely used (Acién, 2011; Di Spiezio Sardo, 2015; Oppelt, 2005).

TABLE 3-3

Classification of Müllerian Anomalies

I.	**Segmental müllerian hypoplasia or agenesis** a. Vaginal b. Cervical c. Uterine fundal d. Tubal e. Combined anomalies
II.	**Unicornuate uterus** a. Communicating rudimentary horn b. Noncommunicating horn c. No endometrial cavity d. No rudimentary horn
III.	**Uterine didelphys**
IV.	**Bicornuate uterus** a. Complete—division to internal os b. Partial
V.	**Septate uterus** a. Complete—septum to internal os b. Partial
VI.	**Arcuate**
VII.	**Diethylstilbestrol related**

Data from American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions, Fertil Steril 1988 Jun;49(6):944–955.

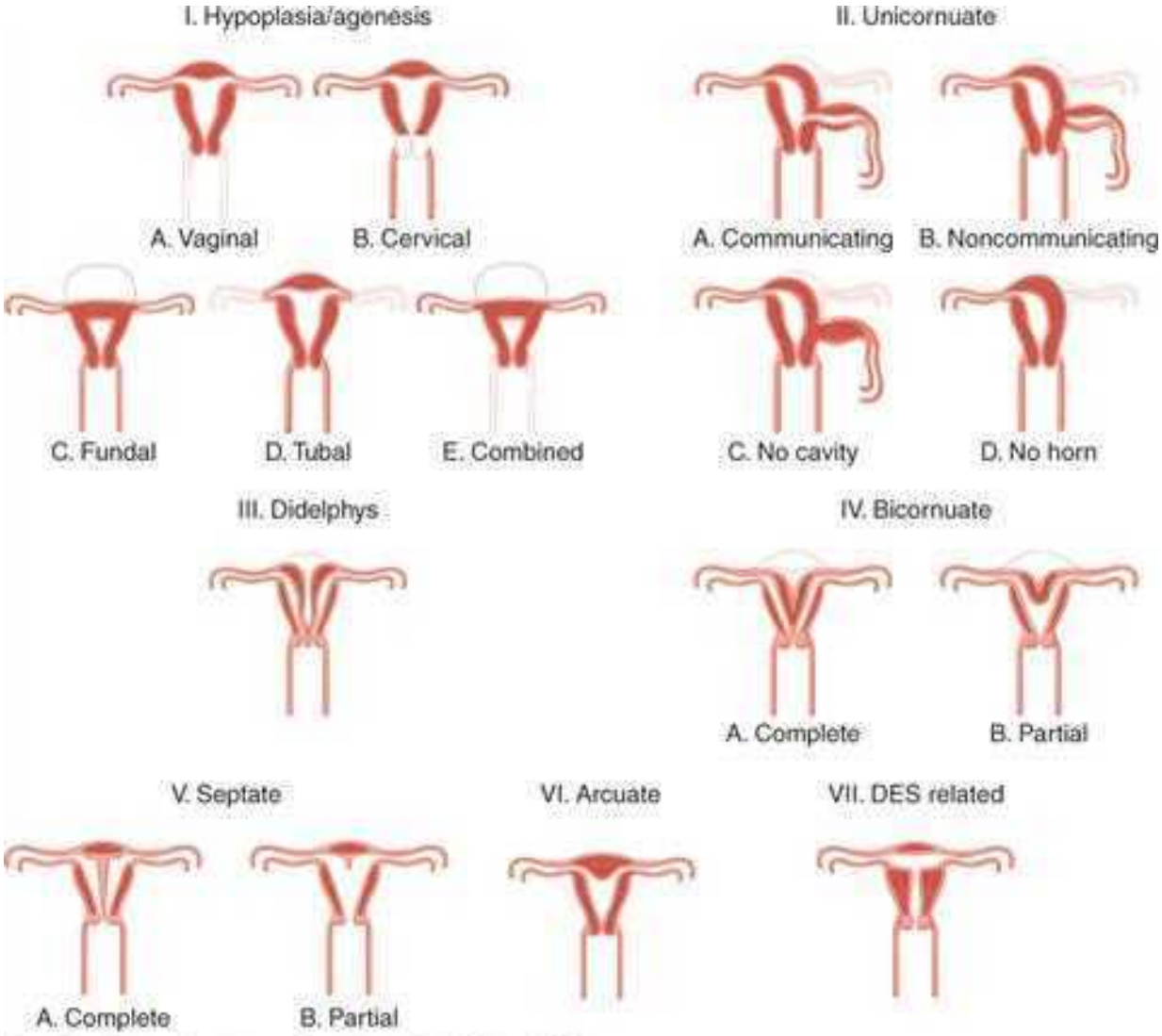
Müllerian anomalies may be suspected by symptoms or physical findings such as vaginal septa, blind-ending vagina, or duplicated cervix. Amenorrhea may be an initial complaint for those with agenesis of a müllerian component. In those with outlet obstruction, pelvic pain from occult blood that accumulates and distends the vagina, uterus, or fallopian tubes may arise from functioning endometrium. Endometriosis and its associated dysmenorrhea, dyspareunia, and chronic pain are also frequent with outlet obstruction.

Müllerian Agenesis

Class I segmental defects are caused by müllerian hypoplasia or agenesis as shown in Figure 3-5. These developmental defects can affect the vagina, cervix, uterus, or fallopian tubes and may be isolated or may coexist with other müllerian defects.

FIGURE 3-5

Classification of müllerian anomalies. DES = diethylstilbestrol. (Modified with permission from American Fertility Society: The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions, Fertil Steril 1988 Jun;49(6):944–55.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Joanna S. Sheffield: Williams Obstetrics, 25th Edition

Vaginal Abnormalities

Of all vaginal anomalies, vaginal agenesis is the most profound and may be isolated or associated with other müllerian anomalies. One example is the Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, in which upper vaginal agenesis is typically associated with uterine hypoplasia or agenesis. Less often, this syndrome also displays abnormalities of the renal, skeletal, and auditory systems. This triad is known by the acronym MURCS, which reflects müllerian duct aplasia, renal aplasia, and cervicothoracic somite dysplasia (Rall, 2015).

The obstetrical significance of vaginal anomalies depends greatly on the degree of obstruction. Complete vaginal agenesis, unless corrected operatively, precludes pregnancy by vaginal intercourse. With MRKH syndrome, a functional vagina can be created, but uterine agenesis proscribes childbearing. In these women, however, ova can be retrieved for in vitro fertilization (IVF) in a surrogate mother (Friedler, 2016). Uterine transplantation is currently experimental but holds future promise for these women (Johannesson, 2016).

Of other vaginal anomalies, congenital septa may form longitudinally or transversely, and each can arise from a fusion or resorption defect. Longitudinal septa divide the vagina into right and left portions. They may be complete and extend the entire vaginal length. Partial septa usually form high in the vagina but may develop at lower levels. Septa are typically associated with other müllerian anomalies (Haddad, 1997). During labor, a complete longitudinal vaginal septum usually does not cause dystocia because the vaginal side through which the fetus descends dilates satisfactorily. An incomplete or partially obstructed longitudinal septum, however, may interfere with descent. Occasionally, a woman with a distal longitudinal septum presents in labor. During second-stage labor, this septum usually becomes attenuated by pressure from the fetal head. After ensuring adequate analgesia, the inferior attachment of the septum is isolated, clamped, transected, and ligated. Following placenta delivery, the superior attachment can be transected while carefully avoiding urethral injury.

A transverse septum poses an obstruction of variable thickness. It may develop at any depth within the vagina, but most are in the lower third (Williams, 2014). These may or may not be perforate, and thus obstruction or infertility is variably present. In labor, perforate strictures may be mistaken for the upper limit of the vaginal vault, and the septal opening is misidentified as an undilated cervical os (Kumar, 2014). If encountered during labor, and after the external

os has dilated completely, the head impinges on the septum and causes it to bulge downward. If the septum does not yield, slight stretching pressure on its opening usually leads to further dilatation, but occasionally cruciate incisions are required to permit delivery (Blanton, 2003). If there is a thick transverse septum, however, cesarean delivery may be necessary.

Cervical Abnormalities

Developmental abnormalities of the cervix include partial or complete agenesis, duplication, and longitudinal septa. Uncorrected complete agenesis is incompatible with pregnancy, and in vitro fertilization with gestational surrogacy is an option. Surgical correction by uterovaginal anastomosis has resulted in successful pregnancy (Kriplani, 2012). Significant complications accompany this corrective surgery, and the need for clear preoperative anatomy delineation has been emphasized by Rock (2010) and Roberts (2011) and their colleagues. For this reason, they recommend hysterectomy for complete cervical agenesis and reserve reconstruction attempts for carefully selected patients with cervical dysgenesis.

Uterine Abnormalities

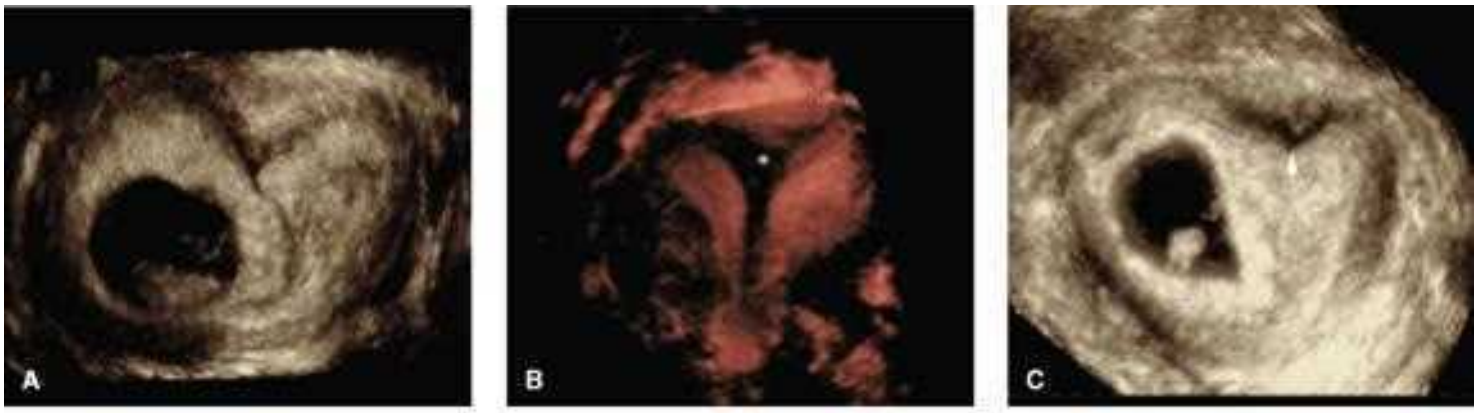
From a large variety, a few of the more common congenital uterine malformations are shown in Table 3-3. An accurate population prevalence of these is difficult to assess because the best diagnostic techniques are invasive. That said, the prevalence found with imaging ranges from 0.4 to 10 percent, and rates in women with recurrent miscarriage are significantly higher (Byrne, 2000; Dreisler, 2014; Saravelos, 2008). In a general population, the most common finding is arcuate uterus, followed in descending order by septate, bicornuate, didelphic, and unicornuate classes (Chan, 2011b).

Müllerian anomalies may be discovered during pelvic examination, cesarean delivery, tubal sterilization, or infertility evaluation. Depending on clinical presentation, diagnostic tools may include sonography, hysterosalpingography, magnetic-resonance imaging, laparoscopy, and hysteroscopy. Each has limitations, and these may be used in combination to completely define anatomy. In women undergoing fertility evaluation, hysterosalpingography (HSG) is commonly selected for uterine cavity and tubal patency assessment. It is contraindicated during pregnancy. HSG poorly defines the external uterine contour and can delineate only patent cavities. Regarding patency, remember that some unicornuate rudimentary horns lack a cavity. Also, outlet obstructions will preclude dye filling.

In most clinical settings, two-dimensional transvaginal sonography (2-D TVS) is initially performed. For this indication, the pooled accuracy for TVS is 90 to 92 percent (Pellerito, 1992). Saline infusion sonography (SIS) improves delineation of the endometrium and internal uterine morphology, but only with a patent endometrial cavity. It also is contraindicated in pregnancy. Three-dimensional (3-D) sonography is more accurate than 2-D sonography because it provides uterine images from virtually any angle. Thus, coronal images can be constructed as shown in Figure 3-6, and these are essential in evaluating both internal and external uterine contours (Grimbizis, 2016). Both 2-D and 3-D sonography are suitable for use in pregnancy.

FIGURE 3-6

Three-dimensional transvaginal sonographic images. **A.** Bicornuate uterus with an 8-week gestation. The external fundal contour (*red dotted line*) dips centrally below the intercornual line, and the endometrial cavities communicate. **B.** Septate uterus with a 5-week gestation. The external fundal contour is normal and convex (*yellow dotted line*), and the long septum (*asterisk*) extends caudad in the midline. **C.** Arcuate uterus with an 8-week gestation. The external fundal contour is normal and convex (*red dotted line*), but the fundal endometrial cavity is slightly indented (*arrow*).



Several studies have reported very good concordance between 3-D TVS and MR imaging of müllerian anomalies (Deutch, 2008; Graupera, 2015). MR imaging is often preferred for complex anatomy, especially cases for which corrective surgery is planned. MR imaging provides clear delineation of both the internal and external uterine anatomy and has a reported accuracy of up to 100 percent for müllerian anomaly evaluation (Bermejo, 2010; Pellerito, 1992). In addition, complex anomalies and commonly associated secondary diagnoses such as renal or skeletal anomalies can be concurrently evaluated. Precautions with MR imaging in pregnancy are discussed in Chapter 46 (Safety).

In some women undergoing an infertility evaluation, hysteroscopy and laparoscopy may be selected to assess for müllerian anomalies; screen for endometriosis, which is often coexistent; and exclude other tubal or uterine cavity pathologies (Puscheck, 2008; Saravelos, 2008). In pregnancy, these approaches are rarely used to diagnose müllerian anomalies, and hysteroscopy is contraindicated.

Unicornuate Uterus (Class II)

With this abnormality, the underdeveloped or rudimentary horn may be absent. If present, it may or may not communicate with the dominant horn and may or may not contain an endometrium-lined cavity (see Fig. 3-5). General population estimates cite an incidence of 1 in 4000 women (Reichman, 2009). This anomaly may be detected during fertility evaluation by HSG. But as noted, noncommunicating or noncavitary rudimentary horns may not fill with dye. If this anomaly is suspected, 3-D sonography increases diagnostic accuracy, but again MR imaging may be preferred. Importantly, 40 percent of affected women will have renal anomalies (Fedele, 1996).

This müllerian anomaly carries significant obstetrical risks, including first- and second-trimester miscarriage, malpresentation, fetal-growth restriction, fetal demise, prematurely ruptured membranes, and preterm delivery (Chan, 2011a; Hua, 2011; Reichman, 2009). Abnormal uterine blood flow, cervical incompetence, and diminished cavity size and muscle mass of the hemiuterus are postulated to underlie these risks (Donderwinkel, 1992).

Rudimentary horns also increase the risk for an ectopic pregnancy within the remnant, which may be disastrous. This risk includes noncommunicating cavitary rudiments, for which transperitoneal sperm migration permits ovum fertilization and pregnancy (Nahum, 2004). In a report of 70 such pregnancies, Rolen and associates (1966) found that the rudimentary uterine horn ruptured prior to 20 weeks in most. Nahum (2002) reviewed the literature from 1900 to 1999 and identified 588 rudimentary horn pregnancies. Half had uterine rupture, and 80 percent did so before the third trimester. Of the total 588, the neonatal survival rate was only 6 percent.

Imaging allows an earlier diagnosis of rudimentary horn pregnancy so that it can be treated either medically with methotrexate or surgically before rupture (Dove, 2017; Edelman, 2003; Khati, 2012; Worley, 2008). Although not emphasized in Figure 3-5, the attachment site between the rudimentary horn at times can be broad and vascular.

If diagnosed in a nonpregnant woman, most recommend prophylactic excision of a horn that has a cavity (Fedele, 2005; Rackow, 2007). Data regarding subsequent pregnancy after excision are scarce. In one series of eight women, all had a preterm cesarean delivery (Pados, 2014).

Uterine Didelphys (Class III)

This müllerian anomaly arises from a complete lack of fusion that results in two entirely separate hemiuteri, cervices, and usually two vaginas (see Fig. 3-5). It is common among marsupials, for example, the American possum—*Didelphys virginiana*. Most women have a double vagina or a longitudinal vaginal septum. Uterine didelphys may be isolated. Or, it may compose a triad with an obstructed hemivagina and with ipsilateral renal agenesis (OHVIRA), also known as Herlyn- Werner-Wunderlich syndrome (Tong, 2013).

These anomalies are suspected on pelvic examination by identification of a longitudinal vaginal septum and two cervices. During HSG for fertility evaluation, contrast shows two separate endocervical canals. These open into separate noncommunicating fusiform endometrial cavities that each ends with a solitary fallopian tube. In women without fertility issues, 2- or 3-D TVS is a logical initial imaging tool, and separate divergent uterine horns with a large intervening fundal cleft are seen. Endometrial cavities are uniformly separate. MR imaging may be valuable in cases without classic findings.

Adverse obstetrical outcomes associated with uterine didelphys are similar but less frequent than those seen with unicornuate uterus. Increased risks include miscarriage, preterm birth, and malpresentation (Chan, 2011a; Grimbizis, 2001; Hua, 2011).

Metroplasty for either uterine didelphys or bicornuate uterus involves resection of intervening myometrium and fundal recombination (Alborzi, 2015). These rarely performed surgeries are chosen for highly selected patients with otherwise unexplained miscarriages. Moreover, no evidence-based data confirm the efficacy of such surgical repair.

Bicornuate Uterus (Class IV)

This fusion anomaly results in two hemiuteri. As shown in Figure 3-5, the central myometrium runs either partially or completely to the cervix. A complete bicornuate uterus may extend to the internal cervical os and have a single cervix (bicornuate unicollis) or reach the external os (bicornuate bicollis). As with uterine didelphys, a coexistent longitudinal vaginal septum is not uncommon.

Radiological discrimination of a bicornuate uterus from a septate uterus can be challenging. This distinction, however, is important because septate uterus can be treated with hysteroscopic septal resection. HSG or 2-D TVS may initially suggest an anomaly, but further distinction is provided by 3-D TVS or MR imaging (see Fig. 3-6). With these, an intercornual angle greater than 105 degrees typifies a bicornuate uterus, whereas one less than 75 degrees indicates a septate uterus. Fundal contour also assists, and a straight line drawn between the imaged tubal ostia serves as the defining threshold. Referent to this, an intrafundal downward cleft measuring ≥1 cm or more is indicative of bicornuate uterus. A septate uterus shows a cleft depth <1 cm, or it may have a normal fundal contour.

Bicornuate uterus carries increased risks for adverse obstetrical outcomes that include miscarriage, preterm birth, and malpresentation. As discussed in the prior section, rare surgical correction by metroplasty is reserved for highly selected patients.

Septate Uterus (Class V)

With this anomaly, a resorption defect leads to a persistent complete or partial longitudinal uterine septum (see Fig. 3-5). Less often, a complete vaginocervicouterine septum is found (Ludwin, 2013). Many septate uteri are identified during evaluation of infertility or recurrent pregnancy loss. Although an abnormality may be identified with HSG or 2-D TVS, typically 3-D TVS or MR imaging is required to differentiate this from a bicornuate uterus (see Fig. 3-6).

Septate anomalies are associated with diminished fertility and increased risks for adverse pregnancy outcomes that include miscarriage, preterm delivery, and malpresentation (Chan, 2011a; Ghi, 2012). Hysteroscopic septal resection has been shown to improve pregnancy rates and outcomes (Mollo, 2009; Pabuçcu, 2004). From their metaanalysis, Valle and colleagues (2013) reported a 63-percent pregnancy rate and 50-percent live birth rate following resection.

Arcuate Uterus (Class VI)

This malformation is a mild deviation from the normally developed uterus. Although some studies report no increased adverse associated outcomes, others have found excessive second-trimester losses, preterm labor, and malpresentation (Chan, 2011a; Mucowski, 2010; Woelfer, 2001).

Treatment with Cerclage

Some women with uterine anomalies and repetitive pregnancy losses may benefit from transvaginal or transabdominal cervical cerclage (Golan, 1992; Groom, 2004). Others with partial cervical atresia or hypoplasia may also benefit (Hampton, 1990; Ludmir, 1991). Candidacy for cerclage is determined by the same criteria used for women without such defects, which is discussed in Chapter 18 (Management).

Diethylstilbestrol Reproductive Tract Abnormalities (Class VII)

During the 1960s, a synthetic nonsteroidal estrogen—diethylstilbestrol (DES)—was used to treat pregnant women for threatened abortion, preterm labor, preeclampsia, and diabetes. The treatment was remarkably ineffective. Later, it was also discovered that women exposed as fetuses had increased risks of developing several specific reproductive-tract abnormalities. These included vaginal clear cell adenocarcinoma, cervical intraepithelial neoplasia, small-cell cervical carcinoma, and vaginal adenosis. Affected women had identifiable structural variations in the cervix and vagina that include transverse septa, circumferential ridges, and cervical collars. Uteri potentially had smaller cavities, shortened upper uterine segments, or T-shaped and other irregular cavities (see Fig. 3-5) (Kaufman, 1984).

These women suffer impaired conception rates and higher rates of miscarriage, ectopic pregnancy, and preterm delivery, especially in those with structural abnormalities (Kaufman, 2000; Palmer, 2001). Now, more than 50 years after DES use was proscribed, most affected women are past childbearing age, but higher rates of earlier menopause, cervical intraepithelial neoplasia, and breast cancer are reported in exposed women (Hatch, 2006; Hoover, 2011; Troisi, 2016).

Fallopian Tube Abnormalities

The fallopian tubes develop from the unpaired distal ends of the müllerian ducts. Congenital anomalies include accessory ostia, complete or segmental tubal agenesis, and several embryonic cystic remnants. The most common is a small, benign cyst attached by a pedicle to the distal end of the fallopian tube—the hydatid of Morgagni. In other cases, benign paratubal cysts may be of mesonephric or mesothelial origin. Last, in utero exposure to DES is associated with various tubal abnormalities. Of these, short, tortuous tubes or ones with shriveled fimbria and small ostia are linked to infertility (DeCherney, 1981).

UTERINE FLEXION

The pregnant uterus may infrequently show exaggerated flexion. Mild or moderate flexion is typically inconsequential, but congenital or acquired extremes may lead to pregnancy complications.

Anteflexion describes forward angling of the uterine fundus in the sagittal plane relative to the cervix. Exaggerated degrees usually pose no problem in early pregnancy. Later, however, particularly when the abdominal wall is lax such as with diastasis recti or ventral hernia, the uterus may fall forward. In extreme cases, the fundus lies below the lower margin of the symphysis. Sometimes, this abnormal uterine position prevents proper transmission of labor contractions, but this is usually overcome by repositioning and application of an abdominal binder.

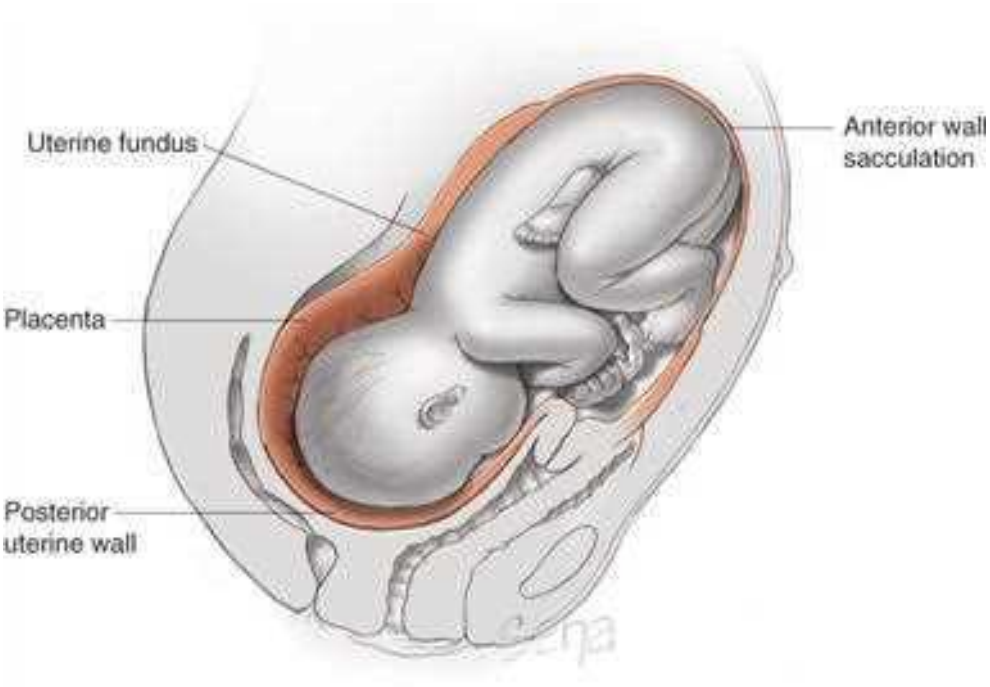
Retroflexion describes posterior uterine fundal angling in the sagittal plane. A growing retroflexed uterus will occasionally become incarcerated in the hollow of the sacrum. Symptoms include abdominal discomfort, pelvic pressure, and voiding dysfunction or retention. During bimanual pelvic examination, the cervix will be anterior and behind the symphysis pubis, whereas the uterus is appreciated as a mass wedged in the pelvis. Sonography or MR imaging can aid the clinical diagnosis (Gardner, 2013; Grossenburg, 2011; van Beekhuizen, 2003).

With continued uterine growth, the incarcerated uterus can spontaneously resolve over 1 to 2 weeks. An indwelling urinary catheter or intermittent self-catheterization may be needed in the interim to empty the bladder. Persistent cases require manual repositioning. For this, after bladder catheterization, the uterus can usually be pushed out of the pelvis when the woman is placed in a knee-chest position. Often, this is best accomplished by digital pressure applied through the rectum. Conscious sedation, spinal analgesia, or general anesthesia may be necessary. Following repositioning, the catheter is left in place until bladder tone returns. Insertion of a soft pessary for a few weeks usually prevents recurrent incarceration.

Lettieri and colleagues (1994) described seven cases of uterine incarceration not amenable to these simple procedures. In two women, laparoscopy was used at 14 weeks' gestation to reposition the uterus using the round ligaments for traction. Alternatively, in case series, advancing a colonoscope or colonoscopic insufflation was used to dislodge an incarcerated uterus (Dierickx, 2011; Newell, 2014; Seubert, 1999).

Rarely, *sacculation* may form as extensive lower uterine segment dilatation due to persistent entrapment of the pregnant uterus in the pelvis (Fig. 3-7). In these extreme cases, sonography and MR imaging are typically required to define anatomy (Gottschalk, 2008; Lee, 2008). Cesarean delivery is necessary when sacculation is marked, and Spearing (1978) stressed the importance of clarifying the distorted anatomy. An elongated vagina passing above the level of a fetal head that is deeply placed into the pelvis suggests a sacculation or an abdominal pregnancy. The Foley catheter is frequently palpated above the level of the umbilicus! Spearing (1978) recommended extending the abdominal incision above the umbilicus and delivering the entire uterus from the abdomen before hysterotomy. This will restore correct anatomical relationships and prevent inadvertent incisions into and through the vagina and bladder. Unfortunately, this may not always be possible (Singh, 2007). As a final caveat, a true uterine diverticulum has been mistaken for uterine sacculation (Rajiah, 2009).

FIGURE 3-7
Anterior sacculation of a pregnant uterus. Note the markedly attenuated anterior uterine wall and atypical location of the true uterine fundus.



The uterus commonly rotates to the maternal right during pregnancy. Rarely, uterine rotation exceeds 180 degrees to cause torsion. Most cases of torsion result from uterine leiomyomas, müllerian anomalies, fetal malpresentation, pelvic adhesions, or laxity of the abdominal wall or uterine ligaments. Jensen (1992) reviewed 212 cases and reported that associated symptoms may include obstructed labor, intestinal or urinary complaints, abdominal pain, uterine hypertonus, vaginal bleeding, and hypotension.

Most cases of uterine torsion are found at the time of cesarean delivery. In some women, torsion can be confirmed preoperatively with MR imaging, which shows a twisted vagina that appears X-shaped rather than its normal H-shape (Nicholson, 1995). As with uterine incarceration, during cesarean delivery, a severely displaced uterus should be repositioned anatomically before hysterotomy. In some cases, an inability to reposition or a failure to recognize the torsion may lead to a posterior hysterotomy incision (Albayrak, 2011; Picone, 2006; Rood, 2014).

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CHAPTER 4: Maternal Physiology

The maternal organism reacts to a greater or lesser extent under the influence of pregnancy, but naturally the most characteristic changes are observed in the generative tract, and especially the uterus, which undergoes a very marked increase in size.

—J. Whitridge Williams (1903)

INTRODUCTION

In the first edition of this textbook, Williams devoted only 10 pages to the physiology of pregnancy, and half were focused on uterine growth. Many gestational changes begin soon after fertilization and continue throughout pregnancy. Equally astounding is that the woman is returned almost completely to her prepregnancy state after delivery and lactation. Most pregnancy-related changes are prompted by stimuli provided by the fetus and placenta. Virtually every organ system undergoes alterations, and these can appreciably modify criteria for disease diagnosis and treatment. Thus, an understanding of pregnancy adaptations is essential to avoid misinterpretation. Moreover, some physiological changes can unmask or worsen preexisting disease.

REPRODUCTIVE TRACT

Uterus

In the nonpregnant woman, the uterus weighs approximately 70 g and is almost solid, except for a cavity of 10 mL or less. During pregnancy, the uterus is transformed into a thin-walled muscular organ of sufficient capacity to accommodate the fetus, placenta, and amnionic fluid. The total volume of the contents at term averages 5 L but may be 20 L or more! Thus, by the end of pregnancy, the uterus has achieved a capacity that is 500 to 1000 times greater than the nonpregnant state. The corresponding increase in uterine weight is such that, by term, the organ weighs nearly 1100 g.

During pregnancy, uterine enlargement involves stretching and marked hypertrophy of muscle cells, whereas the production of new myocytes is limited. Fibrous tissue also accumulates, particularly in the external muscle layer, together with a considerable rise in elastic tissue content. The walls of the corpus considerably thicken and strengthen during the first few months of pregnancy but then gradually thin. By term, the myometrium is only 1 to 2 cm thick, and the fetus usually can be palpated through the soft, readily indentable uterine walls.

Uterine hypertrophy early in pregnancy probably is stimulated by the action of estrogen and perhaps progesterone. Thus, similar uterine changes can be observed with ectopic pregnancy. But after approximately 12 weeks' gestation, uterine growth is related predominantly to pressure exerted by the expanding products of conception.

Within the uterus, enlargement is most marked in the fundus. The extent of uterine hypertrophy is also influenced by the position of the placenta. Namely, the myometrium surrounding the placental site grows more rapidly than does the rest.

Myocyte Arrangement

The uterine musculature during pregnancy is arranged in three strata. The first is an outer hoodlike layer, which arches over the fundus and extends into the various ligaments. The middle layer is a dense network of muscle fibers perforated in all directions by blood vessels. Last is an internal layer, with sphincter-like fibers around the fallopian tube orifices and internal cervical os. Most of the uterine wall is formed by the middle layer. Here, each myocyte has a double curve so that the interlacing of any two cells forms a figure eight. This arrangement is crucial and permits myocytes to contract after delivery and constrict penetrating blood vessels to halt bleeding.

Uterine Shape and Position

For the first few weeks, the uterus maintains its original piriform or pear shape. But, as pregnancy advances, the corpus and fundus become globular and almost spherical by 12 weeks' gestation. Subsequently, the organ grows more rapidly in length than in width and becomes ovoid. By the end of 12 weeks, the enlarged uterus extends out of the pelvis. With this, it contacts the anterior abdominal wall, displaces the intestines laterally and superiorly, and ultimately reaches almost to the liver. With uterine ascent, it usually rotates to the right, and this dextrorotation likely is caused by the rectosigmoid on the left side of the pelvis. As the uterus rises, tension is exerted on the broad and round ligaments.

With the pregnant woman standing, the longitudinal axis of the uterus corresponds to an extension of the pelvic inlet axis. The abdominal wall supports the uterus and maintains this axis, unless the wall is lax. When the pregnant woman lies supine, the uterus falls back to rest on the vertebral column and the adjacent great vessels.

Uterine Contractility

Beginning in early pregnancy, the uterus contracts irregularly, and these may be perceived as mild cramps. During the second trimester, these contractions can be detected by bimanual examination. In 1872, J. Braxton Hicks first brought attention to these contractions, which now bear his name. These appear unpredictably and sporadically and are usually nonrhythmic. Their intensity varies between 5 and 25 mm Hg (Alvarez, 1950). Until near term, these *Braxton Hicks contractions* are infrequent, but their number rises during the last week or two. At this time, the uterus may contract as often as every 10 to 20 minutes and with some degree of rhythmicity. Correspondingly, uterine electrical activity is low and uncoordinated early in gestation, but becomes progressively more intense and synchronized by term (Garfield, 2005; Rabotti, 2015). This synchrony develops twice as fast in multiparas compared with nulliparas (Govindan, 2015). Late in pregnancy, these contractions may cause some discomfort and account for so-called false labor.

Uteroplacental Blood Flow

The delivery of most substances essential for fetal and placental growth, metabolism, and waste removal requires the placental intervillous space to be adequately perfused (Chap. 5, Breaks in the Placental "Barrier"). Placental perfusion depends on total uterine blood flow, but simultaneous measurement of uterine, ovarian, and collateral vessels is not yet possible, even using magnetic resonance (MR) angiography (Pates, 2010). Using ultrasound to study the uterine arteries, uteroplacental blood flow has been measured to increase progressively during pregnancy—from approximately 450 mL/min in the midtrimester to nearly 500 to 750 mL/min at 36 weeks (Flo, 2014; Wilson, 2007). These measures are similar to uterine artery blood flow estimates ascertained indirectly using clearance rates of androstenedione and xenon-133 (Edman, 1981; Kauppila, 1980). These values also mirror older ones—500 to 750 mL/min—obtained with invasive methods (Assali, 1953; Browne, 1953; Metcalfe, 1955). Logically, such massively increased uteroplacental blood flow requires adaptation of the uterine veins as well. The resultant increased venous caliber and distensibility can result in uterine vein varices that in rare instances may rupture (Lim, 2014).

As noted first from animal studies, uterine contractions, either spontaneous or induced, lower uterine blood flow proportionally to contraction intensity (Assali, 1968). A tetanic contraction yields a precipitous fall in uterine blood flow. In humans, three-dimensional power Doppler angiography has also demonstrated reduced uterine blood flow during contractions (Jones, 2009). Using a similar technique, resistance to blood flow in both maternal and fetal vessels was found to be greater during the second stage of labor compared with the first (Baron, 2015). Given that baseline uterine blood flow is diminished in pregnancies complicated by fetal-growth restriction, these fetuses may tolerate spontaneous labor less effectively (Ferrazzi, 2011; Simeone, 2017).

Uteroplacental Blood Flow Regulation

The vessels that supply the uterine corpus widen and elongate yet preserve their contractile function (Mandala, 2012). In contrast, the spiral arteries, which directly supply the placenta, vasodilate but completely lose contractility. This presumably results from endovascular trophoblast invasion that destroys the intramural muscular elements (Chap. 5, Endometrial Invasion). It is this vasodilation that allows maternal–placental blood flow to progressively rise during gestation. Given that blood flow increases proportionally to the fourth power of the radius of the vessel, small increases in vessel diameter result in tremendous augmentation of uterine artery blood flow. For example, in one study, the uterine artery diameter grew from only 3.3 mm to 3.7 mm between 22 and 29 weeks' gestation, but mean velocity increased 50 percent, from 29 to 43 cm/sec (Flo, 2010).

The downstream fall in vascular resistance is another key factor that accelerates flow velocity and shear stress in upstream vessels. In turn, shear stress leads to circumferential vessel growth. Nitric oxide—a potent vasodilator—appears to play a central role in regulating this process and is discussed later (Renin, Angiotensin II, and Plasma Volume). Indeed, endothelial shear stress and several hormones and growth factors all augment endothelial nitric oxide synthase (eNOS) and nitric oxide production (Grummer, 2009; Lim, 2015; Mandala, 2012; Pang, 2015). Factors include estrogen, progesterone, activin, placental growth factor (PlGF), and vascular endothelial growth factor (VEGF), which is a promoter of angiogenesis. As an important aside, VEGF and PlGF signaling is attenuated in response to excess placental secretion of their soluble receptor—*soluble FMS-like tyrosine kinase 1 (sFlt-1).* An elevated maternal sFlt-1 level inactivates and lowers circulating PlGF and VEGF concentrations and is important in preeclampsia pathogenesis (Chap. 40, Endothelial Cell Injury).

Normal pregnancy is also characterized by vascular refractoriness to the pressor effects of infused angiotensin II, and this raises uteroplacental blood flow (Rosenfeld, 1981, 2012). Other factors that augment uteroplacental blood flow include relaxin and certain adipocytokines (Vodstrcil, 2012). *Chemerin* is an adipocytokine secreted by several tissues, including the placenta (Garces, 2013; Kasher-Meron, 2014). Its concentration rises as gestation advances and serves to increase human umbilical eNOS activity, which mediates greater blood flow (Wang, 2015). Another adipocytokine–*visfatin*–raises VEGF secretion and VEGF receptor 2 expression in human epithelial cells derived from the placental amnion (Astern, 2013). Other adipocytokines include *leptin*, *resistin,* and *adiponectin*, which all enhance human umbilical vein endothelial cell proliferation (Połeć, 2014).

Last, certain microRNA species mediate vascular remodeling and uterine blood flow early in placentation (Santa, 2015). In particular, members of the miR-17–92 cluster and miR-34 are important in spiral artery remodeling and invasion. Abnormalities of micro-RNA function have been reported in preeclampsia, fetal-growth restriction, and gestational diabetes.

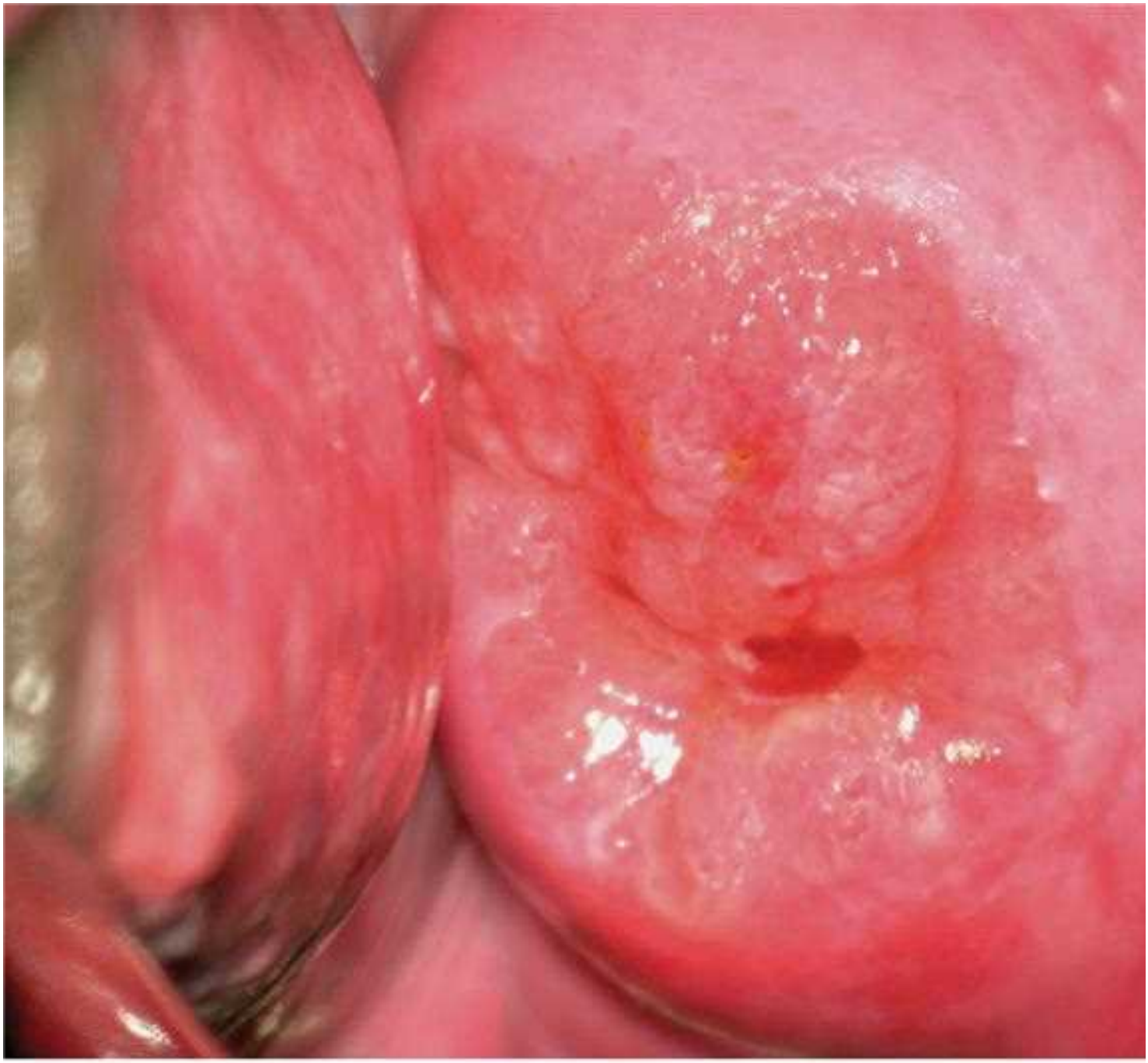
Cervix

As early as 1 month after conception, the cervix begins to soften and gain bluish tones. These result from increased vascularity and edema of the entire cervix, from changes in the collagen network, and from hypertrophy and hyperplasia of the cervical glands (Peralta, 2015; Straach, 2005). Although the cervix contains a small amount of smooth muscle, its major component is connective tissue. Rearrangement of this collagen-rich tissue aids the cervix in retention of the pregnancy until term, in dilatation to aid delivery, and in postpartum repair and reconstitution to permit a subsequent successful pregnancy (Myers, 2015). As detailed in Chapter 21 (Cervical Ripening), cervical ripening involves connective tissue remodeling that lowers collagen and proteoglycan concentrations and raises water content compared with the nonpregnant cervix.

Cervical glands undergo marked proliferation, and by the end of pregnancy, they occupy up to one half of the entire cervical mass. This normal pregnancy-induced change prompts an extension, or *eversion*, of the proliferating columnar endocervical glands onto the ectocervical portio (Fig. 4-1). This tissue appears red and

velvety and bleeds even with minor trauma, such as with Pap testing.

FIGURE 4-1
Cervical eversion of pregnancy as viewed through a colposcope. The eversion represents columnar epithelium on the portio of the cervix. (Used with permission from Dr. Claudia Werner.)



The endocervical mucosal cells produce copious amounts of tenacious mucus that obstruct the cervical canal soon after conception (Bastholm, 2017). This mucus is rich in immunoglobulins and cytokines and may act as an immunological barrier to protect the uterine contents against infection (Hansen, 2014; Wang, 2014). At labor onset, if not before, this *mucus plug* is expelled, resulting in a *bloody show.* Moreover, the cervical mucus consistency changes during pregnancy. Specifically, in most pregnant women, as a result of progesterone, when cervical mucus is spread and dried on a glass slide, it shows poor crystallization, termed *beading.* In some gravidas, as a result of amnionic fluid leakage, an arborization of ice-like crystals, called *fern*ing, is seen microscopically.

Histologically, basal cells near the squamocolumnar junction can be prominent in size, shape, and staining quality in pregnancy. These changes are considered to be estrogen induced. In addition, pregnancy is associated with both endocervical gland hyperplasia and hypersecretory appearance—the *Arias-Stella reaction*—which can make differentiating these from truly atypical glandular cells during Pap test evaluation particularly difficult (Rosai, 2015).

Ovaries

Ovulation ceases during pregnancy, and maturation of new follicles is suspended. The single corpus luteum found in gravidas functions maximally during the first 6 to 7 weeks of pregnancy—4 to 5 weeks postovulation. Thereafter, it contributes relatively little to progesterone production. Surgical removal of the corpus luteum before 7 weeks prompts a rapid fall in maternal serum progesterone levels and spontaneous abortion (Csapo, 1973). After this time, however, corpus luteum excision ordinarily does not cause abortion.

An extrauterine *decidual reaction* on and just beneath the ovarian surface is common in pregnancy and is usually observed at cesarean delivery. These slightly elevated clear or red patches bleed easily and may, on first glance, resemble freshly torn adhesions. Similar decidual reactions are seen on the uterine serosa and other pelvic, or even extrapelvic, abdominal organs (Bloom, 2010). These areas arise from subcoelomic mesenchyme or endometriotic lesions that have been stimulated by progesterone. They histologically appear similar to progestin-stimulated intrauterine endometrial stroma (Kim, 2015).

The enormous caliber of the ovarian veins viewed at cesarean delivery is startling. Hodgkinson (1953) found that the diameter of the ovarian vascular pedicle increased during pregnancy from 0.9 cm to approximately 2.6 cm at term. Again, recall that flow in a tubular structure increases exponentially as the diameter enlarges.

Relaxin

This protein hormone is secreted by the corpus luteum, the decidua, and the placenta in a pattern similar to that of human chorionic gonadotropin (hCG) (Chap. 5, Placental Progesterone Production). Relaxin is also expressed in brain, heart, and kidney. It is mentioned here because its secretion by the corpus luteum appears to aid many maternal physiological adaptations, such as remodeling of reproductive-tract connective tissue to accommodate labor (Conrad, 2013; Vrachnis, 2015). Relaxin also appears important in initiating augmented renal hemodynamics, lowering serum osmolality, and increasing arterial compliance, which are all associated with normal pregnancy (Conrad, 2014a). Despite its name, serum relaxin levels do not contribute to greater peripheral joint laxity or pelvic girdle pain during pregnancy (Aldabe, 2012; Marnach, 2003; Vøllestad, 2012).

Theca-Lutein Cysts

These benign ovarian lesions reflect exaggerated physiological follicle stimulation, which is termed *hyperreactio luteinalis.* These usually bilateral cystic ovaries are moderately to massively enlarged. The reaction is usually linked to markedly elevated serum hCG levels. Logically, theca-lutein cysts are found frequently with gestational trophoblastic disease (Fig. 20-3). They also can develop with the placentomegaly that can accompany diabetes, anti-D alloimmunization, and multifetal gestation (Malinowski, 2015). Hyperreactio luteinalis is associated with preeclampsia and hyperthyroidism, which may contribute to elevated risks for fetal-growth restriction and preterm birth (Cavoretto, 2014; Lynn, 2013; Malinowski, 2015). These cysts also are encountered in women with otherwise uncomplicated pregnancies. In these cases, an exaggerated response of the ovaries to normal levels of circulating hCG is suspected (Sarmento Gonçalves, 2015).

Although usually asymptomatic, hemorrhage into the cysts can cause acute abdominal pain (Amoah, 2011). Maternal virilization may be seen in up to 30 percent of women, however, virilization of the fetus has only rarely been reported (Malinowski, 2015). Maternal findings that include temporal balding, hirsutism, and clitoromegaly are associated with massively elevated levels of androstenedione and testosterone. The diagnosis typically is based on sonographic findings of bilateral enlarged ovaries containing multiple cysts in the appropriate clinical settings. The condition is self-limited and resolves following delivery. Its management is reviewed by Malinowski (2015) and discussed further in Chapter 63 (Pregnancy-Related Ovarian Tumors).

Fallopian Tubes

The fallopian tube musculature, that is, the *myosalpinx*, undergoes little hypertrophy during pregnancy. The epithelium of the *endosalpinx* somewhat flattens. Decidual cells may develop in the stroma of the endosalpinx, but a continuous decidual membrane is not formed.

Rarely, a fallopian tube may twist during uterine enlargement (Macedo, 2017). This torsion is more common with comorbid paratubal or ovarian cysts (Lee, 2015).

Vagina and Perineum

During pregnancy, greater vascularity and hyperemia develop in the skin and muscles of the perineum and vulva, and the underlying abundant connective tissue softens. This augmented vascularity prominently affects the vagina and cervix and results in the violet color characteristic of *Chadwick sign.* Within the vagina, the considerably elevated volume of cervical secretions during pregnancy forms a somewhat thick, white discharge. The pH is acidic, varying from 3.5 to 6. This pH results from increased production of lactic acid by *Lactobacillus acidophilus* during metabolism of glycogen energy stores in the vaginal epithelium. Pregnancy is associated with an elevated risk of vulvovaginal candidiasis, particularly during the second and third trimesters. Higher infection rates may stem from immunological and hormonal changes and from greater vaginal glycogen stores (Aguin, 2015).

The vaginal walls undergo striking changes in preparation for the distention that accompanies labor and delivery. These alterations include considerable epithelial thickening, connective tissue loosening, and smooth muscle cell hypertrophy.

Pelvic Organ Prolapse

Pelvic Organ Prolapse Quantification (POP-Q) and three-dimensional sonography studies show that vaginal support changes across pregnancy. In particular, vaginal lengthening, posterior vaginal wall and hiatal relaxation, increased levator hiatal area, and greater first-trimester vaginal elastase activity are all associated with uncomplicated spontaneous vaginal delivery (Oliphant, 2014). The larger hiatal area persists in women who deliver vaginally compared with women delivering by prelabor or early-labor cesarean delivery. However, all women show greater hiatal distensibility after delivery, which is potentially a factor in later pelvic floor dysfunction (van Veelen, 2015).

In women with apical vaginal prolapse, the cervix, and occasionally a portion of the uterine body, can protrude variably from the vulva during early pregnancy. With further growth, the uterus usually rises above the pelvis and can draw the cervix up with it. If the uterus persists in its prolapsed position, symptoms of incarceration may develop at 10 to 14 weeks' gestation (Chap. 3, Uterine Flexion). As a preventive measure, the uterus can be replaced early in pregnancy and held in position with a suitable pessary.

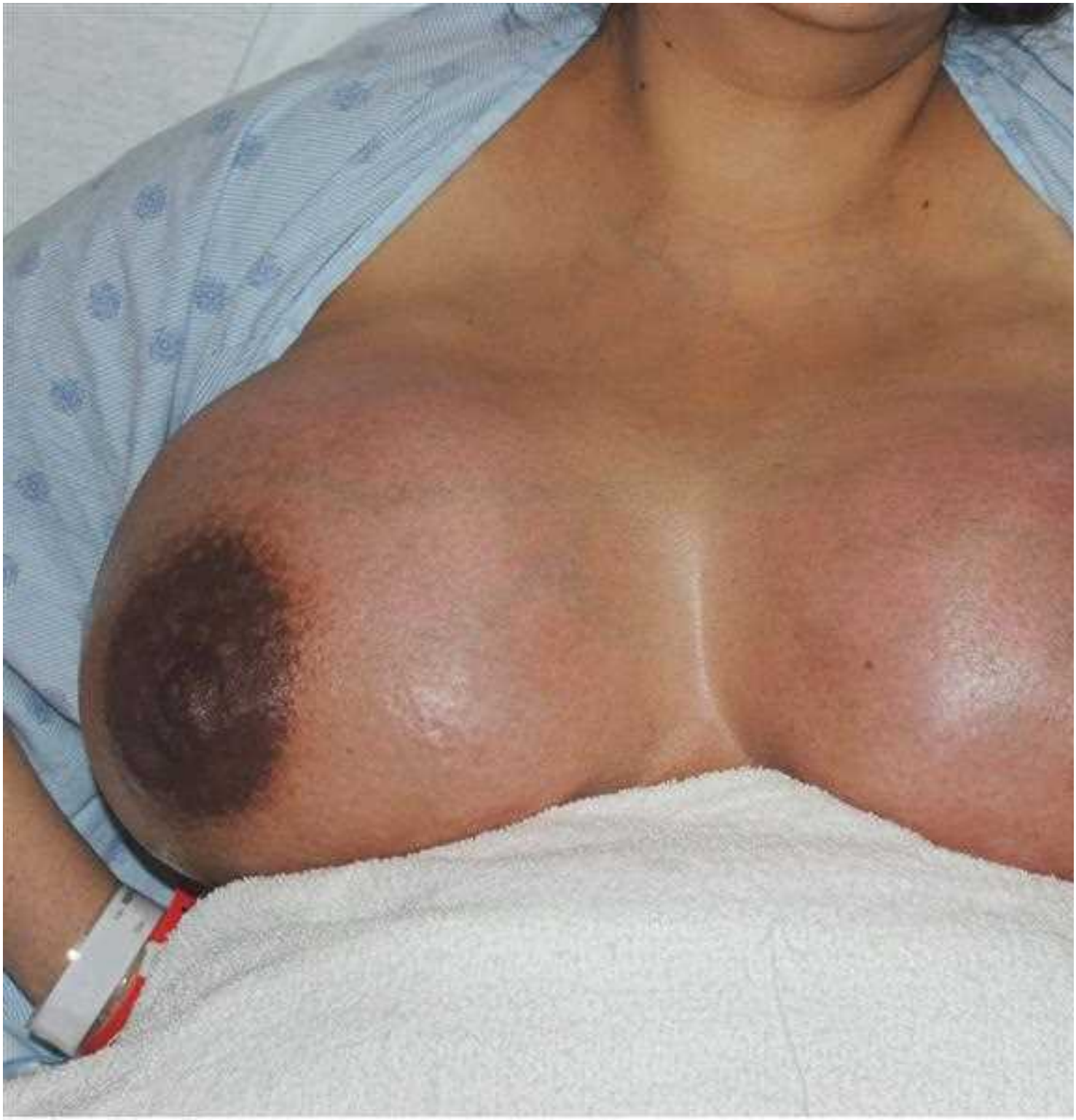
Attenuation of anterior vaginal wall support can lead to prolapse of the bladder, that is, a cystocele. Urinary stasis with a cystocele predisposes to infection. Pregnancy may also worsen coexistent *stress urinary incontinence (SUI)*, likely because urethral closing pressures do not rise sufficiently to compensate for altered bladder neck support. Urinary incontinence affects nearly 20 percent of women during the first trimester and nearly 40 percent during the third trimester. Most cases stem from SUI rather than urgency urinary incontinence (Abdullah, 2016a; Franco, 2014; Iosif, 1980). In primigravidas, maternal age greater than 30 years, obesity, smoking, constipation, and gestational diabetes mellitus are all risk factors associated with SUI development during pregnancy (Sangsawang, 2014).

Attenuation of posterior vaginal wall support can result in a rectocele. A large defect may fill with feces that occasionally can be evacuated only digitally. During labor, a cystocele or rectocele can block fetal descent unless they are emptied and pushed out of the way. Rarely, an enterocele of considerable size may bulge into the vagina. If the mass interferes with delivery, the hernia sac and its abdominal contents are gently reduced to permit fetal descent.

BREASTS

In early pregnancy, women often experience breast tenderness and paresthesias. After the second month, the breasts grow in size, and delicate veins are visible just beneath the skin. The nipples become considerably larger, more deeply pigmented, and more erectile. After the first few months, a thick, yellowish fluid—*colostrum*—can often be expressed from the nipples by gentle massage. During the same months, the areolae become broader and more deeply pigmented. Scattered through each areola are several small elevations, the *glands of Montgomery,* which are hypertrophic sebaceous glands. If breasts gain extensive size, skin striae similar to those observed in the abdomen may develop. Rarely, breasts can become pathologically enlarged—referred to as *gigantomastia*—which may require postpartum surgical reduction (Fig. 4-2) (Eler Dos Reis, 2014; Rezai, 2015).

FIGURE 4-2
Gigantomastia in a woman near term. (Used with permission from Dr. Patricia Santiago-Munoz.)



For most normal pregnancies, prepregnancy breast size and ultimate volume of breast milk do not correlate, as multiple factors influence milk production (Hartmann, 2007). These factors and gestation breast changes are further discussed in Chapter 36 (Lactation and Breastfeeding).

SKIN

Skin changes are common, and Fernandes and Amaral (2015) described dermatological changes in more than 900 pregnant women. They found at least one physiological cutaneous change in 89 percent of the women examined. Dermatologic pathologies during pregnancy are found in Chapter 62.

Abdominal Wall

Beginning after midpregnancy, reddish, slightly depressed streaks commonly develop in the abdominal skin and sometimes in the skin over the breasts and thighs. These are called *striae gravidarum* or *stretch marks.* In multiparas, glistening, silvery lines that represent the cicatrices of previous striae frequently coexist. In one study of 800 primiparas, 70 percent developed striae gravidarum on their abdomen; 33 percent on their breasts; and 41 percent on their hips and thighs (Picard, 2015). The strongest associated risk factors included younger maternal age, family history, and prepregnancy weight and weight gain during pregnancy. The etiology of striae gravidarum is unknown, and there are no preventive steps or definitive treatments (Korgavkar, 2015).

Occasionally, the muscles of the abdominal walls do not withstand the tension of the expanding pregnancy. As a result, rectus muscles separate in the midline, creating *diastasis recti* of varying extent. If severe, a considerable portion of the anterior uterine wall is covered by only a layer of skin, attenuated fascia, and peritoneum to form a ventral hernia.

Hyperpigmentation

This develops in up to 90 percent of women and is usually more accentuated in those with darker complexion (Ikino, 2015). Of specific sites, the pigmented skin line in the midline of the anterior abdominal wall—the *linea alba*—takes on dark brown-black pigmentation to form the *linea nigra.* Occasionally, irregular brownish patches of varying size appear on the face and neck, giving rise to *chloasma* or *melasma gravidarum*—the *mask of pregnancy*. Pigmentation of the areolae and genital skin may also be accentuated. After delivery, these pigmentary changes usually disappear or at least regress considerably. Oral contraceptives may cause similar alterations (Handel, 2014).

The etiology of these pigmentary changes is incompletely understood, however, hormonal and genetic factors play a role. For example, levels of melanocyte-stimulating hormone, a polypeptide similar to corticotropin, are elevated remarkably throughout pregnancy, and estrogen and progesterone also are reported to have melanocyte-stimulating effects.

Vascular Changes

Angiomas, called *vascular spiders,* are particularly common on the face, neck, upper chest, and arms. These are minute, red skin papules with radicles branching out from a central lesion. The condition is often designated as nevus, angioma, or telangiectasis. *Palmar erythema* is encountered during pregnancy. Both conditions lack clinical significance and disappear in most gravidas shortly after pregnancy. They are likely the consequence of hyperestrogenemia. In addition to these discrete lesions, increased cutaneous blood flow in pregnancy serves to dissipate excess heat generated by the augmented metabolism.

Hair Changes

Throughout life, the human hair follicle undergoes a pattern of cyclic activity that includes periods of hair growth (anagen phase), apoptosis-driven involution (catagen phase), and a resting period (telogen phase). Based on a study of 116 healthy pregnant women, the anagen phase lengthens during pregnancy and the telogen rate increases postpartum (Gizlenti, 2014). Neither is exaggerated in most gravidas, but excessive hair loss in the puerperium is termed *telogen effluvium*.

METABOLIC CHANGES

In response to the greater demands of the rapidly growing fetus and placenta, the pregnant woman undergoes metabolic changes that are numerous and intense. By the third trimester, maternal basal metabolic rate rises by 20 percent compared with that of the nonpregnant state (Berggren, 2015). This rate grows by an additional 10 percent in women with a twin gestation (Shinagawa, 2005). Viewed another way, the additional total pregnancy energy demand associated with normal pregnancy approximates 77,000 kcal (World Health Organization, 2004). This is stratified as 85, 285, and 475 kcal/d during the first, second, and third trimester, respectively (Table 4-1). Of note, Abeysekera and coworkers (2016) reported that women accrue fat mass during pregnancy despite the increased total energy expenditure and without significant change in energy intake. This suggests more efficient energy storage.

TABLE 4-1

Additional Energy Demands During Normal Pregnancy[a]

	Rates of Tissue Deposition			
	1st Trimester g/d	**2nd Trimester g/d**	**3rd Trimester g/d**	**Total Deposition g/280 d**
Weight gain	17	60	54	12,000
Protein deposition	0	1.3	5.1	597
Fat deposition	5.2	18.9	16.9	3741
Energy Cost of Pregnancy Estimated from Basal Metabolic Rate and Energy Deposition				
	1st Trimester kJ/d	**2nd Trimester kJ/d**	**3rd Trimester kJ/d**	**Total Energy Cost**
				MJ / **Kcal**
Protein deposition	0	30	121	14.1 / 3370
Fat deposition	202	732	654	144.8 / 34,600
Efficiency of energy utilization[b]	20	76	77	15.9 / 3800
Basal metabolic rate	199	397	993	147.8 / 35,130
Total energy cost of pregnancy	**421**	**1235**	**1845**	**322.6 / 77,100**

[a]Assumes an average gestational weight gain of 12 kg.

[b]Efficiency of food energy utilization for protein and fat deposition estimated as 0.90.

Adapted from the World Health Organization, 2004.

Weight Gain

Most of the normal weight gain in pregnancy is attributable to the uterus and its contents, the breasts, and expanded blood and extravascular extracellular fluid volumes. A smaller fraction results from metabolic alterations that promote accumulation of cellular water, fat, and protein, which are so-called maternal reserves. The average weight gain during pregnancy approximates 12.5 kg or 27.5 lb, and this value has remained consistent across studies and over time (Hytten, 1991; Jebeile, 2016). Weight gain is considered in further detail in Table 4-2 and in Chapter 9 (Nutritional Counseling).

TABLE 4-2

Weight Gain Based on Pregnancy-Related Components

	Cumulative Increase in Weight (g)			
Tissues and Fluids	**10 Weeks**	**20 Weeks**	**30 Weeks**	**40 Weeks**
Fetus	5	300	1500	3400
Placenta	20	170	430	650
Amnionic fluid	30	350	750	800
Uterus	140	320	600	970
Breasts	45	180	360	405
Blood	100	600	1300	1450
Extravascular fluid	0	30	80	1480
Maternal stores (fat)	310	2050	3480	3345
Total	**650**	**4000**	**8500**	**12,500**

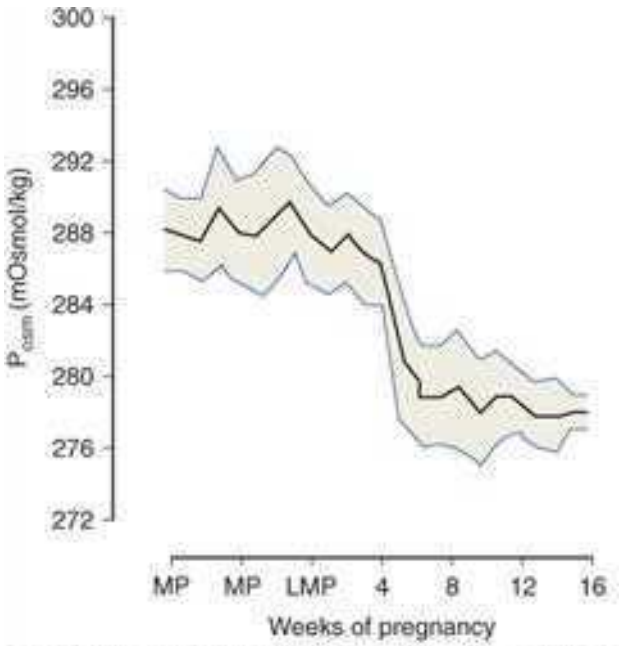
Modified from Hytten, 1991.

Water Metabolism

In pregnancy, greater water retention is normal and mediated in part by a drop in plasma osmolality of 10 mOsm/kg. This decline develops in early pregnancy and is induced by a reset of osmotic thresholds for thirst and vasopressin secretion (Fig. 4-3) (Davison, 1981; Lindheimer, 2001). Relaxin and other hormones are thought to play a role (Conrad, 2013).

FIGURE 4-3

Mean values (*black line*) ± standard deviations (*blue lines*) for plasma osmolality (P_{osm}) measured at weekly intervals in nine women from preconception to 16 weeks. LMP = last menstrual period; MP = menstrual period. (Redrawn with permission from Davison JM, Dunlop W: Renal hemodynamics and tubular function in normal human pregnancy. Kidney Int 18:152, 1980.)



At term, the water content of the fetus, placenta, and amnionic fluid approximates 3.5 L. Another 3.0 L accumulates from expanded maternal blood volume and from uterus and breast growth. Thus, the minimum amount of extra water that the average woman accrues during normal pregnancy approximates 6.5 L. This corresponds to 14.3 lb.

Clearly demonstrable pitting edema of the ankles and legs is seen in most pregnant women, especially at the end of the day. This fluid accumulation, which may amount to a liter or so, results from greater venous pressure below the level of the uterus as a consequence of partial vena cava occlusion. A decline in interstitial colloid osmotic pressure induced by normal pregnancy also favors edema late in pregnancy (Øian, 1985).

Longitudinal studies of body composition show a progressive accumulation of total body water and fat mass during pregnancy. These two components as well as initial maternal weight and weight gained during pregnancy are highly associated with neonatal birthweight (Lederman, 1999; Mardones-Santander, 1998). "Over-nourished" women are more likely to deliver oversized neonates, even when glucose tolerant (Di Benedetto, 2012).

Protein Metabolism

The products of conception, the uterus, and maternal blood are relatively rich in protein rather than fat or carbohydrate. At term, the normally grown fetus and placenta together weigh about 4 kg and contain approximately 500 g of protein, or about half of the total pregnancy increase. The remaining 500 g is added to the uterus as contractile protein, to the breasts primarily in the glands, and to maternal blood as hemoglobin and plasma proteins.

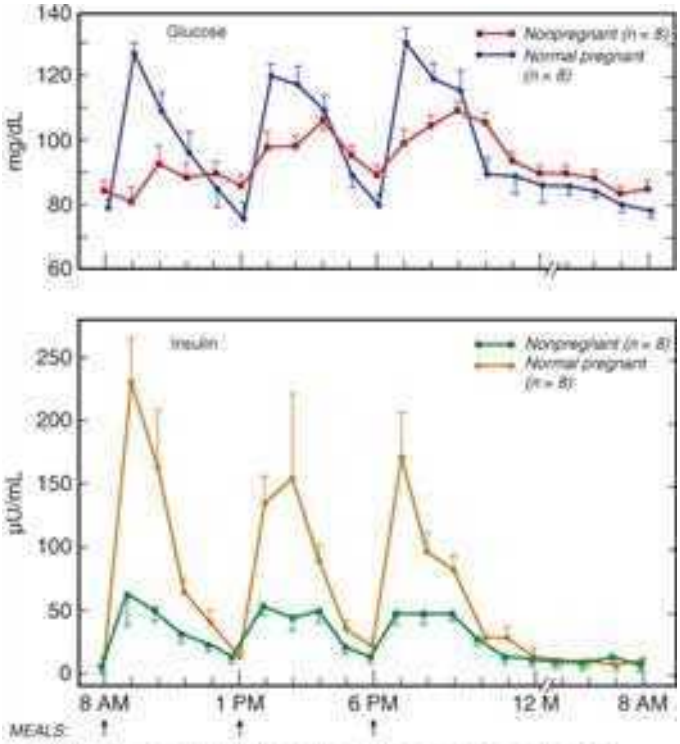
Amino acid concentrations are higher in the fetal than in the maternal compartment and generally result from facilitated transport across the placenta (Cleal, 2011; Panitchob, 2015). This greater concentration is largely regulated by the placenta through an incompletely understood process. In particular, placental transport is variable for individuals and for different amino acids. For example, tyrosine is a conditionally essential amino acid in the preterm neonate but not in the fetus (Van den Akker, 2010, 2011). The placenta concentrates amino acids into the fetal circulation and is also involved in protein synthesis, oxidation, and transamination of some nonessential amino acids (Galan, 2009).

Maternal protein intake does not appear to be a critical determinant for birthweight among well-nourished women (Chong, 2015). Still, recent data suggest that current recommendations for protein intake may be too low. These guidelines are extrapolated from nonpregnant adults and may underestimate actual needs. Stephens and colleagues (2015) prospectively analyzed maternal protein intake and metabolism. They estimated average requirements of 1.22 g/kg/d of protein for early pregnancy and 1.52 g/kg/d for late pregnancy. These levels are higher than the current recommendation of 0.88 g/kg/d. The daily requirements for dietary protein intake during pregnancy are discussed in Chapter 9 (Dietary Reference Intakes—Recommended Allowances).

Carbohydrate Metabolism

Normal pregnancy is characterized by mild fasting hypoglycemia, postprandial hyperglycemia, and hyperinsulinemia (Fig. 4-4). This elevated basal level of plasma insulin in normal pregnancy is associated with several unique responses to glucose ingestion. Specifically, after an oral glucose meal, gravidas demonstrate prolonged hyperglycemia and hyperinsulinemia and a greater suppression of glucagon (Phelps, 1981). This cannot be explained by an increased metabolism of insulin because its half-life during pregnancy is not changed appreciably (Lind, 1977). Instead, this response reflects a pregnancy-induced state of peripheral insulin resistance, which ensures a sustained postprandial supply of glucose to the fetus. Indeed, insulin sensitivity in late normal pregnancy is 30 to 70 percent lower than that of nonpregnant women (Lowe, 2014).

FIGURE 4-4
Diurnal changes in plasma glucose and insulin in normal late pregnancy. (Redrawn from Phelps, 1981.)



The mechanisms responsible for this reduced insulin sensitivity include numerous endocrine and inflammatory factors (Angueira, 2015). In particular, pregnancy-related hormones such as progesterone, placentally derived growth hormone, prolactin, and cortisol; cytokines such as tumor necrosis factor; and hormones derived from central adiposity, particularly leptin and its interplay with prolactin, all have a role in the insulin resistance of pregnancy. Even so, insulin resistance is not the only factor to elevate postprandial glucose values. Hepatic gluconeogenesis is augmented during both diabetic and nondiabetic pregnancies, particularly in the third trimester (Angueira, 2015).

Overnight, the pregnant woman changes from a postprandial state characterized by elevated and sustained glucose levels to a fasting state characterized by decreased plasma glucose and some amino acids. Plasma concentrations of free fatty acids, triglycerides, and cholesterol are also higher in the fasting state. This pregnancy-induced switch in fuels from glucose to lipids has been called *accelerated starvation.* Certainly, when fasting is prolonged in the pregnant woman, these alterations are exaggerated and ketonemia rapidly appears.

Fat Metabolism

The concentrations of lipids, lipoproteins, and apolipoproteins in plasma rise appreciably during pregnancy (Appendix, Serum and Blood Constituents). Increased insulin resistance and estrogen stimulation during pregnancy are responsible for the maternal hyperlipidemia. Augmented lipid synthesis and food intake contribute to maternal fat accumulation during the first two trimesters (Herrera, 2014). In the third trimester, however, fat storage declines or ceases. This is a consequence of enhanced lipolytic activity, and decreased lipoprotein lipase activity reduces circulating triglyceride uptake into adipose tissue. This transition to a catabolic state favors maternal use of lipids as an energy source and spares glucose and amino acids for the fetus.

Maternal hyperlipidemia is one of the most consistent and striking changes of lipid metabolism during late pregnancy. Triacylglycerol and cholesterol levels in very-low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) are increased during the third trimester compared with those in nonpregnant women. During the third trimester, the average level of total serum cholesterol is 267 ± 30 mg/dL, of LDL-C is 136 ± 33 mg/dL, of HDL-C is 81 ± 17 mg/dL, and of triglycerides is 245 ± 73 mg/dL (Lippi, 2007). After delivery, the concentrations of these lipids, lipoproteins, and apolipoproteins decline. Breastfeeding drops maternal triglyceride levels but increases those of HDL-C. The effects of breastfeeding on total cholesterol and LDL-C levels are unclear (Gunderson, 2014).

Hyperlipidemia is theoretically a concern because it is associated with endothelial dysfunction. From studies, however, endothelium-dependent vasodilation responses actually improve across pregnancy (Saarelainen, 2006). This is partly because increased HDL-C concentrations likely inhibit LDL oxidation and thus protect the endothelium. These findings suggest that the increased cardiovascular disease risk in multiparas may be related to factors other than maternal hypercholesterolemia.

Leptin

This peptide hormone is primarily secreted by adipose tissue in nonpregnant humans. It plays a key role in body fat and energy expenditure regulation and in reproduction. For example, leptin is important for implantation, cell proliferation, and angiogenesis (Vazquez, 2015). Leptin deficiency is associated with anovulation and infertility, whereas certain leptin mutations cause extreme obesity (Tsai, 2015).

Among normal-weight pregnant women, serum leptin levels rise and peak during the second trimester and plateau until term in concentrations two to four times higher than those in nonpregnant women. Among obese women, leptin levels correlate with adiposity (Ozias, 2015; Tsai, 2015). In all cases, leptin levels fall after

delivery, reflecting the significant amounts produced by the placenta (Vazquez, 2015).

Leptin participates in regulating energy metabolism during pregnancy. Interestingly, despite the rise in leptin concentrations during pregnancy, reduced leptin sensitivity to food intake during pregnancy has been described (Chehab, 2014; Vazquez, 2015). This "leptin resistance" may serve to promote energy storage during pregnancy and for later lactation. Higher leptin levels during pregnancy may be disadvantageous under certain situations, such as in maternal obesity. Leptin functions as a proinflammatory cytokine in white adipose tissue, which may dysregulate the inflammatory cascade and lead to placental dysfunction in obese women (Vazquez, 2015). In addition, abnormally elevated leptin levels have been associated with preeclampsia and gestational diabetes (Bao, 2015; Taylor, 2015).

Fetal leptin is important for the development of several organs that include the pancreas, kidney, heart, and brain. Fetal levels correlate with maternal body mass index (BMI) and birthweight. Lower levels are linked to fetal-growth restriction (Briffa, 2015; Tsai, 2015).

Other Adipocytokines

Dozens of hormones with metabolic and/or inflammatory functions are produced by adipose tissue. *Adiponectin* is a peptide produced primarily in maternal fat but not in the placenta (Haghiac, 2014). Adiponectin levels inversely correlate with adiposity, and it acts as a potent insulin sensitizer. Despite reduced adiponectin levels in women with gestational diabetes, directed assays are not useful for predicting diabetes development (Hauguel-de Mouzon, 2013).

Ghrelin is a peptide secreted principally by the stomach in response to hunger. It cooperates with other neuroendocrine factors, such as leptin, in energy homeostasis modulation. Ghrelin is also expressed in the placenta and likely has a role in fetal growth and cell proliferation (González-Domínguez, 2016). Angelidis and associates (2012) have reviewed the many functions of ghrelin in the regulation of reproductive function.

Visfatin is a peptide that was first identified as a growth factor for B lymphocytes, but it is mainly produced within adipose tissue. Mumtaz and colleagues (2015) propose that elevated levels of visfatin and leptin impair uterine contractility. Such findings may provide a physiological basis for the observation that maternal obesity raises the risk for dysfunctional labor.

Electrolyte and Mineral Metabolism

During normal pregnancy, nearly 1000 mEq of *sodium* and 300 mEq of *potassium* are retained (Lindheimer, 1987). Although the glomerular filtration rate of sodium and potassium is increased, the excretion of these electrolytes is unchanged during pregnancy as a result of enhanced tubular resorption (Brown, 1986, 1988). Although total accumulations of sodium and potassium are elevated, their serum concentrations are diminished slightly (Appendix, Serum and Blood Constituents). Several mechanisms may explain these lower levels (Odutayo, 2012). In the case of potassium, it possibly involves the expanded plasma volume of pregnancy. With respect to sodium, osmoregulation is altered and the threshold for arginine vasopressin release is lowered. This promotes free water retention and diminished sodium levels.

Total serum *calcium* levels, which include both ionized and nonionized calcium, decrease during pregnancy. This reduction follows lowered plasma albumin concentrations and in turn a consequent decline in the amount of circulating protein-bound nonionized calcium. Serum ionized calcium levels, however, remain unchanged (Olausson, 2012).

The developing fetus imposes a significant demand on maternal calcium homeostasis. For example, the fetal skeleton accretes approximately 30 g of calcium by term, 80 percent of which is deposited during the third trimester. This demand is largely met by a doubling of maternal intestinal calcium absorption mediated partly by 1,25-dihydroxyvitamin D_3. These higher levels of vitamin D are possibly stimulated by a twofold rise in PTH-related peptide levels produced by several tissues including the placenta (Kovacs, 2006; Olausson, 2012). To help compensate, dietary intake of sufficient calcium is necessary to prevent excess depletion from the mother. A list of all recommended daily allowances is found in Table 9-5. This is especially important for pregnant adolescents, in whom bones are still developing. Unfortunately, a lack of robust data prevents drawing firm conclusions regarding the utility of calcium and vitamin D supplements during pregnancy (De-Regil, 2016).

Serum *magnesium* levels also decline during pregnancy. Bardicef and colleagues (1995) concluded that pregnancy is actually a state of extracellular magnesium depletion. Compared with nonpregnant women, both total and ionized magnesium concentrations are significantly lower during normal pregnancy (Rylander, 2014).

Serum *phosphate* levels lie within the nonpregnant range (Larsson, 2008). Although calcitonin is an important regulator of serum calcium and phosphate, the importance of calcitonin as it relates to pregnancy is poorly understood (Olausson, 2012).

Iodine requirements increase during normal pregnancy for several reasons (Moleti, 2014; Zimmermann, 2012). First, maternal thyroxine production rises to maintain maternal euthyroidism and to transfer thyroid hormone to the fetus prior to fetal thyroid functioning. Second, fetal thyroid hormone production increases during the second half of pregnancy. This contributes to greater maternal iodine requirements because iodide readily crosses the placenta. Third, the primary route of iodine excretion is through the kidney. Beginning in early pregnancy, the iodide glomerular filtration rate increases by 30 to 50 percent. In sum, because of greater thyroid hormone production, fetal iodine requirements, and augmented renal clearance, dietary iodine needs are higher during normal gestation. Although the placenta has the ability to store iodine, whether this organ functions to protect the fetus from inadequate maternal dietary iodine is currently unknown (Burns, 2011). Iodine deficiency is discussed later in this chapter (Parathyroid Glands) and in Chapter 58 (Iodine Deficiency). At the other extreme, maternal supplements containing excessive iodine have been associated with congenital hypothyroidism. This stems from autoregulation in the thyroid gland—known as the *Wolff-Chaikoff effect*—to curb thyroxine production in response to iodide overconsumption (Connelly, 2012).

With respect to most other minerals, pregnancy induces little change in their metabolism other than their retention in amounts equivalent to those needed for growth. An important exception is the considerably greater requirement for *iron,* which is discussed subsequently.

HEMATOLOGICAL CHANGES

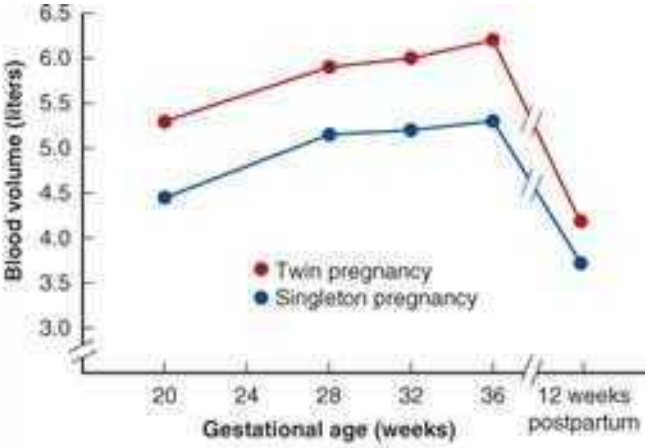
Blood Volume

The well-known hypervolemia associated with normal pregnancy averages 40 to 45 percent above the nonpregnant blood volume after 32 to 34 weeks' gestation (Pritchard, 1965; Zeeman, 2009). In individual women, expansion varies considerably. In some, accumulated volume rises only modestly, whereas in others blood volume nearly doubles. A fetus is not essential, as augmented blood volume develops in some with hydatidiform mole.

Pregnancy-induced hypervolemia serves several functions. First, it meets the metabolic demands of the enlarged uterus and its greatly hypertrophied vascular system. Second, it provides abundant nutrients and elements to support the rapidly growing placenta and fetus. Third, the expanded intravascular volume protects the mother, and in turn the fetus, against the deleterious effects of impaired venous return in the supine and erect positions. Last, it safeguards the mother against the adverse effects of parturition-associated blood loss.

Maternal blood volume begins to accrue during the first trimester. By 12 menstrual weeks, plasma volume expands by approximately 15 percent compared with that prior to pregnancy (Bernstein, 2001). Maternal blood volume grows most rapidly during the midtrimester, rises at a much slower rate during the third trimester, and reaches a plateau during the last several weeks of pregnancy (Fig. 4-5). Blood volume accrues even more dramatically in twin gestations. During blood volume expansion, plasma volume and erythrocyte number rise. Although more plasma than erythrocytes is usually added to the maternal circulation, the increase in erythrocyte volume is considerable and averages 450 mL (Pritchard, 1960). Moderate erythroid hyperplasia develops in the bone marrow, and the reticulocyte count is elevated slightly during normal pregnancy. These changes are almost certainly related to an elevated maternal plasma erythropoietin level.

FIGURE 4-5
Blood volume expansion during pregnancy in twins (n = 10) and singletons (n = 40). Data shown as medians. (Data from Thomsen, 1994.)



Hemoglobin Concentration and Hematocrit

Because of great plasma augmentation, both hemoglobin concentration and hematocrit decline slightly during pregnancy (Appendix, Serum and Blood Constituents). As a result, whole blood viscosity decreases (Huisman, 1987). Hemoglobin concentration at term averages 12.5 g/dL, and in approximately 5 percent of women it is below 11.0 g/dL. Thus, a hemoglobin concentration below 11.0 g/dL, especially late in pregnancy, is considered abnormal and usually due to iron-deficiency anemia rather than pregnancy hypervolemia.

Iron Metabolism

The total iron content of normal adult women ranges from 2.0 to 2.5 g, or approximately half that found normally in men. Most of this is incorporated in hemoglobin or myoglobin, and thus, iron stores of normal young women only approximate 300 mg (Pritchard, 1964). Although the lower iron levels in women may be partly due to menstrual blood loss, other factors have a role, particularly hepcidin–a peptide hormone that functions as a homeostatic regulator of systemic iron metabolism. Hepcidin levels rise with inflammation, but drop with iron deficiency and several hormones, including testosterone, estrogen, vitamin D, and possibly prolactin (Liu, 2016; Wang, 2015). Lower hepcidin levels are associated with greater absorption of iron via ferroportin in enterocytes (Camaschella, 2015).

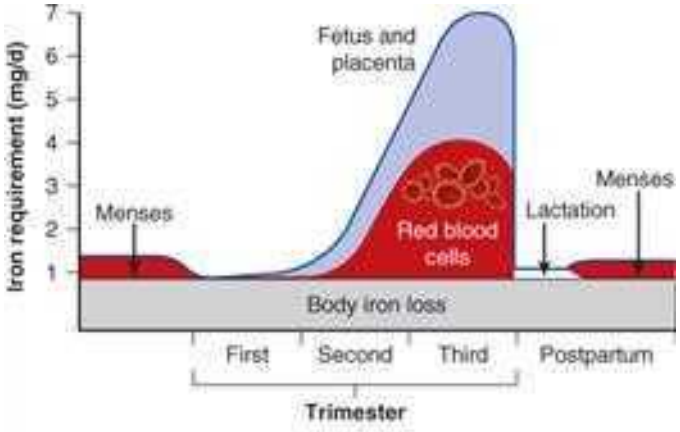
Iron Requirements

Of the approximate 1000 mg of iron required for normal pregnancy, about 300 mg is actively transferred to the fetus and placenta, and another 200 mg is lost through various normal excretion routes, primarily the gastrointestinal tract. These are obligatory losses and accrue even when the mother is iron deficient. The average increase in the total circulating erythrocyte volume—about 450 mL—requires another 500 mg. Recall that each 1 mL of erythrocytes contains 1.1 mg of iron.

As shown in Figure 4-6, because most iron is used during the latter half of pregnancy, the iron requirement becomes large after midpregnancy and averages 6 to 7 mg/d (Pritchard, 1970). In most women, this amount is usually not available from iron stores or diet. Thus, without supplemental iron, the optimal rise in maternal erythrocyte volume will not develop, and the hemoglobin concentration and hematocrit will fall appreciably as plasma volume rises. At the same time, fetal red cell production is not impaired because the placenta transfers iron even if the mother has severe iron-deficiency anemia. In severe cases, we have documented maternal hemoglobin values of 3 g/dL, and at the same time, fetuses had hemoglobin concentrations of 16 g/dL. The mechanisms of placental iron transport and regulation are complex (Koenig, 2014; McArdle, 2014).

FIGURE 4-6

Estimated daily iron requirements during pregnancy in a 55-kg woman. (Modified from Koenig, 2014.)



If the nonanemic pregnant woman is not given supplemental iron, then serum iron and ferritin concentrations decline after midpregnancy. Importantly, hepcidin levels drop early in pregnancy (Hedengran, 2016; Koenig, 2014). As noted, lower hepcidin levels aid iron transfer into the maternal circulation via ferroportin in enterocytes. Lower hepcidin levels also augment iron transport into the fetus via ferroportin in syncytiotrophoblast.

With normal vaginal delivery, 500 to 600 mL of blood is typically lost, and thus not all the maternal iron added in the form of hemoglobin is spent (Pritchard, 1965). The excess hemoglobin iron becomes stored iron.

Immunological Functions

Pregnancy is associated with suppression of various humoral and cell-mediated immunological functions (Chap. 5, Amnion). This permits accommodation of the "foreign" semiallogeneic fetal graft that contains antigens of both maternal and paternal origin (Redman, 2014). The tolerance that exists at the maternal-fetal interface remains a great unsolved medical mystery. This tolerance is complex and involves certain immune system adaptations and crosstalk among the maternal microbiome, uterine decidua, and trophoblast. In particular, areas of the uterus that were previously considered sterile are colonized with bacteria. In most cases, these microbes are believed to be commensal and play a tolerizing and protective role. Indeed, commensal organisms may inhibit the proliferation of certain pathogens. Several reviewers have described these relationships (Mor, 2015; Racicot, 2014; Sisti, 2016).

One immune adaptation that promotes tolerance and protection at the maternal-fetal interface involves the expression of special major histocompatibility complex (MHC) molecules on the trophoblast. Recall that all cells of the body express a "badge" that identifies "self" and therefore privilege against attack by immune responses. For most cells of the body, this "badge" is known as MHC Class Ia. However, it is uncommon for two unrelated individuals to share compatible MHC class Ia. This creates a potential problem for reproduction because half of the fetus is composed of paternally derived antigens. To circumvent this problem, trophoblast cells express a form of MHC that does not vary between individuals. This "nonclassic" MHC is known as human leukocyte antigen class Ib and includes HLA-E, HLA-F, and HLA-G. Recognition of these HLA class Ib proteins by natural killer cells residing within the decidua inhibits their activity and promotes immune quiescence (Djurisic, 2014).

Another immune adaptation that promotes tolerances stems from important changes in CD4 T lymphocyte subpopulations in pregnancy. First, Th1-mediated immunity shifts to Th2-mediated immunity. Indeed, an important antiinflammatory component of pregnancy involves suppression of T-helper (Th) 1 and T-cytotoxic (Tc) 1 cells, which lower secretion of interleukin-2 (IL-2), interferon-α, and tumor necrosis factor (TNF). Moreover, suppressed Th1 response is thought to be a requisite for pregnancy continuation. It also may explain pregnancy-related remission of some autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, and Hashimoto thyroiditis—which are cell-mediated immune diseases stimulated by Th1 cytokines (Kumru, 2005). With suppression of Th1 cells, there is upregulation of Th2 cells to increase secretion of IL-4, IL-10, and IL-13 (Michimata, 2003). These Th2 cytokines promote humoral, or antibody-based, immunity. Thus, autoimmune diseases mediated mainly by autoantibodies, such as systemic lupus erythematosus, may flare if the disease is already active in early pregnancy. But, the transition to an antibody-mediated immunity is an important defense during pregnancy and early puerperium. In cervical mucus, peak levels of immunoglobulins A and G (IgA and IgG) are significantly higher during pregnancy, and the immunoglobulin-rich cervical mucus plug creates a barrier to ascending infection (Hansen, 2014; Wang, 2014). Similarly, IgG is transferred to the developing fetus in the third trimester as a form of passive immunity, ostensibly in anticipation of birth. Further, immunoglobulins secreted into breast milk during lactation augment neonatal defenses against infection.

Other subpopulations of CD4 T lymphocytes serve mucosal and barrier immunity. These specific CD4-positive cells are known as Th17 cells and Treg cells. Th17 cells are proinflammatory and express the cytokine IL-17 and the retinoic acid receptor-related orphan receptors (RORs). Treg cells express the transcription factor forkhead box protein-3 (FOXP3) and confer tolerizing activity. There is a shift toward Treg CD4 cells in the first trimester, which peaks during the second trimester and falls toward delivery (Figueiredo, 2016). This shift may promote tolerance at the maternal-fetal interface (La Rocca, 2014). In particular, failure of these CD4 T lymphocyte subpopulation alterations may be related to preeclampsia development (Vargas-Rojas, 2016).

Leukocytes and Lymphocytes

Normal leukocyte counts during pregnancy can be higher than nonpregnant values, and upper values approach 15,000/µL (Appendix, Serum and Blood Constituents). During labor and the early puerperium, values may become markedly elevated, attaining levels of 25,000/µL or greater. The cause is unknown, but the same response occurs during and after strenuous exercise. The leukocytosis possibly represents the reappearance of leukocytes previously shunted out of active circulation.

The distribution of lymphocyte cell types is also altered during pregnancy. Specifically, B lymphocytes numbers are unchanged, but the absolute numbers of T lymphocytes rise and create a relative increase. Concurrently, the ratio of CD4 to CD8 T lymphocytes does not change (Kühnert, 1998).

Inflammatory Markers

Many tests performed to diagnose inflammation cannot be used reliably during pregnancy. For example, *leukocyte alkaline phosphatase* levels—used to evaluate myeloproliferative disorders—are elevated beginning early in pregnancy. The concentration of *C-reactive protein,* an acute-phase serum reactant, rises rapidly in response to tissue trauma or inflammation. Median C-reactive protein levels in pregnancy and labor are higher than for nonpregnant women (Anderson, 2013; Watts, 1991). Of nonlaboring gravidas, 95 percent had levels of 1.5 mg/dL or less, and gestational age did not affect serum levels. Another marker of inflammation, the *erythrocyte sedimentation rate (ESR),* is increased in normal pregnancy because of elevated plasma globulins and fibrinogen levels. *Complement factors C3* and *C4* levels also significantly rise during the second and third trimesters (Gallery, 1981; Richani, 2005). Last, concentrations of *procalcitonin*, a normal precursor of calcitonin, increase at the end of the third trimester and through the first few postpartum days. Procalcitonin levels rise with severe bacterial infections but remain low in viral infections and nonspecific inflammatory disease. However, measured levels poorly predict development of overt or subclinical chorioamnionitis after premature rupture of membranes (Thornburg, 2016).

Coagulation and Fibrinolysis

During normal pregnancy, both coagulation and fibrinolysis are augmented but remain balanced to maintain hemostasis (Kenny, 2014). Evidence of activation includes increased concentrations of all clotting factors except factors XI and XIII (Table 4-3).

TABLE 4-3

Changes in Measures of Hemostasis During Normal Pregnancy

Parameter	Nonpregnant	Term Pregnant
Activated PTT (sec)	31.6 ± 4.9	31.9 ± 2.9
Fibrinogen (mg/dL)	256 ± 58	473 ± 72[a]
Factor VII (%)	99.3 ± 19.4	181.4 ± 48.0[a]
Factor X (%)	97.7 ± 15.4	144.5 ± 20.1[a]
Plasminogen (%)	105.5 ± 14.1	136.2 ± 19.5[a]
tPA (ng/mL)	5.7 ± 3.6	5.0 ± 1.5
Antithrombin III (%)	98.9 ± 13.2	97.5 ± 33.3
Protein C (%)	77.2 ± 12.0	62.9 ± 20.5[a]
Total protein S (%)	75.6 ± 14.0	49.9 ± 10.2[a]

[a] $p < .05$.

Data shown as mean ± standard deviation.

PTT = partial thromboplastin time; tPA = tissue plasminogen activator.

Data from Uchikova, 2005.

Of procoagulants, the level and rate of thrombin generation throughout gestation progressively increase (McLean, 2012). In normal nonpregnant women, plasma fibrinogen (factor I) averages 300 mg/dL and ranges from 200 to 400 mg/dL. During normal pregnancy, the fibrinogen concentration rises approximately 50 percent. In late pregnancy, it averages 450 mg/dL, with a range from 300 to 600 mg/dL. This contributes greatly to the striking increase in the ESR. Also, levels of factor XIII—*fibrin stabilizing factor*—significantly drop as normal pregnancy advances (Sharief, 2014).

The end product of the coagulation cascade is fibrin formation, and the main function of the fibrinolytic system is to remove excess fibrin (Fig. 41-29). Tissue plasminogen activator (tPA) converts plasminogen into plasmin, which causes fibrinolysis and produces fibrin-degradation products such as d-dimers. Although

somewhat conflicting, most evidence suggests that fibrinolytic activity is reduced in normal pregnancy (Kenny, 2014). As reviewed by Cunningham and Nelson (2015), these changes favor fibrin formation. Although this is countered by increased levels of plasminogen, the net result is that pregnancy is a procoagulant state. Such changes serve to ensure hemostatic control during normal pregnancy, particularly during delivery when a certain amount of blood loss is expected.

Regulatory Proteins

Several proteins are natural inhibitors of coagulation, including proteins C and S and antithrombin (Fig. 52-1). Inherited or acquired deficiencies of these and other natural regulatory proteins—collectively referred to as *thrombophilias*—account for many thromboembolic episodes during pregnancy. They are discussed in Chapter 52 (Inherited Thrombophilias).

Activated protein C, along with the cofactors protein S and factor V, functions as an anticoagulant by neutralizing the procoagulants factor Va and factor VIIIa. During pregnancy, resistance to activated protein C grows progressively and is related to a concomitant drop in free protein S levels and greater factor VIII concentrations. Between the first and third trimesters, activated protein C levels decline from 2.4 to 1.9 U/mL, and free protein S concentrations diminish from 0.4 to 0.16 U/mL (Cunningham, 2015; Walker, 1997). Antithrombin levels decrease by 13 percent between midpregnancy and term and fall 30 percent from this baseline until 12 hours after delivery. By 72 hours after delivery, there is a return to baseline (James, 2014).

Platelets

Normal pregnancy promotes platelet changes. In one study, the average platelet count declined slightly during pregnancy to 213,000/µL compared with 250,000/µL in nonpregnant controls (Boehlen, 2000). Thrombocytopenia defined as below the 2.5th percentile corresponded to a platelet count of 116,000/µL. Lower platelet concentrations are partially due to hemodilution. Also, platelet consumption is likely augmented and creates a greater proportion of younger and therefore larger platelets (Han, 2014; Valera, 2010). Further, levels of several markers of platelet activation rise with gestational age but drop postpartum (Robb, 2010). Because of splenic enlargement, there may be an element of "hypersplenism," in which platelets are prematurely destroyed (Kenny, 2014).

Spleen

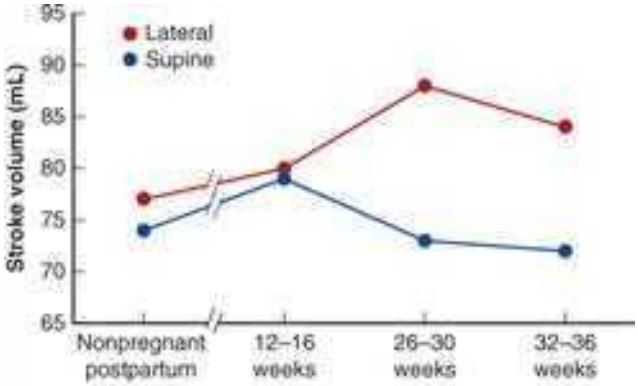
By the end of normal pregnancy, the spleen enlarges by up to 50 percent compared with that in the first trimester (Maymon, 2007). Moreover, Gayer and coworkers (2012) found that splenic size was 68-percent greater compared with that of nonpregnant controls. The cause of this splenomegaly is unknown, but it might follow the increased blood volume and/or the hemodynamic changes of pregnancy.

CARDIOVASCULAR SYSTEM

Changes in cardiac function become apparent during the first 8 weeks of pregnancy (Hibbard, 2014). Cardiac output is increased as early as the fifth week and reflects a reduced systemic vascular resistance and an increased heart rate. Compared with prepregnancy measurements, brachial systolic blood pressure, diastolic blood pressure, and central systolic blood pressure are all significantly lower 6 to 7 weeks from the last menstrual period (Mahendru, 2012). The resting pulse rate rises approximately 10 beats/min during pregnancy. Nelson and associates (2015) found that for both normal and overweight women, heart rate increased significantly between 12 and 16 weeks' and between 32 and 36 weeks' gestation. Between weeks 10 and 20, plasma volume expansion begins, and preload rises. This augmented preload results in significantly larger left atrial volumes and ejection fractions (Cong, 2015).

Ventricular performance during pregnancy is influenced by both the decrease in systemic vascular resistance and changes in pulsatile arterial flow. Multiple factors contribute to this overall altered hemodynamic function, which allows the physiological demands of the fetus to be met while maintaining maternal cardiovascular integrity (Hibbard, 2014). These changes during the last half of pregnancy and effects of maternal posture are summarized in Figure 4-7.

FIGURE 4-7
Left ventricular stroke volume across pregnancy compared with 12-week postpartum (nonpregnant) values for normal-weight women in the supine and lateral positions. (Data from Nelson, 2015.)



Heart

As the diaphragm becomes progressively elevated, the heart is displaced to the left and upward and is rotated on its long axis. As a result, the apex is moved somewhat laterally from its usual position and produces a larger cardiac silhouette in chest radiographs. Furthermore, gravidas normally have some degree of benign pericardial effusion, which may enlarge the cardiac silhouette (Enein, 1987). These factors make it difficult to precisely identify moderate degrees of cardiomegaly by simple radiographic studies.

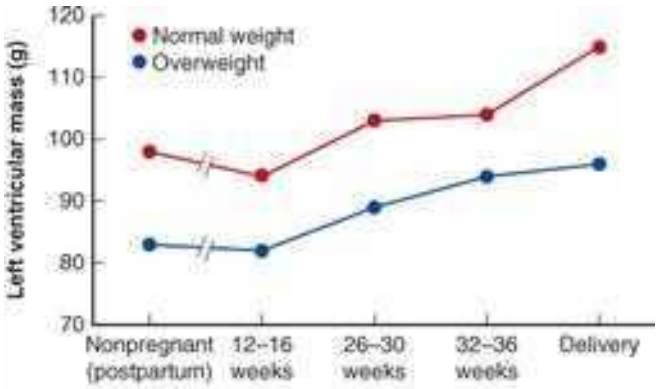
Normal pregnancy induces characteristic electrocardiographic changes, and the most common is slight left-axis deviation due to the altered heart position. Q waves in leads II, III and avF and flat or inverted T-waves in leads III, V1-V3 may also occur (Sunitha, 2014).

During pregnancy, many of the normal *cardiac sounds* are modified. These include: (1) an exaggerated splitting of the first heart sound and increased loudness of both components, (2) no definite changes in the aortic and pulmonary elements of the second sound, and (3) a loud, easily heard third sound (Cutforth, 1966). In 90 percent of gravidas, they also heard a systolic murmur that was intensified during inspiration in some or expiration in others and that disappeared shortly after delivery. A soft diastolic murmur was noted transiently in 20 percent, and continuous murmurs arising from the breast vasculature in 10 percent (Fig. 49-1).

Structurally, the expanding plasma volume seen during normal pregnancy is reflected by enlarging cardiac end-systolic and end-diastolic dimensions. Concurrently, however, septal thickness or ejection fraction does not change. This is because the dimensional changes are accompanied by substantive ventricular remodeling, which is characterized by left-ventricular mass expansion of 30 to 35 percent near term. In the nonpregnant state, the heart is capable of remodeling in response to stimuli such as hypertension and exercise. Such cardiac *plasticity* likely is a continuum that encompasses physiological growth—such as that in exercise, and pathological hypertrophy—such as with hypertension (Hill, 2008).

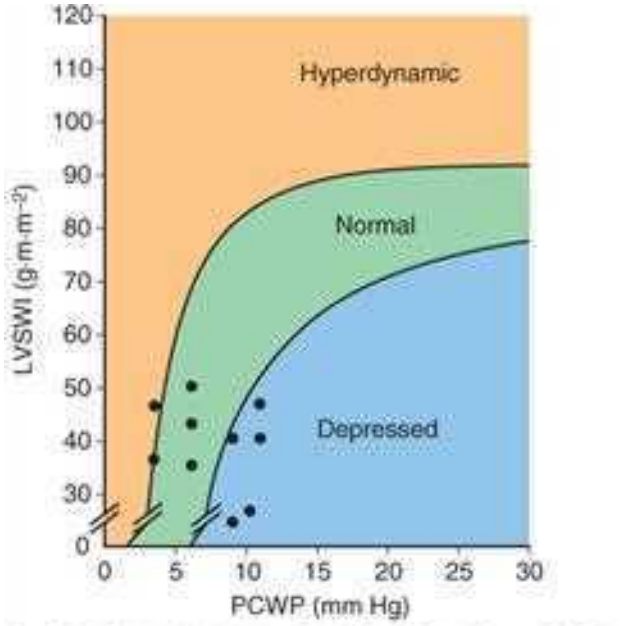
Stewart and colleagues (2016) used cardiac MR imaging to prospectively evaluate cardiac remodeling during pregnancy. Compared with the first trimester, left ventricular mass increased significantly beginning at 26 to 30 weeks' gestation, and this continued until delivery (Fig. 4-8). This remodeling is concentric and proportional to maternal size for both normal and overweight women and resolved within 3 months of delivery.

FIGURE 4-8
Left ventricular mass of normal-weight and overweight women across pregnancy compared with 12-week postpartum (nonpregnant) values. (Data from Stewart, 2016.)



Certainly for clinical purposes, ventricular function during pregnancy is normal, as estimated by the *Braunwald ventricular function* graph (Fig. 4-9). For the given filling pressures, cardiac output is appropriate and thus cardiac function during pregnancy is eudynamic. Of the metabolic changes that occur in the heart during pregnancy, the efficiency of cardiac work—which is the product of cardiac output × mean arterial pressure—is estimated to rise by approximately 25 percent. The associated increase in oxygen consumption is primarily accomplished via increased coronary blood flow rather than increased extraction (Liu, 2014).

FIGURE 4-9
Relationship between left ventricular stroke work index (LVSWI), cardiac output, and pulmonary capillary wedge pressure (PCWP) in 10 normal pregnant women in the third trimester. (Data from Clark, 1989.)



Cardiac Output

When measured in the lateral recumbent position at rest, cardiac output increases significantly beginning in early pregnancy. It continues to rise and remains elevated during the remainder of pregnancy. In a supine woman, a large uterus rather consistently compresses veins and diminishes venous return from the lower body. It also may compress the aorta (Bieniarz, 1968). In response, cardiac filling may be reduced and cardiac output lessened. Specifically, cardiac MR imaging shows that when a woman rolls from her back onto her left side, cardiac output at 26 to 30 weeks' gestation rises by approximately 20 percent and at 32 to 34 weeks by 10 percent (Nelson, 2015). Consistent with this, Simpson and James (2005) found that fetal oxygen saturation is approximately 10 percent higher if a laboring woman lies in a lateral recumbent position compared with supine. Upon standing, cardiac output falls to the same degree as in the nonpregnant woman (Easterling, 1988).

In multifetal pregnancies, compared with singletons, maternal cardiac output is augmented further by almost another 20 percent. Ghi and coworkers (2015) used transthoracic echocardiography to show that first-trimester cardiac output with twins (mean 5.50 L/min) was more than 20 percent greater than postpartum values. Cardiac output values in the second (6.31 L/min) and third (6.29 L/min) trimesters were increased an additional 15 percent compared with first-trimester output. Left atrial and left ventricular end-diastolic diameters are also longer with twins due to augmented preload (Kametas, 2003). The greater heart rate and inotropic contractility imply that cardiovascular reserve is reduced in multifetal gestations.

During first-stage labor, cardiac output rises moderately. During the second stage, with vigorous expulsive efforts, it is appreciably greater. The pregnancy-induced increase is lost after delivery, at times dependent on blood loss.

Hemodynamic Function in Late Pregnancy

Clark and associates (1989) conducted invasive studies to measure hemodynamic function late in pregnancy (Table 4-4). Right heart catheterization was performed in 10 healthy nulliparas at 35 to 38 weeks' gestation, and again at 11 to 13 weeks postpartum. Late pregnancy was associated with the expected increases in heart rate, stroke volume, and cardiac output. Systemic vascular and pulmonary vascular resistance both dropped significantly, as did colloid osmotic pressure. Pulmonary capillary wedge pressure and central venous pressure did not change appreciably. Thus, although cardiac output rises, left ventricular function as measured by stroke work index remains similar to the nonpregnant normal range (see Fig. 4-9). Put another way, normal pregnancy is not a continuous "high-output" state.

TABLE 4-4

Central Hemodynamic Changes in 10 Normal Nulliparous Women Near Term and Postpartum

	Pregnant[a] (35–38 wk)	Postpartum (11–13 wk)	Change[b]
Mean arterial pressure (mm Hg)	90 ± 6	86 ± 8	NSC
Pulmonary capillary wedge pressure (mm Hg)	8 ± 2	6 ± 2	NSC
Central venous pressure (mm Hg)	4 ± 3	4 ± 3	NSC
Heart rate (beats/min)	83 ± 10	71 ± 10	+17%
Cardiac output (L/min)	6.2 ± 1.0	4.3 ± 0.9	+43%
Systemic vascular resistance (dyn/sec/cm^{-5})	1210 ± 266	1530 ± 520	−21%
Pulmonary vascular resistance (dyn/sec/cm^{-5})	78 ± 22	119 ± 47	−34%
Serum colloid osmotic pressure (mm Hg)	18.0 ± 1.5	20.8 ± 1.0	−14%
COP-PCWP gradient (mm Hg)	10.5 ± 2.7	14.5 ± 2.5	−28%
Left ventricular stroke work index (g/m/m^2)	48 ± 6	41 ± 8	NSC

[a]Measured in lateral recumbent position.

[b]Changes significant unless NSC = no significant change.

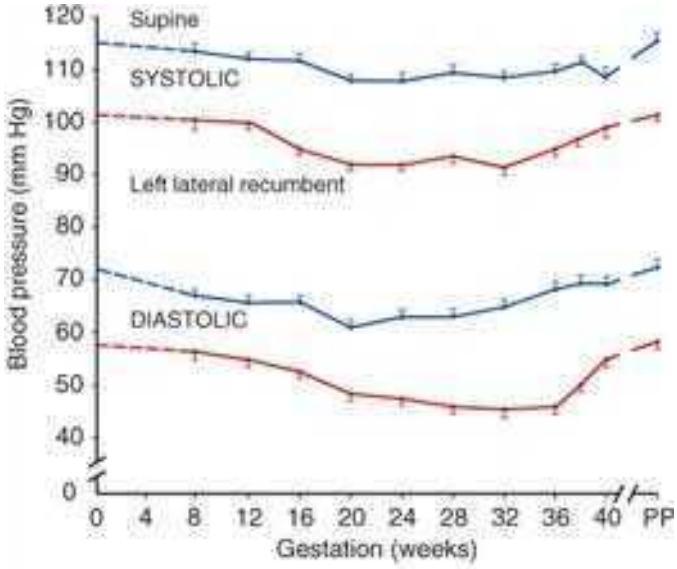
COP = colloid osmotic pressure; PCWP = pulmonary capillary wedge pressure.

Data from Clark, 1989.

Circulation and Blood Pressure

Changes in posture affect arterial blood pressure (Fig. 4-10). Brachial artery pressure when sitting is lower than that when in the lateral recumbent supine position (Bamber, 2003). Additionally, systolic blood pressure is lower in the lateral positions compared with either the flexed sitting or supine positions (Armstrong, 2011). Arterial pressure usually declines to a nadir at 24 to 26 weeks' gestation and rises thereafter. Diastolic pressure decreases more than systolic.

FIGURE 4-10
Sequential changes (±SEM) in blood pressure throughout pregnancy in 69 women in supine (*blue lines*) and left lateral recumbent positions (*red lines*). PP = postpartum. (Adapted from Wilson, 1980.)



Morris and associates (2015) studied measures of vascular compliance before pregnancy, during pregnancy, and postpartum. Compared with healthy nonpregnant controls, significant declines in mean arterial pressure and arterial stiffness, measured using pulse wave velocity, were observed between the prepregnant and the postpartum time periods. These findings suggest that pregnancy confers a favorable effect on maternal cardiovascular remodeling and may possibly help explain why the risk of preeclampsia is reduced in subsequent pregnancies.

Antecubital venous pressure remains unchanged during pregnancy. In the supine position, however, femoral venous pressure rises steadily, from approximately 8 mm Hg early in pregnancy to 24 mm Hg at term. Venous blood flow in the legs is retarded during pregnancy except when the lateral recumbent position is assumed (Wright, 1950). This tendency toward blood stagnation in the lower extremities during later pregnancy is attributable to occlusion of the pelvic veins and inferior vena cava by the enlarged uterus. The elevated venous pressure returns to normal when the pregnant woman lies on her side and immediately after delivery (McLennan, 1943). These alterations contribute to the dependent edema frequently experienced and to the development of varicose veins in the legs and vulva, as well as hemorrhoids. These changes also predispose to deep-vein thrombosis.

Supine Hypotension

In approximately 10 percent of women, supine compression of the great vessels by the uterus causes significant arterial hypotension, sometimes referred to as the *supine hypotensive syndrome* (Kinsella, 1994). Also when supine, uterine arterial pressure—and thus uterine blood flow—is significantly lower than that in the brachial artery. Evidence to support whether this directly affects fetal heart rate patterns in uncomplicated low-risk pregnancies is conflicting (Armstrong, 2011; Ibrahim, 2015; Tamás, 2007). Similar changes can also be seen with hemorrhage or with spinal analgesia.

Renin, Angiotensin II, and Plasma Volume

The renin-angiotensin-aldosterone axis is intimately involved in blood pressure control via sodium and water balance. All components of this system show increased levels in normal pregnancy. Renin is produced by both the maternal kidney and the placenta, and greater amounts of renin substrate (angiotensinogen) are produced by both maternal and fetal liver. Elevated angiotensinogen levels result, in part, from augmented estrogen production during normal pregnancy and are important in first-trimester blood pressure maintenance (Lumbers, 2014).

Gant and associates (1973) reported that nulliparas who remained normotensive became and stayed refractory to the pressor effects of infused angiotensin II. Conversely, those who ultimately became hypertensive developed, but then lost, this refractoriness. The diminished vascular responsiveness to angiotensin II may be progesterone related. Normally, pregnant women lose their acquired vascular refractoriness to angiotensin II within 15 to 30 minutes after the placenta is delivered. Large amounts of intramuscular progesterone given during late labor delay this diminishing refractoriness.

Cardiac Natriuretic Peptides

At least two species of these—*atrial natriuretic peptide (ANP)* and *brain natriuretic peptide (BNP)*—are secreted by cardiomyocytes in response to chamber-wall stretching. These peptides regulate blood volume by provoking natriuresis, diuresis, and vascular smooth-muscle relaxation. In nonpregnant and pregnant patients, levels of BNP and of amino-terminal pro-brain natriuretic peptide (Nt pro-BNP), as well as newer analytes such as suppressor of tumorigenicity 2 (ST2), may be useful in screening for depressed left ventricular systolic function and determining chronic heart failure prognosis (Ghashghaei, 2016).

During normal pregnancy, plasma ANP and BNP levels are maintained in the nonpregnant range despite greater plasma volume (Yurteri-Kaplan, 2012). In one study, median BNP levels were stable across pregnancy with values <20 pg/mL (Resnik, 2005). BNP levels are increased in severe preeclampsia, and this may be caused by cardiac strain from increased afterload (Afshani, 2013). It would appear that ANP-induced physiological adaptations participate in extracellular fluid volume expansion and in the elevated plasma aldosterone concentrations characteristic of normal pregnancy.

Prostaglandins

Elevated prostaglandin production during pregnancy is thought to have a central role in control of vascular tone, blood pressure, and sodium balance. Renal medullary prostaglandin E_2 synthesis is markedly elevated during late pregnancy and is presumed to be natriuretic. Levels of prostacyclin (PGI_2), the principal prostaglandin of endothelium, also rise during late pregnancy. PGI_2 regulates blood pressure and platelet function. It helps maintain vasodilation during pregnancy, and its deficiency is associated with pathological vasoconstriction (Shah, 2015). Thus, the ratio of PGI_2 to thromboxane in maternal urine and blood is considered important in preeclampsia pathogenesis (Majed, 2012).

Endothelin

Several endothelins are generated in pregnancy. Endothelin-1 is a potent vasoconstrictor produced in endothelial and vascular smooth muscle cells and regulates local vasomotor tone (George, 2011; Lankhorst, 2016). Its production is stimulated by angiotensin II, arginine vasopressin, and thrombin. Endothelins, in turn, stimulate secretion of ANP, aldosterone, and catecholamines. Vascular sensitivity to endothelin-1 is not altered during normal pregnancy. Pathologically elevated levels may play a role in preeclampsia (Saleh, 2016).

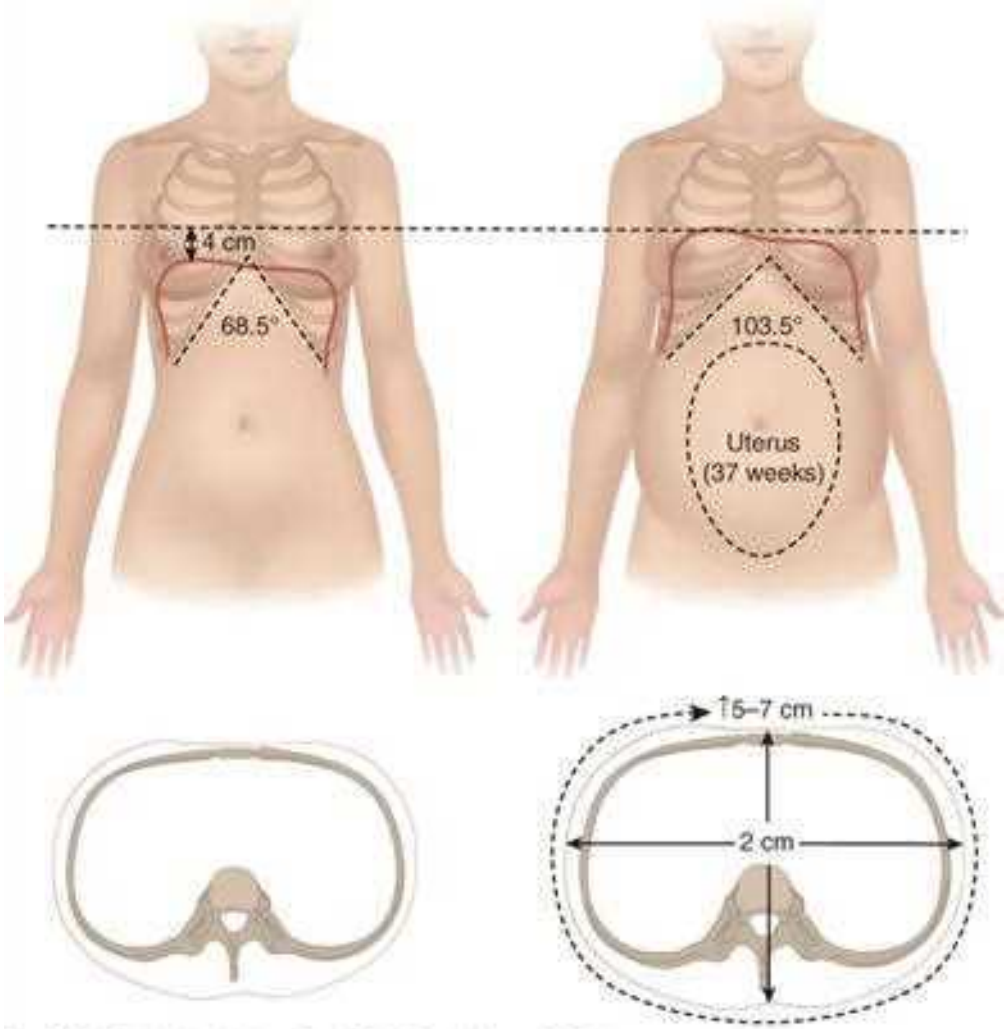
Nitric Oxide

This potent vasodilator is released by endothelial cells and may modify vascular resistance during pregnancy. Moreover, nitric oxide is an important mediator of placental vascular tone and development (Krause, 2011; Kulandavelu, 2013). Abnormal nitric oxide synthesis has been linked to preeclampsia development (Laskowska, 2015; Vignini, 2016).

RESPIRATORY TRACT

Of anatomic changes, the diaphragm rises approximately 4 cm during pregnancy (Fig. 4-11). The subcostal angle widens appreciably as the transverse diameter of the thoracic cage lengthens approximately 2 cm. The thoracic circumference increases about 6 cm, but not sufficiently to prevent reduced residual lung volumes created by the elevated diaphragm. Even so, diaphragmatic excursion is greater in pregnant than in nonpregnant women.

FIGURE 4-11
Chest wall measurements in nonpregnant (*left*) and pregnant women (*right*). The subcostal angle increases, as does the anteroposterior and transverse diameters of the chest wall and chest wall circumference. These changes compensate for the 4-cm elevation of the diaphragm so that total lung capacity is not significantly reduced. (Redrawn with permission from Hegewald MJ, Crapo RO: Respiratory physiology in pregnancy. Clin Chest Med 32(1):1, 2011.)

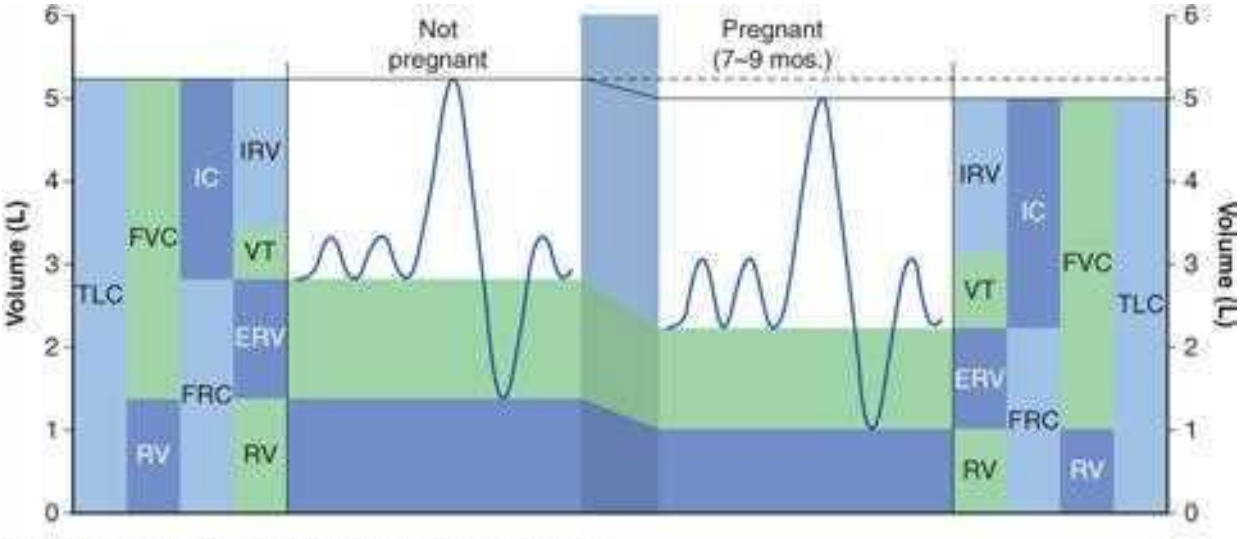


Pulmonary Function

Of physiological lung changes, *functional residual capacity (FRC)* decreases by approximately 20 to 30 percent or 400 to 700 mL during pregnancy (Fig. 4-12). This capacity is composed of *expiratory reserve volume*—which drops 15 to 20 percent or 200 to 300 mL—and *residual volume*—which decreases 20 to 25 percent or 200 to 400 mL. FRC and residual volume decline progressively across pregnancy due to diaphragm elevation. Significant reductions are observed by the sixth month. *Inspiratory capacity,* the maximum volume that can be inhaled from FRC, rises by 5 to 10 percent or 200 to 350 mL during pregnancy. *Total lung capacity*—the combination of FRC and inspiratory capacity—is unchanged or decreases by less than 5 percent at term (Hegewald, 2011).

FIGURE 4-12

Changes in lung volumes with pregnancy. The most significant changes are reduction in functional residual capacity (FRC) and its subcomponents, expiratory reserve volume (ERV) and residual volume (RV), as well as increases in inspiratory capacity (IC) and tidal volume (VT). (Redrawn with permission from Hegewald MJ, Crapo RO: Respiratory physiology in pregnancy. Clin Chest Med 32(1):1, 2011.)



The respiratory rate is essentially unchanged, but *tidal volume* and *resting minute ventilation* increase significantly as pregnancy advances. Kolarzyk and coworkers (2005) reported significantly greater mean tidal volumes—0.66 to 0.8 L/min—and resting minute ventilations—10.7 to 14.1 L/min—compared with those of nonpregnant women. The elevated minute ventilation is caused by several factors. These include enhanced respiratory drive primarily due to the stimulatory action of progesterone, low expiratory reserve volume, and compensated respiratory alkalosis (Heenan, 2003). Decreased plasma osmolality also results in less respiratory depression (Moen, 2014). This provides an additional mechanism for the increased minute ventilation seen in pregnancy, and one that is not dependent on progesterone.

Regarding pulmonary function, *peak expiratory flow rates* rise progressively as gestation advances (Grindheim, 2012). *Lung compliance* is unaffected by pregnancy. *Airway conductance* is increased and *total pulmonary resistance* reduced, possibly as a result of progesterone. The *maximum breathing capacity* and *forced* or *timed vital capacity* are not altered appreciably. It is unclear whether the critical *closing volume*—the lung volume at which airways in the dependent parts of the lung begin to close during expiration—is higher in pregnancy (Hegewald, 2011). Pulmonary function with a singleton pregnancy does not significantly differ from that with twins (McAuliffe, 2002; Siddiqui, 2014). Importantly, the greater oxygen requirements and perhaps the increased critical closing volume imposed by pregnancy make respiratory diseases more serious.

Demir and colleagues (2015) studied nasal physiology in 85 pregnant women. Although the minimal cross-sectional area decreased between the first and third trimesters, subjective reports of nasal congestion or total nasal resistance did not significantly differ among trimesters or compared with nonpregnant controls.

Oxygen Delivery

The amount of oxygen delivered into the lungs by the increased tidal volume clearly exceeds oxygen requirements imposed by pregnancy. Moreover, the total hemoglobin mass and, in turn, total oxygen-carrying capacity rise appreciably during normal pregnancy, as does cardiac output. Consequently, the *maternal arteriovenous oxygen* difference is diminished. Oxygen consumption grows approximately 20 percent during pregnancy, and it is approximately 10 percent higher in multifetal gestations (Ajjimaporn, 2014). During labor, oxygen consumption increases 40 to 60 percent (Bobrowski, 2010).

Acid–Base Equilibrium

A greater awareness of a desire to breathe is common even early in pregnancy (Milne, 1978). This may be interpreted as dyspnea, which may suggest pulmonary or cardiac abnormalities when none exist. This physiological dyspnea, which should not interfere with normal physical activity, is thought to result from greater tidal volume that lowers the blood P_{CO_2} slightly and paradoxically causes dyspnea. The increased respiratory effort during pregnancy, and in turn the reduction in the partial pressure of carbon dioxide in blood (P_{CO_2}), is likely induced in large part by progesterone and to a lesser degree by estrogen. Progesterone acts centrally, where it lowers the threshold and raises the sensitivity of the chemoreflex response to carbon dioxide (CO_2) (Jensen, 2005).

To compensate for the resulting respiratory alkalosis, plasma bicarbonate levels normally drop from 26 to 22 mmol/L. Although blood pH is increased only minimally, it does shift the oxygen dissociation curve to the left. This shift increases the affinity of maternal hemoglobin for oxygen—the *Bohr effect*—thereby lowering the oxygen-releasing capacity of maternal blood. This is offset because the slight pH rise also stimulates an increase in 2,3-diphosphoglycerate in maternal erythrocytes. This shifts the curve back to the right (Tsai, 1982). Thus, reduced P_{CO_2} from maternal hyperventilation aids CO_2 (waste) transfer from the fetus to the mother while also aiding oxygen release to the fetus.

URINARY SYSTEM

Kidney

The urinary system undergoes several remarkable changes in pregnancy (Table 4-5). *Kidney size* grows approximately 1.0 cm (Cietak, 1985). Both the *glomerular filtration rate (GFR)* and *renal plasma flow* increase early in pregnancy. The GFR rises as much as 25 percent by the second week after conception and 50 percent by the beginning of the second trimester. This hyperfiltration results from two principal factors. First, hypervolemia-induced hemodilution lowers the protein concentration and oncotic pressure of plasma entering the glomerular microcirculation. Second, renal plasma flow increases by approximately 80 percent before the end of the first trimester (Conrad, 2014b; Odutayo, 2012). As shown in Figure 4-13, elevated GFR persists until term, even though renal plasma flow declines during late pregnancy. Primarily as a consequence of this elevated GFR, approximately 60 percent of nulliparas during the third trimester experience urinary frequency, and 80 percent experience nocturia (Frederice, 2013).

TABLE 4-5

Renal Changes in Normal Pregnancy

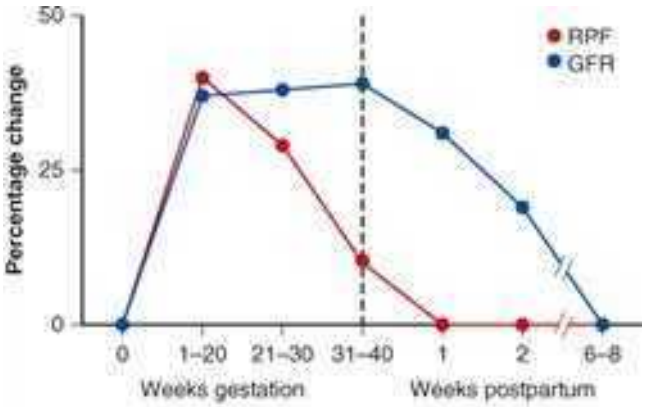
Parameter	Alteration	Clinical Relevance
Kidney size	Approximately 1 cm longer on radiograph	Size returns to normal postpartum
Dilatation	Resembles hydronephrosis on sonogram or IVP (more marked on right)	Can be confused with obstructive uropathy; retained urine leads to collection errors; renal infections are more virulent; may be responsible for "distention syndrome"; elective pyelography should be deferred to at least 12 weeks postpartum
Renal function	Glomerular filtration rate and renal plasma flow increase ~50%	Serum creatinine decreases during normal gestation; >0.8 mg/dL (>72 µmol/L) creatinine already borderline; protein, amino acid, and glucose excretion all increase
Maintenance of acid-base	Decreased bicarbonate threshold; progesterone stimulates respiratory center	Serum bicarbonate decreased by 4–5 mEq/L; P_{CO_2} decreased 10 mm Hg; a P_{CO_2} of 40 mm Hg already represents CO_2 retention
Plasma osmolality	Osmoregulation altered; osmotic thresholds for AVP release and thirst decrease; hormonal disposal rates increase	Serum osmolality decreases 10 mOsm/L (serum Na ~5 mEq/L) during normal gestation; increased placental metabolism of AVP may cause transient diabetes insipidus during pregnancy

AVP = vasopressin; IVP = intravenous pyelography; P_{CO_2}= partial pressure carbon dioxide.

Modified from Lindheimer, 2000.

FIGURE 4-13

Percentage increment in glomerular filtration rate (GFR) and renal plasma flow (RPF) across gestation and in the puerperium. (Data from Odutayo, 2012.)



During the puerperium, a marked GFR persists during the first postpartum day, principally from the reduced glomerular capillary oncotic pressure. A reversal of the gestational hypervolemia and hemodilution, still evident on the first postpartum day, eventuates by the second week postpartum (Odutayo, 2012).

Studies suggest that relaxin, discussed earlier (Fallopian Tubes), may mediate both increased GFR and renal blood flow during pregnancy (Conrad, 2014a; Helal, 2012). Relaxin boosts renal nitric oxide production, which leads to renal vasodilation and lowered renal afferent and efferent arteriolar resistance. This augments renal blood flow and GFR (Bramham, 2016). Relaxin may also increase vascular gelatinase activity during pregnancy, which leads to renal vasodilation, glomerular hyperfiltration, and reduced myogenic reactivity of small renal arteries (Odutayo, 2012).

As with blood pressure, maternal posture may considerably influence several aspects of renal function. Late in pregnancy, the sodium excretion rate in the supine position averages less than half that in the lateral recumbent position. The effects of posture on GFR and renal plasma flow vary.

One unusual feature of the pregnancy-induced changes in renal excretion is the remarkably increased amounts of some nutrients lost in the urine. Amino acids and water-soluble vitamins are excreted in much greater amounts (Shibata, 2013).

Renal Function Tests

Of renal function tests, serum creatinine levels decline during normal pregnancy from a mean of 0.7 to 0.5 mg/dL. *Values of 0.9 mg/dL or greater suggest underlying renal disease and prompt further evaluation.* Creatinine clearance in pregnancy averages 30 percent higher than the 100 to 115 mL/min in nonpregnant women. This is a useful test to estimate renal function, provided that complete urine collection is made during an accurately timed period. If this is not done precisely, results are misleading (Lindheimer, 2000, 2010). During the day, pregnant women tend to accumulate water as dependent edema, and at night, while recumbent, they mobilize this fluid with diuresis. This reversal of the usual nonpregnant diurnal pattern of urinary flow causes nocturia, and urine is more dilute than in nonpregnant women. Failure of a pregnant woman to excrete concentrated urine after withholding fluids for approximately 18 hours does not necessarily signify renal damage. In fact, the kidneys in these circumstances function perfectly normally by excreting mobilized extracellular fluid of relatively low osmolality.

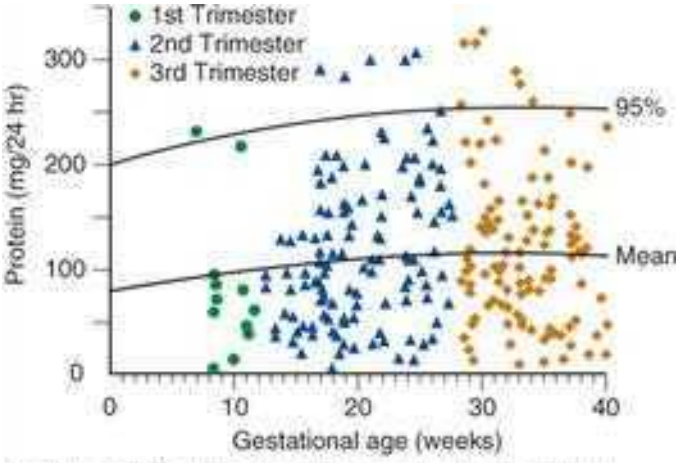
Urinalysis

Glucosuria during pregnancy may not be abnormal. The appreciably increased GFR, together with impaired tubular reabsorptive capacity for filtered glucose, accounts for most cases of glucosuria. Chesley (1963) calculated that about a sixth of pregnant women will spill glucose in the urine. That said, although common during pregnancy, when glucosuria is identified, a search for diabetes mellitus is pursued.

Hematuria frequently results from contamination during collection. If not, it most often suggests urinary tract disease or infection. Hematuria is common after difficult labor and delivery because of trauma to the bladder and urethra.

Proteinuria is typically defined in nonpregnant subjects as a protein excretion rate of more than 150 mg/d. Because of the aforementioned hyperfiltration and possible reduction of tubular reabsorption, proteinuria during pregnancy is usually considered significant once a protein excretion threshold of at least 300 mg/d is reached (Odutayo, 2012). Higby and coworkers (1994) measured protein excretion in 270 normal women throughout pregnancy (Fig. 4-14). Mean 24-hour excretion for all three trimesters was 115 mg, and the upper 95-percent confidence limit was 260 mg/d without significant differences by trimester. They showed that albumin excretion is minimal and ranges from 5 to 30 mg/d. Proteinuria increases with gestational age, which corresponds with the peak in GFR (see Fig. 4-13)(Odutayo, 2012).

FIGURE 4-14
Scatter plot of women showing 24-hour urinary total protein excretion by gestational age. Mean and 95-percent confidence limits are outlined. (Redrawn with permission from Higby K, Suiter CR, Phelps JY, et al: Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol 171:984, 1994.)



Measuring Urine Protein

The three most commonly employed approaches for assessing proteinuria are the qualitative classic dipstick, the quantitative 24-hour collection, and the albumin/creatinine or protein/creatinine ratio of a single voided urine specimen. The pitfalls of each approach have been reviewed by Conrad (2014b) and Bramham (2016) and their colleagues. The principal problem with dipstick assessment is that it fails to account for renal concentration or dilution of urine. For example, with polyuria and extremely dilute urine, a negative or trace dipstick could actually be associated with excessive protein excretion.

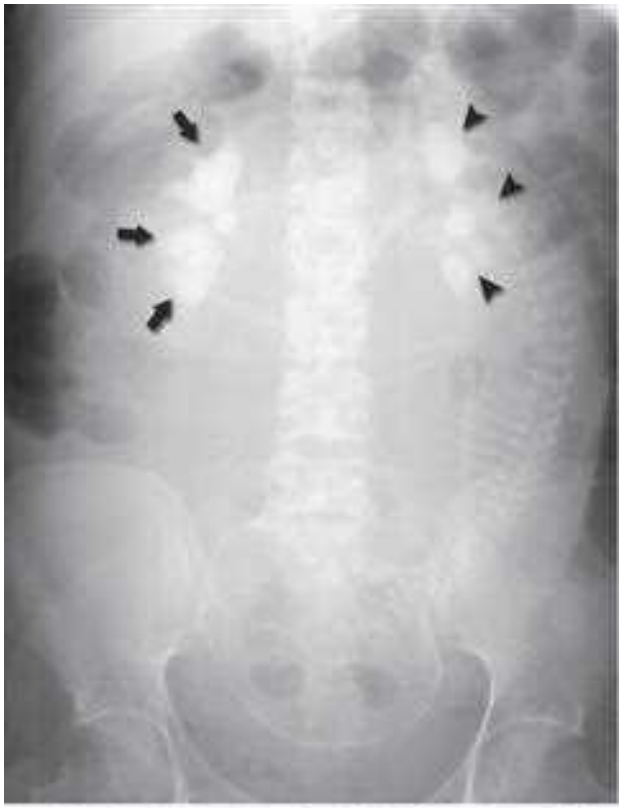
The 24-hour urine collection is affected by urinary tract dilatation, which is discussed in the next section. The dilated tract may lead to errors related both to retention—hundreds of milliliters of urine remaining in the dilated tract—and to timing—the remaining urine may have formed hours before the collection. To minimize these pitfalls, the patient is first hydrated and positioned in lateral recumbency—the definitive nonobstructive posture—for 45 to 60 minutes. After this, she is asked to void, and this specimen is discarded. Immediately following this void, her 24-hour collection begins. During the final hour of collection, the patient is again placed in the lateral recumbent position. But, at the end of this hour, the final collected urine is incorporated into the total collected volume (Lindheimer, 2010).

Last, the protein/creatinine ratio is a promising approach because data can be obtained quickly and collection errors are avoided. Disadvantageously, the amount of protein per unit of creatinine excreted during a 24-hour period is not constant, and the thresholds to define abnormal vary. Nomograms for urinary microalbumin and creatinine ratios during uncomplicated pregnancies have been developed (Waugh, 2003).

Ureters

After the uterus completely rises out of the pelvis, it rests on the ureters. This laterally displaces and compresses them at the pelvic brim. Above this level, elevated intraureteral tonus results, and ureteral dilatation is impressive (Rubi, 1968). It is right sided in 86 percent of women (Fig. 4-15) (Schulman, 1975). This unequal dilatation may result from cushioning provided the left ureter by the sigmoid colon and perhaps from greater right ureteral compression exerted by the dextrorotated uterus. The right ovarian vein complex, which is remarkably dilated during pregnancy, lies obliquely over the right ureter and may also contribute to right ureteral dilatation.

FIGURE 4-15
Hydronephrosis. Plain film from the 15-minute image of an intravenous pyelogram (IVP). Moderate hydronephrosis on the right (*arrows*) and mild hydronephrosis on the left (*arrowheads*) are both normal for this 35-week gestation.



Progesterone likely has some additional effect. Van Wagenen and Jenkins (1939) described continued ureteral dilatation after removal of the monkey fetus but with the placenta left in situ. The relatively abrupt onset of dilatation in women at midpregnancy, however, seems more consistent with ureteral compression.

Ureteral elongation accompanies distention, and the ureter is frequently thrown into curves of varying size, the smaller of which may be sharply angulated. These so-called kinks are poorly named, because the term connotes obstruction. They are usually single or double curves that, when viewed in a radiograph taken in the same plane as the curve, may appear as acute angulations. Another exposure at right angles nearly always identifies them to be gentle curves. Despite these anatomical changes, complication rates associated with ureteroscopy in pregnant and nonpregnant patients do not differ significantly (Semins, 2014).

Bladder

The bladder shows few significant anatomical changes before 12 weeks' gestation. Subsequently, however, increased uterine size, the hyperemia that affects all pelvic organs, and hyperplasia of bladder muscle and connective tissues elevate the trigone and thicken its intraureteric margin. Continuation of this process to term produces marked deepening and widening of the trigone. The bladder mucosa is unchanged other than an increase in the size and tortuosity of its blood vessels.

Bladder pressure in primigravidas increases from 8 cm H_2O early in pregnancy to 20 cm H_2O at term (Iosif, 1980). To compensate for reduced bladder capacity, absolute and functional urethral lengths increased by 6.7 and 4.8 mm, respectively. Concurrently, maximal intraurethral pressure rises from 70 to 93 cm H_2O, and thus continence is maintained. Still, at least half of women experience some degree of urinary incontinence by the third trimester (Abdullah, 2016a). Indeed, this is always considered in the differential diagnosis of ruptured membranes. Near term—particularly in nulliparas, in whom the presenting part often engages before labor—the entire base of the bladder is pushed ventral and cephalad. This converts the normally convex surface into a concavity. As a result, difficulties in diagnostic

and therapeutic procedures are greatly accentuated. Moreover, pressure from the presenting part impairs blood and lymph drainage from the bladder base, often rendering the area edematous, easily traumatized, and possibly more susceptible to infection.

GASTROINTESTINAL TRACT

As pregnancy progresses, the stomach and intestines are displaced cephalad by the enlarging uterus. Consequently, the physical findings in certain diseases are altered. The appendix, for instance, is usually displaced upward and somewhat laterally. At times, it may reach the right flank.

Pyrosis (heartburn) is common during pregnancy and is most likely caused by reflux of acidic secretions into the lower esophagus. Although the altered stomach position probably contributes to its frequency, lower esophageal sphincter tone also is decreased. In addition, intraesophageal pressures are lower and intragastric pressures higher in pregnant women. Concurrently, esophageal peristalsis has lower wave speed and lower amplitude (Ulmsten, 1978).

Gastric emptying time is unchanged during each trimester and compared with nonpregnant women (Macfie, 1991; Wong, 2002, 2007). During labor, however, and especially after administration of analgesics, gastric emptying time may be appreciably prolonged. As a result, one danger of general anesthesia for delivery is regurgitation and aspiration of either food-laden or highly acidic gastric contents.

Hemorrhoids are common during pregnancy (Shin, 2015). They are caused in large measure by constipation and elevated pressure in rectal veins below the level of the enlarged uterus.

Liver

Liver size does not enlarge during human pregnancy. Hepatic arterial and portal venous blood flow, however, increase substantively (Clapp, 2000).

Some laboratory test results of hepatic function are altered in normal pregnancy (Appendix, Serum and Blood Constituents). Total alkaline phosphatase activity almost doubles, but much of the rise is attributable to heat-stable placental alkaline phosphatase isozymes. Serum aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transpeptidase (GGT), and bilirubin levels are slightly lower compared with nonpregnant values (Cattozzo, 2013; Ruiz-Extremera, 2005).

The serum albumin concentration declines during pregnancy. By late pregnancy, albumin levels may be near 3.0 g/dL compared with approximately 4.3 g/dL in nonpregnant women (Mendenhall, 1970). Total body albumin levels rise, however, because of pregnancy-associated increased plasma volume. Serum globulin levels are also slightly higher.

Leucine aminopeptidase is a proteolytic liver enzyme whose serum levels may be increased with liver disease. Its activity is markedly elevated in pregnant women. The rise, however, results from a pregnancy-specific enzyme(s) with distinct substrate specificities (Song, 1968). Pregnancy-induced aminopeptidase has oxytocinase and vasopressinase activity that occasionally causes transient diabetes insipidus.

Gallbladder

During normal pregnancy, gallbladder contractility is reduced and leads to greater residual volume (Braverman, 1980). Progesterone potentially impairs gallbladder contraction by inhibiting cholecystokinin-mediated smooth muscle stimulation, which is the primary regulator of gallbladder contraction. Impaired emptying, subsequent stasis, and the increased cholesterol saturation of bile in pregnancy contribute to the increased prevalence of cholesterol gallstones in multiparas. In one study, approximately 8 percent of women had gallbladder sludge or stones when imaged at 18 and/or 36 weeks' gestation (Ko, 2014).

The pregnancy effects on maternal serum bile acid concentrations are still incompletely characterized. This is despite the long-acknowledged propensity for pregnancy to cause intrahepatic cholestasis and pruritus gravidarum from retained bile salts. Cholestasis of pregnancy is described in Chapter 55 (Intrahepatic Cholestasis of Pregnancy).

ENDOCRINE SYSTEM

Pituitary Gland

During normal pregnancy, the pituitary gland enlarges by approximately 135 percent (Gonzalez, 1988). This increase may sufficiently compress the optic chiasma to reduce visual fields. Impaired vision from this is rare and usually due to macroadenomas (Lee, 2014). Pituitary enlargement is primarily caused by estrogen-stimulated hypertrophy and hyperplasia of the lactotrophs (Feldt-Rasmussen, 2011). And, as discussed subsequently, maternal serum prolactin levels parallel the increasing size. Gonadotrophs decline in number, and corticotrophs and thyrotrophs remain constant. Somatotrophs are generally suppressed due to negative feedback by the placental production of growth hormone.

Peak pituitary size may reach 12 mm in MR images in the first days postpartum. The gland then involutes rapidly and reaches normal size by 6 months postpartum (Feldt-Rasmussen, 2011). The incidence of pituitary prolactinomas is not increased during pregnancy (Scheithauer, 1990). When these tumors are large before pregnancy—a macroadenoma measuring ≥10 mm—then growth during pregnancy is more likely (Chap. 58, Pituitary Disorders).

The maternal pituitary gland is not essential for pregnancy maintenance. Many women have undergone hypophysectomy, completed pregnancy successfully, and entered spontaneous labor while receiving compensatory glucocorticoids, thyroid hormone, and vasopressin.

Growth Hormone

During the first trimester, growth hormone is secreted predominantly from the maternal pituitary gland, and concentrations in serum and amnionic fluid lie within the nonpregnant range of 0.5 to 7.5 ng/mL (Kletzky, 1985). As early as 6 weeks' gestation, growth hormone secreted from the placenta becomes detectable, and by approximately 20 weeks, the placenta is the principal source of growth hormone secretion (Pérez-Ibave, 2014). Maternal serum values rise slowly from approximately 3.5 ng/mL at 10 weeks to plateau at about 14 ng/mL after 28 weeks. Growth hormone in amnionic fluid peaks at 14 to 15 weeks and slowly declines thereafter to reach baseline values after 36 weeks.

Placental growth hormone—which differs from pituitary growth hormone by 13 amino acid residues—is secreted by syncytiotrophoblast in a nonpulsatile fashion (Newbern, 2011). Its regulation and physiological effects are incompletely understood, but it influences fetal growth via upregulation of insulin-like growth factor 1 (IGF-1). Higher levels have been linked with development of preeclampsia (Mittal, 2007; Pérez-Ibave, 2014). Further, placental expression correlates positively with birthweight but negatively with fetal-growth restriction (Koutsaki, 2011). Maternal serum levels are associated with uterine artery resistance changes (Schiessl, 2007). That said, fetal growth still progresses in the complete absence of this hormone. Although not absolutely essential, the hormone may act in concert with placental lactogen to regulate fetal growth (Newbern, 2011).

Prolactin

Maternal plasma prolactin levels increase markedly during normal pregnancy. Concentrations are usually tenfold greater at term—about 150 ng/mL—compared with those of nonpregnant women. Paradoxically, plasma concentrations drop after delivery even in women who are breastfeeding. During early lactation, pulsatile bursts of prolactin secretion are a response to suckling.

The principal function of maternal prolactin is to ensure lactation. Early in pregnancy, prolactin acts to initiate DNA synthesis and mitosis of glandular epithelial cells and presecretory alveolar cells of the breast. Prolactin also augments the number of estrogen and prolactin receptors in these cells. Finally, prolactin promotes mammary alveolar cell RNA synthesis, galactopoiesis, and production of casein, lactalbumin, lactose, and lipids (Andersen, 1982). A woman with isolated prolactin deficiency failed to lactate after two pregnancies (Kauppila, 1987). This establishes prolactin as a requisite for lactation but not for pregnancy. Grattan (2015) has reviewed the numerous physiological roles of prolactin for facilitating maternal adaptations to pregnancy. A possible role is proposed for a prolactin fragment in the genesis of peripartum cardiomyopathy (Chap. 49, Dilated Cardiomyopathy) (Cunningham, 2012).

Prolactin is present in amnionic fluid in high concentrations. Levels of up to 10,000 ng/mL are found at 20 to 26 weeks' gestation. Thereafter, levels decline and reach a nadir after 34 weeks. Uterine decidua is the synthesis site of prolactin found in amnionic fluid. Although the exact function of amnionic fluid prolactin is unknown, impaired water transfer from the fetus into the maternal compartment to thereby prevent fetal dehydration is one suggestion.

Oxytocin and Antidiuretic Hormone

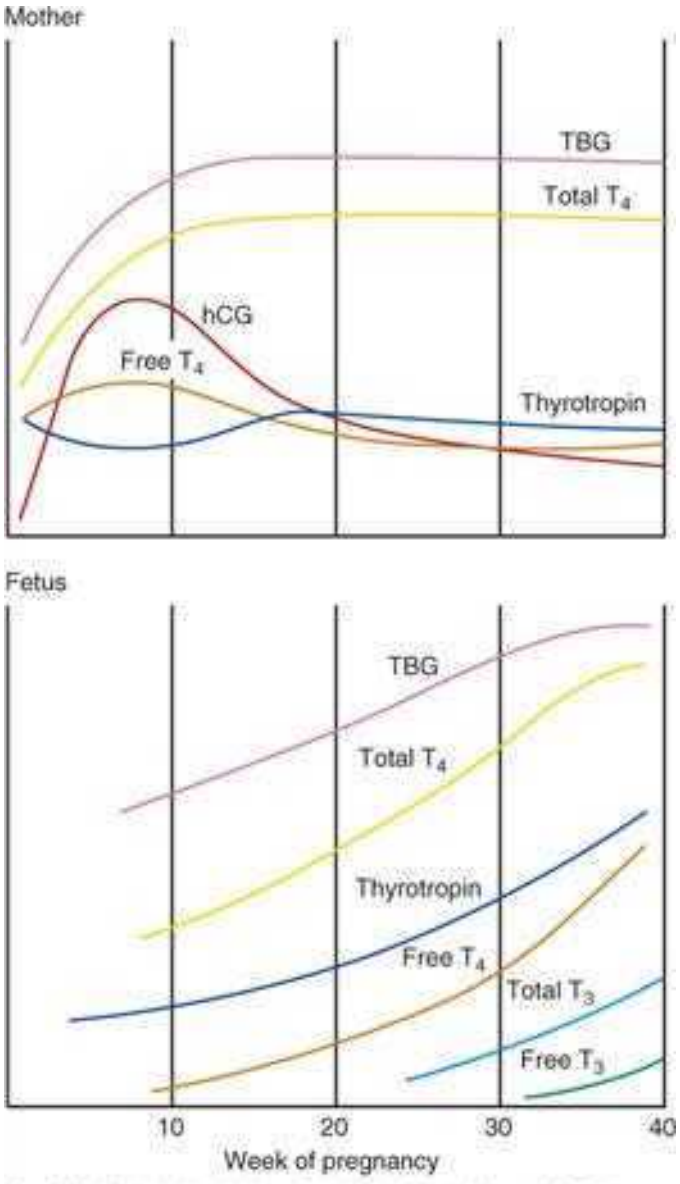
These two hormones are secreted from the posterior pituitary gland. The roles of oxytocin in parturition and lactation are discussed in Chapters 21 (Uterotonins in Parturition Phase 3) and 36 (Endocrinology of Lactation), respectively. Brown and colleagues (2013) have reviewed the complex mechanisms that promote quiescence of oxytocin systems during pregnancy. Levels of antidiuretic hormone, also called vasopressin, do not change during pregnancy.

Thyroid Gland

Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates thyrotrope cells of the anterior pituitary to release *thyroid-stimulating hormone (TSH),* also called *thyrotropin.* TRH levels do not rise during normal pregnancy. However, TRH does cross the placenta and may serve to stimulate the fetal pituitary to secrete TSH (Thorpe-Beeston, 1991).

Serum TSH and hCG levels vary with gestational age (Fig. 4-16). As discussed in Chapter 5 (Placental Hormones), the α-subunits of the two glycoproteins are identical, whereas the β-subunits, although similar, differ in their amino acid sequence. As a result of this structural similarity, hCG has intrinsic thyrotropic activity, and thus, high serum hCG levels cause thyroid stimulation. Indeed, TSH levels in the first trimester decline in more than 80 percent of pregnant women, however, they still remain in the normal range for nonpregnant women

FIGURE 4-16
Relative changes in maternal and fetal thyroid function across pregnancy. Maternal changes include a marked and early increase in hepatic production of thyroxine-binding globulin (TBG) and placental production of human chorionic gonadotropin (hCG). Increased TBG increases serum thyroxine (T_4) concentrations. hCG has thyrotropin-like activity and stimulates maternal free T_4 secretion. This transient hCG-induced increase in serum T_4 levels inhibits maternal secretion of thyrotropin. Except for minimally increased free T_4 levels when hCG peaks, these levels are essentially unchanged. Fetal levels of all serum thyroid analytes increase incrementally across pregnancy. Fetal triiodothyronine (T_3) does not increase until late pregnancy. (Modified from Burrow, 1994.)



The thyroid gland boosts production of thyroid hormones by 40 to 100 percent to meet maternal and fetal needs (Moleti, 2014). To accomplish this, the thyroid gland undergoes moderate enlargement during pregnancy caused by glandular hyperplasia and greater vascularity. Mean thyroid volume increases from 12 mL in the first trimester to 15 mL at term (Glinoer, 1990). That said, normal pregnancy does not typically cause significant thyromegaly, and thus any goiter warrants evaluation.

Early in the first trimester, levels of the principal carrier protein—*thyroid-binding globulin (TBG)*—rise, reach their zenith at about 20 weeks, and stabilize at approximately double baseline values for the remainder of pregnancy (see Fig. 4-16). The greater TBG concentrations result from both higher hepatic synthesis rates—due to estrogen stimulation—and lower metabolism rates due to greater TBG sialylation and glycosylation. These elevated TBG levels increase total serum thyroxine (T_4) and triiodothyronine (T_3) concentrations, but do not affect the physiologically important serum *free* T_4 and *free* T_3 levels. Specifically, total serum T_4 levels rise sharply beginning between 6 and 9 weeks' gestation and reach a plateau at 18 weeks. Serum free T_4 levels rise only slightly and peak along with hCG levels, and then they return to normal.

Interestingly, T_4 and T_3 secretion is not similar for all pregnant women (Glinoer, 1990). Approximately a third of women experience relative hypothyroxinemia, preferential T_3 secretion, and higher, albeit normal, serum TSH levels. Thus, thyroidal adjustments during normal pregnancy may vary considerably.

The fetus relies on maternal T_4, which crosses the placenta in small quantities to maintain normal fetal thyroid function (Chap. 58, Thyroid Disorders). Recall that the fetal thyroid does not begin to concentrate iodine until 10 to 12 weeks' gestation. The synthesis and secretion of thyroid hormone by fetal pituitary TSH ensues at approximately 20 weeks. At birth, approximately 30 percent of the T_4 in umbilical cord blood is of maternal origin (Leung, 2012).

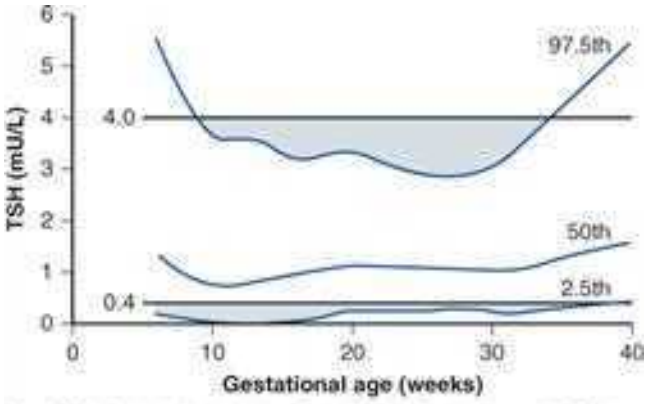
Thyroid Function Tests

Normal suppression of TSH during pregnancy may lead to a misdiagnosis of subclinical hyperthyroidism. Of greater concern is the potential failure to identify women with early hypothyroidism because of suppressed TSH concentrations. To mitigate the likelihood of such misdiagnoses, Dashe and coworkers (2005) conducted a

population-based study at Parkland Hospital to develop gestational-age-specific TSH normal curves for both singleton and twin pregnancies (Fig. 4-17). Similarly, Ashoor and associates (2010) established normal ranges for maternal TSH, free T_4, and free T_3 at 11 to 13 weeks' gestation.

FIGURE 4-17

Gestational age-specific thyroid-stimulating hormone (TSH) nomogram derived from 13,599 singleton pregnancies. The nonpregnant reference values of 4.0 and 0.4 mU/L are represented as solid black lines. Upper shaded area represents the 28 percent of singleton pregnancies with TSH values above the 97.5th percentile threshold that would not have been identified as abnormal based on the assay reference value of 4.0 mU/L. Lower shaded area represents singleton pregnancies that would have been (falsely) identified as having TSH suppression based on the assay reference value of 0.4 mU/L. (Data from Dashe, 2005.)



These complex alterations of thyroid regulation do not appear to alter maternal thyroid status as measured by metabolic studies. Although basal metabolic rate increases progressively by as much as 25 percent during normal pregnancy, most of this greater oxygen consumption can be attributed to fetal metabolic activity. If fetal body surface area is considered along with that of the mother, the predicted and observed basal metabolic rates are similar to those in nonpregnant women.

Iodine Status

Iodine requirements increase during normal pregnancy (Chap. 58, Congenital Hypothyroidism). In women with low or marginal intake, deficiency may manifest as low T_4 and higher TSH levels. Importantly, more than a third of the world population lives in areas where iodine intake is marginal. For the fetus, early exposure to thyroid hormone is essential for the nervous system, and despite public health programs to supplement iodine, severe iodine deficiency resulting in cretinism affects more than 2 million people globally (Syed, 2015).

Parathyroid Glands

In one longitudinal investigation of 20 women, all markers of bone turnover rose during normal pregnancy and failed to reach baseline levels by 12 months postpartum (More, 2003). Investigators concluded that the calcium needed for fetal growth and lactation may be drawn at least in part from the maternal skeleton. The factors affecting bone turnover yield a net result favoring fetal skeletal formation at the expense of the mother, such that pregnancy is a vulnerable period for osteoporosis (Sanz-Salvador, 2015). That said, prevention is difficult due to a paucity of identifiable risk factors.

Parathyroid Hormone

Acute or chronic declines in plasma calcium or acute drops in magnesium levels stimulate parathyroid hormone (PTH) release. Conversely, greater calcium and magnesium levels suppress PTH levels. The action of this hormone on bone resorption, intestinal absorption, and kidney reabsorption is to raise extracellular fluid calcium concentrations and lower phosphate levels.

Fetal skeleton mineralization requires approximately 30 g of calcium, primarily during the third trimester (Sanz-Salvador, 2015). Although this amounts to only 3 percent of the total calcium held within the maternal skeleton, the provision of calcium still challenges the mother. In most circumstances, augmented maternal calcium absorption provides the additional calcium. During pregnancy, the amount of calcium absorbed rises gradually and reaches approximately 400 mg/d in the third trimester. Greater calcium absorption appears to be mediated by elevated maternal 1,25-dihydroxyvitamin D concentrations. This occurs despite decreased PTH levels during early pregnancy, which is the normal stimulus for active vitamin D production within the kidney. Indeed, PTH plasma concentrations decline during the first trimester and then rise progressively throughout the remainder of pregnancy (Pitkin, 1979).

The increased production of active vitamin D is likely due to placental production of either PTH or a PTH-related protein (PTH-rP). Outside pregnancy and lactation, PTH-rP is usually detectable only in serum of women with hypercalcemia due to malignancy. During pregnancy, however, PTH-rP concentrations increase significantly. This protein is synthesized in both fetal tissues and maternal breasts.

Calcitonin

The C cells that secrete calcitonin are located predominantly in the perifollicular areas of the thyroid gland. Calcitonin opposes actions of PTH and vitamin D and protects the maternal skeleton during times of calcium stress. Pregnancy and lactation cause profound maternal calcium stress, ostensibly for the sake of the fetus.

Indeed, fetal calcitonin levels are at least twofold higher than maternal levels (Ohata, 2016). And although maternal levels fall during pregnancy, they generally rise postpartum (Møller, 2013).

Calcium and magnesium promote the biosynthesis and secretion of calcitonin. Various gastric hormones—gastrin, pentagastrin, glucagon, and pancreozymin—and food ingestion also increase calcitonin plasma levels.

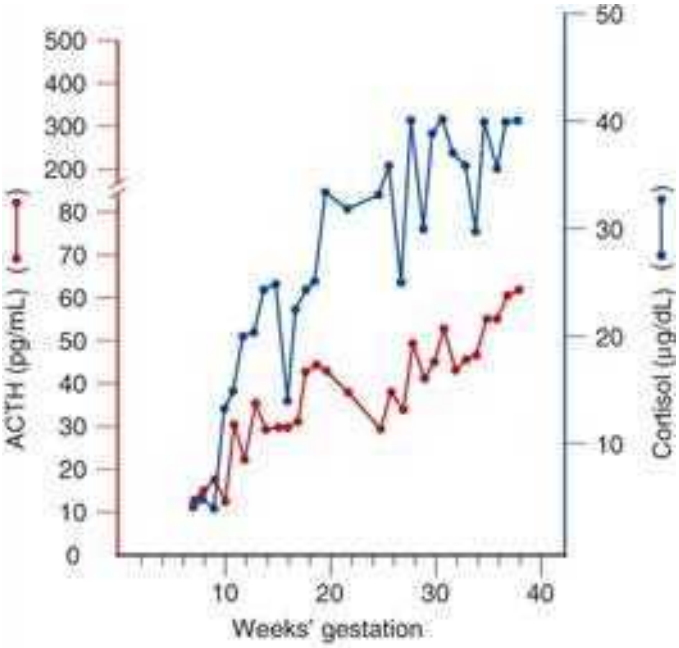
Adrenal Glands

Cortisol

In normal pregnancy, unlike their fetal counterparts, the maternal adrenal glands undergo little, if any, morphological change. The serum concentration of circulating cortisol rises, but much of it is bound by *transcortin*, the cortisol-binding globulin. The adrenal secretion rate of this principal glucocorticoid is not elevated, and probably it is lower than in the nonpregnant state. The metabolic clearance rate of cortisol, however, is diminished during pregnancy because its half-life is nearly doubled compared with that for nonpregnant women (Migeon, 1957). Administration of estrogen, including most oral contraceptives, causes changes in serum cortisol levels and transcortin similar to those of pregnancy (Jung, 2011).

During early pregnancy, the levels of circulating *adrenocorticotropic hormone* (*ACTH*), also known as *corticotropin*, are dramatically reduced. As pregnancy progresses, ACTH and free cortisol levels rise equally and strikingly (Fig. 4-18). This apparent paradox is not understood completely. Some suggest that greater free cortisol levels in pregnancy result from a "resetting" of the maternal feedback mechanism to higher thresholds (Nolten, 1981). This might result from *tissue refractoriness* to cortisol. Others assert that these incongruities stem from an antagonistic action of progesterone on mineralocorticoids (Keller-Wood, 2001). Thus, in response to elevated progesterone levels during pregnancy, an elevated free cortisol is needed to maintain homeostasis. Other theories include possible roles for higher free cortisol in preparation for the stress of pregnancy, delivery, and lactation. This pattern might also influence postpartum behavior and parenting roles (Conde, 2014).

FIGURE 4-18
Serial increases in serum cortisol (*blue line*) and adrenocorticotropic hormone (ACTH) (*red line*) across normal pregnancy. (Data redrawn from Carr, 1981.)



Aldosterone

As early as 15 weeks' gestation, the maternal adrenal glands secrete considerably increased amounts of aldosterone, the principal mineralocorticoid. By the third trimester, approximately 1 mg/d is released. If sodium intake is restricted, aldosterone secretion is even further elevated (Watanabe, 1963). Concurrently, levels of renin and angiotensin II substrate normally rise, especially during the latter half of pregnancy. This scenario promotes greater plasma levels of angiotensin II, which acts on the zona glomerulosa of the maternal adrenal glands and accounts for the markedly elevated aldosterone secretion. Some suggest the increased aldosterone secretion during normal pregnancy affords protection against the natriuretic effect of progesterone and atrial natriuretic peptide. Gennari-Moser and colleagues (2011) provide evidence that aldosterone, as well as cortisol, may modulate trophoblast growth and placental size.

Deoxycorticosterone

Maternal plasma levels of this potent mineralocorticosteroid progressively increase during pregnancy. Indeed, plasma levels of deoxycorticosterone rise to near 1500 pg/mL by term, a more than 15-fold increase (Parker, 1980). This marked elevation does not derive from adrenal secretion but instead represents augmented kidney

production resulting from estrogen stimulation. The levels of deoxycorticosterone and its sulfate in fetal blood are appreciably higher than those in maternal blood, which suggests transfer of fetal deoxycorticosterone into the maternal compartment.

Androgens

In balance, androgenic activity rises during pregnancy, and both maternal plasma levels of *androstenedione* and *testosterone* are increased. This finding is not totally explained by alterations in their metabolic clearance. Both androgens are converted to estradiol in the placenta, which increases their clearance rates. Conversely, greater plasma sex hormone-binding globulin levels in gravidas retard testosterone clearance. Thus, the production rates of maternal testosterone and androstenedione during human pregnancy are increased. The source of this higher C_{19}-steroid production is unknown, but it likely originates in the ovary.

Interestingly, little or no testosterone in maternal plasma enters the fetal circulation as testosterone. Even when massive testosterone levels are found in the circulation of pregnant women, as with androgen-secreting tumors, testosterone concentrations in umbilical cord blood are likely to be undetectable. This results from the near complete trophoblastic conversion of testosterone to 17β-estradiol.

Maternal serum and urine levels of *dehydroepiandrosterone sulfate* are lower during normal pregnancy. This stems from a greater metabolic clearance through extensive maternal hepatic 16α-hydroxylation and placental conversion to estrogen (Chap. 5, Placental Estrogen Production).

MUSCULOSKELETAL SYSTEM

Progressive lordosis is a characteristic feature of normal pregnancy. Compensating for the anterior position of the enlarging uterus, lordosis shifts the center of gravity back over the lower extremities. The sacroiliac, sacrococcygeal, and pubic joints have increased mobility during pregnancy. However, as discussed earlier (Fallopian Tubes), increased joint laxity and associated discomfort during pregnancy do not correlate with increased maternal serum levels of estradiol, progesterone, or relaxin (Aldabe, 2012; Marnach, 2003; Vøllestad, 2012). Most relaxation takes place in the first half of pregnancy. It may contribute to maternal posture alterations and in turn create lower back discomfort. As discussed in Chapter 36 (Pain, Mood, and Cognition), although some symphyseal separation likely accompanies many deliveries, those greater than 1 cm may cause significant pain (Shnaekel, 2015).

Aching, numbness, and weakness also occasionally are experienced in the upper extremities. This may result from the marked lordosis and associated anterior neck flexion and shoulder girdle slumping, which produce traction on the ulnar and median nerves (Crisp, 1964). The latter may give rise to symptoms mistaken for the *carpal tunnel syndrome* (Chap. 60, Spinal Cord Injury). Joint strengthening begins immediately following delivery and is usually complete within 3 to 5 months. Pelvic dimensions measured by MR imaging up to 3 months after delivery are not significantly different from prepregnancy measurements (Huerta-Enochian, 2006).

CENTRAL NERVOUS SYSTEM

Memory

Central nervous system changes are relatively few and mostly subtle. Women often report problems with attention, concentration, and memory throughout pregnancy and the early puerperium. Systematic studies of memory in pregnancy, however, are limited and often anecdotal. Keenan and associates (1998) longitudinally investigated memory in pregnant women and a matched control group. They found pregnancy-related memory decline that was limited to the third trimester. This decline was not attributable to depression, anxiety, sleep deprivation, or other physical changes associated with pregnancy. It was transient and quickly resolved following delivery. Others have found poorer verbal recall and processing speed and worse spatial recognition memory in pregnancy (Farrar, 2014; Henry, 2012).

Zeeman and coworkers (2003) used MR imaging to measure cerebral blood flow across pregnancy. They found that mean blood flow in the middle and posterior cerebral arteries declined progressively from 147 and 56 mL/min when nonpregnant to 118 and 44 mL/min late in pregnancy, respectively. Mechanisms and significance of the decline are unknown. Pregnancy does not affect cerebrovascular autoregulation (Bergersen, 2006; Cipolla, 2014).

Eyes

Intraocular pressure drops during pregnancy and is attributed partly to greater vitreous outflow. Corneal sensitivity is decreased, and the greatest changes are late in gestation. Most pregnant women demonstrate a measurable but slight increase in corneal thickness, thought to be due to edema. Consequently, they may have difficulty with previously comfortable contact lenses. Brownish-red opacities on the posterior surface of the cornea—*Krukenberg spindles*—are observed with a higher than expected frequency during pregnancy. Hormonal effects similar to those observed for skin lesions are believed to cause this increased pigmentation. Other than transient loss of accommodation reported with both pregnancy and lactation, visual function is unaffected by pregnancy. These changes during pregnancy and pathological eye aberrations were reviewed by Grant and Chung (2013).

Sleep

Beginning as early as 12 weeks' gestation and extending through the first 2 months postpartum, women have difficulty with falling asleep, frequent awakenings, fewer hours of night sleep, and reduced sleep efficiency (Pavlova, 2011). Abdullah and colleagues (2016b) concluded that sleep apnea is more common in pregnancy, especially in obese patients. The greatest disruption of sleep is encountered postpartum and may contribute to postpartum blues or to frank depression (Juulia Paavonen, 2017).

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CHAPTER 5: Implantation and Placental Development

Almost immediately after the implantation of the ovum, its trophoblast begins to proliferate and invade the surrounding decidual tissue. As it does so, it breaks through the walls of the maternal capillaries, from which the blood escapes and forms cavities, which are bounded partly by trophoblast and partly by decidua. The maternal blood spaces established in this manner represent the earliest stages of the intervillous blood spaces of the future placenta.

—J. Whitridge Williams (1903)

INTRODUCTION

In 1903, the histopathological and embryological descriptions of ovum implantation and placental development had been extensively studied and described. However, the origins and functions of pregnancy hormones were largely unknown. Indeed, it was another 25 to 30 years before estrogen and progesterone were discovered. In the past 50 years, remarkable strides have followed to uncover the steps of implantation and placental structure and function.

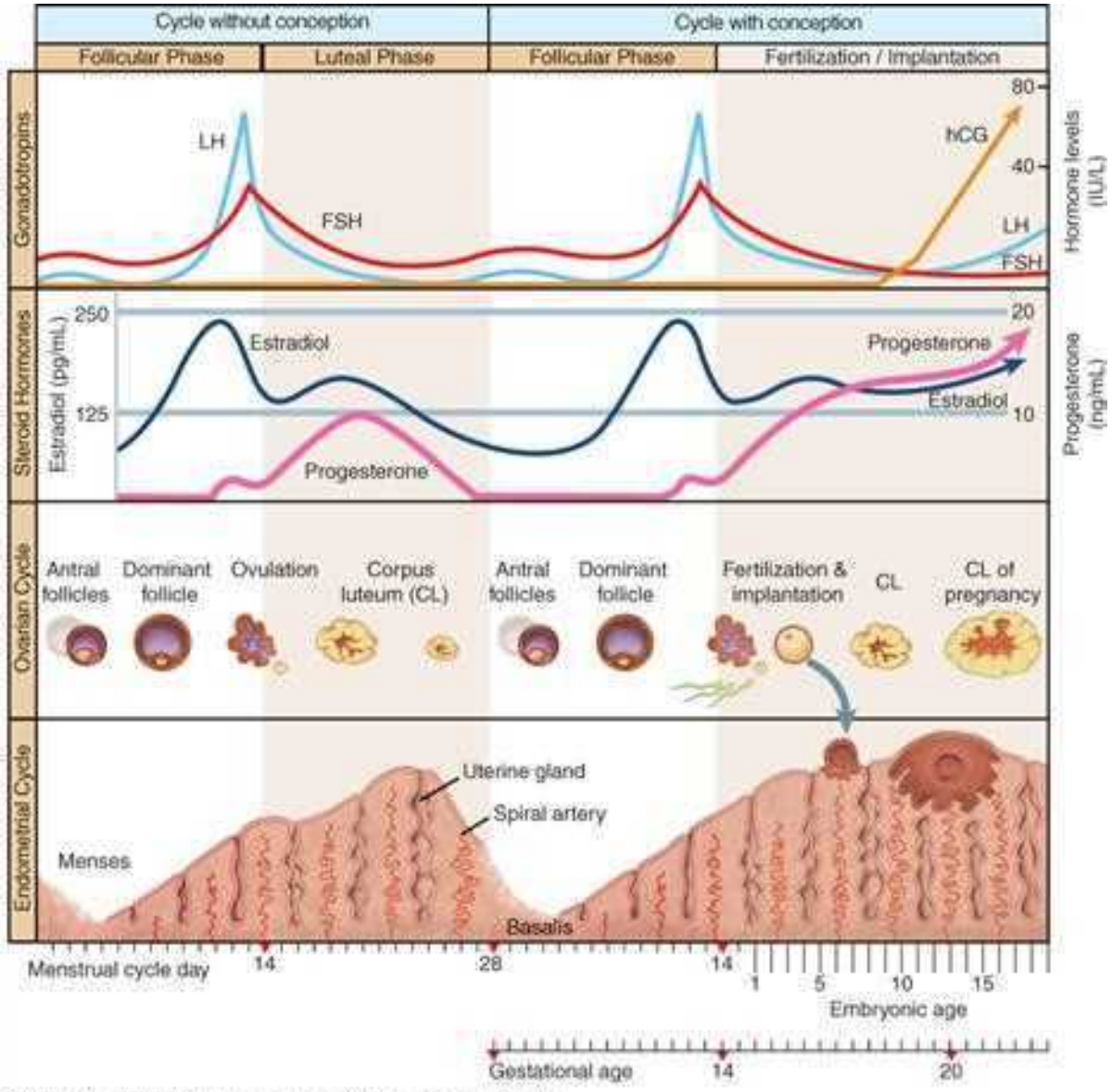
All obstetricians should understand the basic biological steps required for women to successfully achieve pregnancy. Several abnormalities can affect each of these and lead to infertility or pregnancy loss. In most women, spontaneous, cyclical ovulation continues during almost 40 years between menarche and menopause. Without contraception, there are approximately 400 opportunities for pregnancy, namely, the day of ovulation and its few preceding days. This narrow window for fertilization is controlled by tightly regulated production of ovarian steroids. Moreover, these hormones promote optimal endometrial regeneration after menstruation in preparation for the next implantation window.

If fertilization occurs, events that begin after blastocyst implantation persist until parturition. These derive from a unique interaction between fetal trophoblasts and the maternal endometrium, which has been transformed into the *decidua*. The ability of a mother and her fetus to coexist as two distinct immunological systems results from endocrine, paracrine, and immunological modification of fetal and maternal tissues in a manner not seen elsewhere. In addition, the placenta mediates a unique fetal–maternal communication system, which creates a hormonal environment that initially maintains pregnancy and eventually initiates events leading to parturition.

OVARIAN–ENDOMETRIAL CYCLE

Predictable, regular, cyclical, and spontaneous ovulatory menstrual cycles are regulated by complex interactions of the hypothalamic-pituitary-ovarian axis. Concurrently, cyclical changes in endometrial histology are faithfully reproduced (Fig. 5-1). Essentials players in this process include follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are pituitary-derived gonadotropins, and the ovarian sex steroid hormones estrogen and progesterone.

FIGURE 5-1
Gonadotropin control of the ovarian and endometrial cycles. The ovarian-endometrial cycle has been structured as a 28-day cycle. The follicular phase (days 1 to 14) is characterized by rising estrogen levels, endometrial thickening, and selection of the dominant “ovulatory” follicle. During the luteal phase (days 14 to 21), the corpus luteum (CL) produces estrogen and progesterone, which prepare the endometrium for implantation. If implantation occurs, the developing blastocyst begins to produce human chorionic gonadotropin (hCG) and rescues the corpus luteum, thus maintaining progesterone production. FSH = follicle-stimulating hormone; LH = luteinizing hormone.



The average cycle duration approximates 28 days but ranges from 25 to 32 days, even for a given woman. The follicular or proliferative phase shows considerable phase-length variation. This contrasts with the luteal or secretory postovulatory phase of the cycle, which is remarkably constant at 12 to 14 days.

Ovarian Cycle

Follicular Phase

The human ovary contains 2 million oocytes at birth, and approximately 400,000 follicles are present at puberty onset (Baker, 1963). These are depleted at a rate of approximately 1000 follicles per month until age 35, when this rate accelerates (Faddy, 1992). Only 400 follicles are normally released during female reproductive life. Therefore, more than 99.9 percent of these undergo atresia through a process of cell death termed apoptosis (Gougeon, 1996; Kaipia, 1997).

Follicular development consists of several stages. Primordial follicles undergo gonadotropin-independent recruitment from the resting pool and then progress from primary and secondary follicles to the antral stage. This appears to be controlled by locally produced growth factors. Two members of the transforming growth factor-β family include growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP-15), which regulate granulosa cell proliferation and differentiation as primary follicles grow (Trombly, 2009; Yan, 2001). They also stabilize and expand the cumulus oocyte complex in the oviduct (Hreinsson, 2002). These factors are produced by oocytes, suggesting that the early steps in follicular development are, in part, oocyte controlled. As antral follicles develop, surrounding stromal cells are recruited, by a yet-to-be-defined mechanism, to become thecal cells.

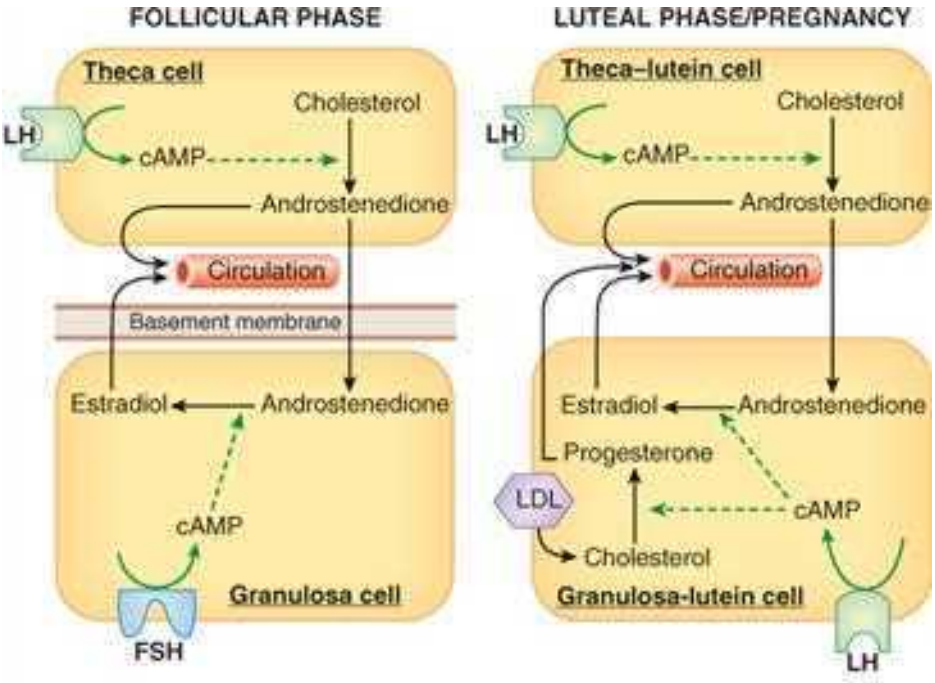
Although not required for early follicular maturation, FSH is required for further development of large antral follicles (Hillier, 2001). During each ovarian cycle, a group of antral follicles, known as a cohort, begins a phase of semisynchronous growth based on their maturation state during the FSH rise in the late luteal phase of the previous cycle. This FSH increase leading to further follicular development is called the *selection window* of the ovarian cycle (Macklon, 2001). Only follicles progressing to this stage develop the capacity to produce estrogen.

During the follicular phase, estrogen levels rise in proportion to growth of a dominant follicle and to the increase in its number of granulosa cells (see Fig. 5-1). These cells are the exclusive site of FSH receptor expression. The elevation of circulating FSH levels during the late luteal phase of the previous cycle stimulates an increase

in FSH receptors and subsequently, the ability of cytochrome P450 aromatase within granulosa cells to convert androstenedione into estradiol. The requirement for thecal cells, which respond to LH, and granulosa cells, which respond to FSH, represents the two-gonadotropin, two-cell hypothesis for estrogen biosynthesis (Short, 1962). As shown in Figure 5-2, FSH induces aromatase and expansion of the antrum of growing follicles. The follicle within the cohort that is most responsive to FSH is likely to be the first to produce estradiol and initiate expression of LH receptors.

FIGURE 5-2

The two-cell, two-gonadotropin principle of ovarian steroid hormone production. During the follicular phase (*left panel*), luteinizing hormone (LH) controls theca cell production of androstenedione, which diffuses into the adjacent granulosa cells and acts as precursor for estradiol biosynthesis. The granulosa cell capacity to convert androstenedione to estradiol is controlled by follicle-stimulating hormone (FSH). After ovulation (*right panel*), the corpus luteum forms and both theca-lutein and granulosa-lutein cells respond to LH. The theca-lutein cells continue to produce androstenedione, whereas granulosa-lutein cells greatly increase their capacity to produce progesterone and to convert androstenedione to estradiol. LH and hCG bind to the same LH-hCG receptor. If pregnancy occurs (*right panel*), human chorionic gonadotropin (hCG) rescues the corpus luteum through their shared LH-hCG receptor. Low-density lipoproteins (LDL) are an important source of cholesterol for steroidogenesis. cAMP = cyclic adenosine monophosphate.



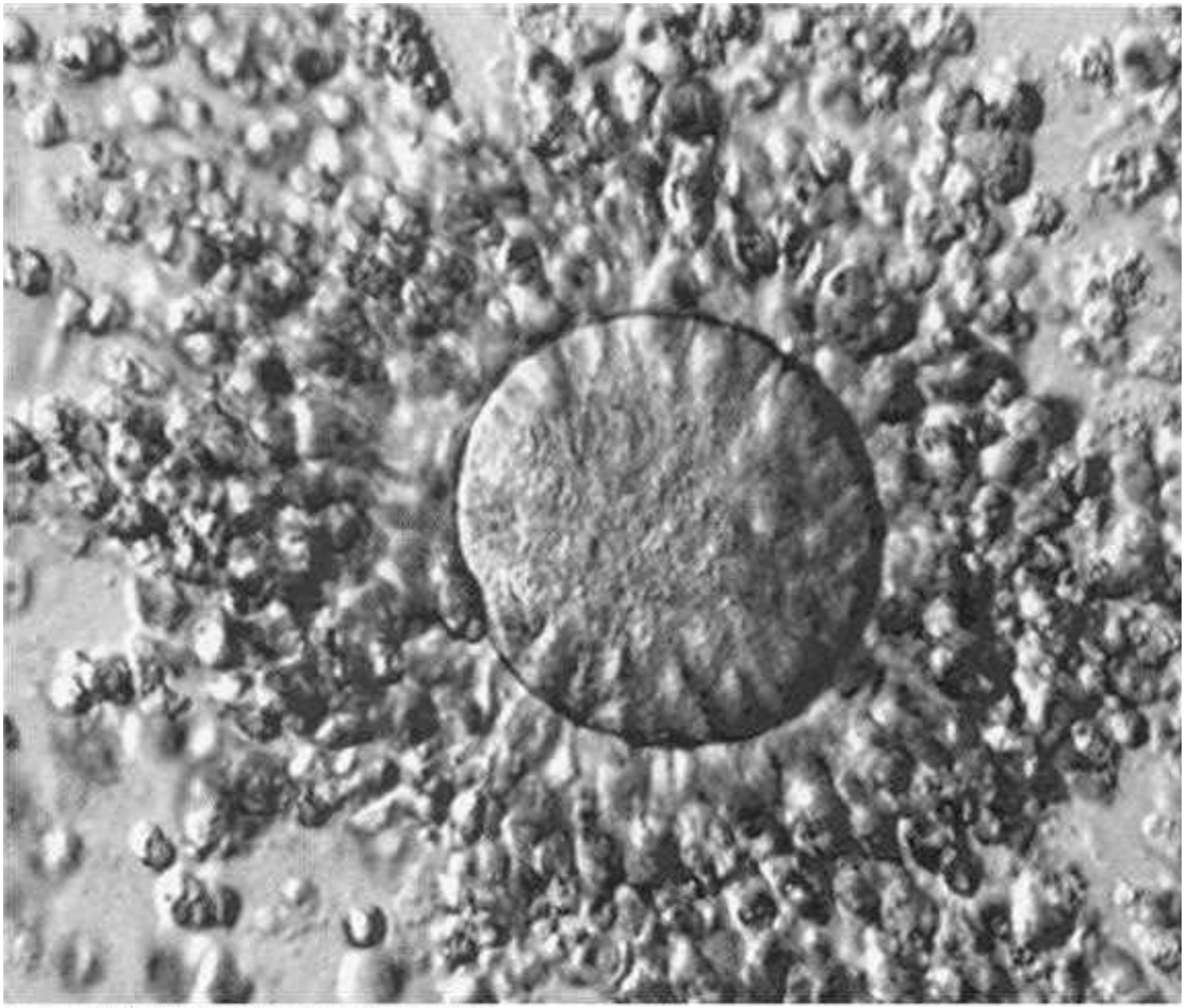
After the appearance of LH receptors, the preovulatory granulosa cells begin to secrete small quantities of progesterone. The preovulatory progesterone secretion, although somewhat limited, is believed to exert positive feedback on the estrogen-primed pituitary to either cause or augment LH release. In addition, during the late follicular phase, LH stimulates thecal cell production of androgens, particularly androstenedione, which are then transferred to the adjacent follicles where they are aromatized to estradiol (see Fig. 5-2). During the early follicular phase, granulosa cells also produce inhibin B, which can feed back on the pituitary to inhibit FSH release (Groome, 1996). As the dominant follicle begins to grow, estradiol and inhibin production rises and results in a decline of follicular-phase FSH. This drop in FSH levels is responsible for the failure of other follicles to reach preovulatory status—the Graafian follicle stage—during any one cycle. Thus, 95 percent of plasma estradiol produced at this time is secreted by the dominant follicle—the one destined to ovulate. Concurrently, the contralateral ovary is relatively inactive.

Ovulation

The onset of the gonadotropin surge resulting from increasing estrogen secretion by preovulatory follicles is a relatively precise predictor of ovulation. It occurs 34 to 36 hours before ovum release from the follicle (see Fig. 5-1). LH secretion peaks 10 to 12 hours before ovulation and stimulates resumption of meiosis in the ovum and release of the first polar body. Studies suggest that in response to LH, greater progesterone and prostaglandin production by the cumulus cells, as well as GDF9 and BMP-15 by the oocyte, activates expression of genes critical to formation of a hyaluronan-rich extracellular matrix by the cumulus complex (Richards, 2007). As seen in Figure 5-3, during synthesis of this matrix, cumulus cells lose contact with one another and move outward from the oocyte along the hyaluronan polymer—this process is called expansion. This results in a 20-fold augmentation of the cumulus complex volume and coincides with an LH-induced remodeling of the ovarian extracellular matrix. These allow release of the mature oocyte and its surrounding cumulus cells through the surface epithelium. Activation of proteases likely plays a pivotal role in weakening the follicular basement membrane and ovulation (Curry, 2006; Ny, 2002).

FIGURE 5-3

An ovulated cumulus–oocyte complex. An oocyte is at the center of the complex. Cumulus cells are widely separated from each other by the hyaluronan-rich extracellular matrix. (Used with permission from Dr. Kevin J. Doody.)



Luteal Phase

Following ovulation, the corpus luteum develops from the remains of the Graafian follicle in a process referred to as *luteinization*. The basement membrane separating the granulosa-lutein and theca-lutein cells breaks down, and by day 2 postovulation, blood vessels and capillaries invade the granulosa cell layer. The rapid neovascularization of the once-avascular granulosa may be due to angiogenic factors that include vascular endothelial growth factor (VEGF) and others produced by theca-lutein and granulosa-lutein cells in response to LH (Albrecht, 2003; Fraser, 2001). During luteinization, these cells undergo hypertrophy and increase their capacity to synthesize hormones.

LH is the primary luteotropic factor responsible for corpus luteum maintenance (Vande Wiele, 1970). Indeed, LH injections can extend the corpus luteum life span in normal women by 2 weeks (Segaloff, 1951).

The hormone secretion pattern of the corpus luteum differs from that of the follicle (see Fig. 5-1). As depicted in Figure 5-2, the greater capacity of granulosa-lutein cells to produce progesterone results from enhanced access to considerably more steroidogenic precursors through blood-borne, low-density lipoprotein (LDL)-derived cholesterol (Carr, 1981a). Ovarian progesterone production peaks at 25 to 50 mg/d during the midluteal phase. With pregnancy, the corpus luteum continues progesterone production in response to placental human chorionic gonadotropin (hCG), which binds to the same receptor as LH.

Estrogen levels follow a more complex pattern of secretion. Specifically, just after ovulation, estrogen levels decline, but then exhibit a secondary rise that reaches a peak production of 0.25 mg/d of 17β-estradiol in the midluteal phase. Toward the end of the luteal phase, estradiol production again drops.

The human corpus luteum is a transient endocrine organ that, in the absence of pregnancy, will rapidly regress 9 to 11 days after ovulation via apoptosis (Vaskivuo, 2002). The mechanisms that control luteolysis, that is, the regression of the corpus luteum, remain unclear. However, it results in part from dropping levels of

circulating LH in the late luteal phase and rising LH insensitivity by luteal cells (Duncan, 1996; Filicori, 1986). The role of other factors is less established. The dramatic drop in circulating estradiol and progesterone levels initiate molecular events that lead to menstruation.

Estrogen and Progesterone Action

Estrogen is the essential hormonal signal on which most events in the normal menstrual cycle depend. They function in many cell types to regulate follicular development, uterine receptivity, and blood flow. The most biologically potent naturally occurring estrogen is 17β-estradiol, which is secreted by granulosa cells of the dominant follicle and luteinized granulosa cells of the corpus luteum. Estradiol action is complex and appears to involve two classic nuclear hormone receptors designated estrogen receptor α (ERα) and β (ERβ) (Katzenellenbogen, 2001). These isoforms are the products of separate genes and can exhibit distinct tissue expression. Both estradiol-receptor complexes act as transcriptional factors that become associated with the estrogen-response element of specific genes. They share a robust activation by estradiol. However, differences in their binding affinities to other estrogens and their cell-specific expression patterns suggest that ERα and ERβ receptors may have both distinct and overlapping function (Saunders, 2005).

Most progesterone actions on the female reproductive tract are mediated through the nuclear hormone receptors, progesterone-receptor type A (PR-A) and B (PR-B). Progesterone enters cells by diffusion, and in responsive tissues it becomes associated with its receptors (Conneely, 2002). Progesterone-receptor isoforms arise from a single gene and regulate transcription of target genes. These receptors have unique actions. When PR-A and PR-B receptors are coexpressed, it appears that PR-A can inhibit PR-B gene regulation. The endometrial glands and stroma appear to have different expression patterns for progesterone receptors that vary during the menstrual cycle (Mote, 1999).

Progesterone can also evoke rapid responses, such as changes in intracellular free calcium levels, which cannot be explained by genomic mechanisms. G-protein–coupled membrane receptors for progesterone have been identified, but their role in the ovarian–endometrial cycle remains to be elucidated (Peluso, 2007).

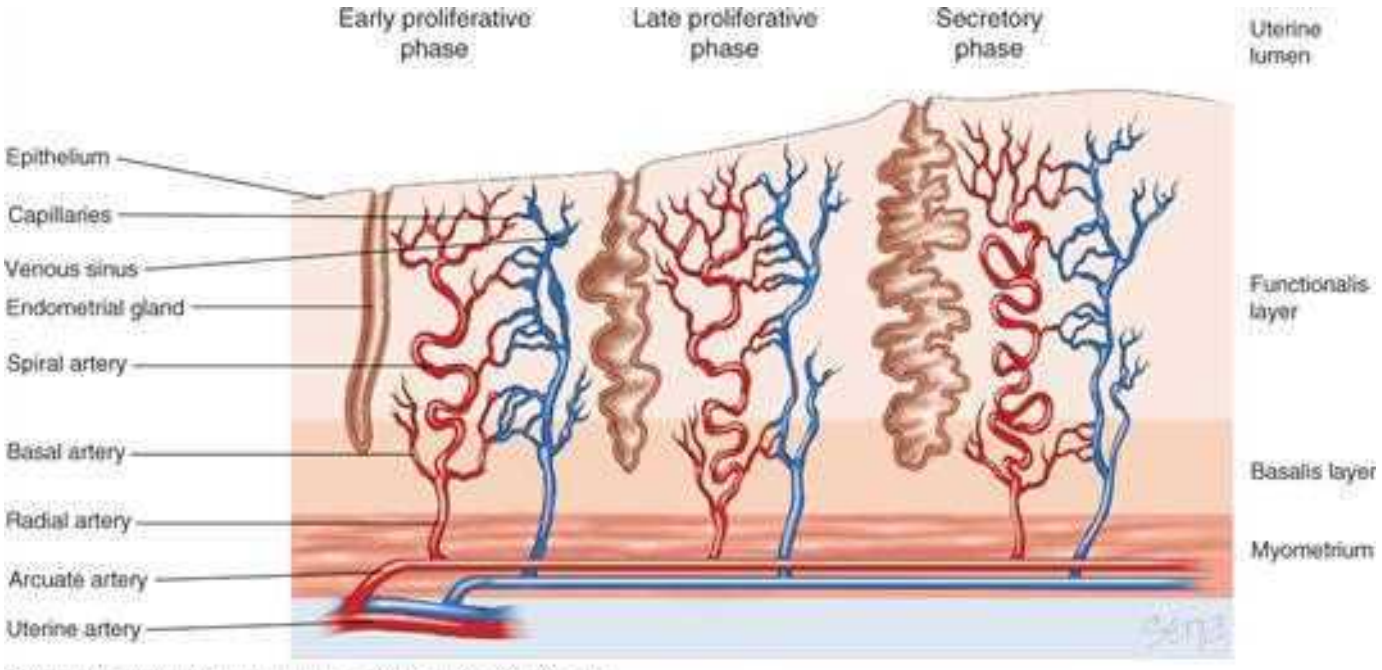
Endometrial Cycle

Proliferative Phase

In the endometrium, epithelial cells line the endometrial glands and are supported by stromal cells. These cells and supplying blood vessels replicate rapidly and cyclically in reproductive-aged women and are regenerated each ovarian–endometrial cycle. The superficial endometrium, termed the *functionalis layer*, is shed and reconstructed from the deeper *basalis layer* (Fig. 5-4). There is no other example in humans of such cyclical shedding and regrowth of an entire tissue.

FIGURE 5-4

The endometrium consists of two layers, the functionalis layer and basalis layer. These are supplied by the spiral and basal arteries, respectively. Numerous glands also span these layers. As the menstrual cycle progresses, greater coiling of the spiral arteries and increased gland folding can be seen. Near the end of the menstrual cycle (day 27), the coiled arteries constrict, deprive blood supply to the functionalis layer, and lead to necrosis and sloughing of this layer.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Fluctuations in estrogen and progesterone levels produce striking effects on the endometrium. Follicular-phase estradiol production is the most important factor in endometrial recovery following menstruation, and both ERα and ERβ receptors are expressed here. Although up to two thirds of the functionalis endometrium is fragmented and shed with menses, reepithelialization begins even before menstrual bleeding has ceased. By the fifth day of the endometrial cycle—fifth day of menses-the epithelial surface of the endometrium has been restored, and revascularization has begun. The preovulatory endometrium is characterized by proliferation of glandular, stromal, and vascular endothelial cells. During the early part of the proliferative phase, the endometrium is usually less than 2 mm thick. The glands are narrow, tubular structures that pursue almost a straight and parallel course from the basalis layer toward the endometrial cavity. Mitotic figures,

especially in the glandular epithelium, are identified by the fifth cycle day. Mitotic activity in both epithelium and stroma persists until day 16 to 17, that is, 2 to 3 days after ovulation. Blood vessels are numerous and prominent.

Clearly, reepithelialization and angiogenesis are important to cessation of endometrial bleeding (Chennazhi, 2009; Rogers, 2009). These are dependent on tissue regrowth, which is estrogen regulated. Epithelial cell growth also is regulated in part by epidermal growth factor and transforming growth factor α (TGFα). Stromal cells proliferate through paracrine and autocrine actions of estrogen and greater local levels of fibroblast growth factor-9 (Tsai, 2002). Estrogens also raise local production of VEGF, which causes angiogenesis through vessel elongation in the basalis (Gargett, 2001; Sugino, 2002).

By the late proliferative phase, the endometrium thickens from both glandular hyperplasia and augmented stromal ground substance, which is edema and proteinaceous material. The loose stroma is especially prominent, and the glands in the functionalis layer are widely separated. This is compared with those of the basalis layer, in which the glands are more crowded and the stroma is denser.

At midcycle, as ovulation nears, glandular epithelium becomes taller and pseudostratified. The surface epithelial cells acquire numerous microvilli, which increase epithelial surface area, and develop cilia, which move endometrial secretions during the secretory phase (Ferenczy, 1976).

Secretory Phase

After ovulation, the estrogen-primed endometrium responds to rising progesterone levels in a highly predictable manner. By day 17, glycogen accumulates in the basal portion of glandular epithelium, creating subnuclear vacuoles and pseudostratification. These changes likely result from direct progesterone action through receptors expressed in glandular cells (Mote, 2000). On day 18, vacuoles move to the apical portion of the secretory nonciliated cells. By day 19, these cells begin to secrete glycoprotein and mucopolysaccharide contents into the gland lumen (Hafez, 1975). Glandular cell mitosis ceases with secretory activity due to rising progesterone levels, which antagonize the mitotic effects of estrogen. Estradiol action also diminishes because of glandular expression of the type 2 isoform of 17β-hydroxysteroid dehydrogenase. This converts estradiol to the less active estrone (Casey, 1996). On cycle days 21 to 24, the stroma becomes edematous. Next, on days 22 to 25, stromal cells surrounding the spiral arterioles begin to enlarge, and stromal mitosis becomes apparent. Days 23 to 28 are characterized by predecidual cells, which surround spiral arterioles.

Between days 22 and 25, the secretory-phase endometrium undergoes striking changes associated with predecidual transformation of the upper two thirds of the functionalis layer. The glands exhibit extensive coiling, and luminal secretions become visible. Changes within the endometrium also can mark the so-called window of implantation seen on days 20 to 24. Epithelial surface cells show fewer microvilli and cilia, but luminal protrusions appear on the apical cell surface (Nikas, 2003). These pinopodes help prepare for blastocyst implantation. They also coincide with changes in the surface glycocalyx that allow acceptance of a blastocyst (Aplin, 2003).

Another highlight of the secretory phase is the continuing growth and development of the spiral arteries. These vessels arise from the radial arteries, which are myometrial branches of the arcuate and, ultimately, uterine vessels (see Fig. 5-4). The morphological and functional properties of the spiral arteries are unique and essential to blood flow changes seen during menstruation or implantation. During endometrial growth, spiral arteries lengthen at a rate appreciably greater than the rate of endometrial tissue thickening. This growth discordance obliges even greater coiling. Spiral artery development reflects a marked induction of angiogenesis, with widespread vessel sprouting and extension. Such rapid angiogenesis is regulated, in part, through estrogen- and progesterone-regulated synthesis of VEGF (Ancelin, 2002; Chennazhi, 2009).

Menstruation

The midluteal–secretory phase of the endometrial cycle is a critical branch point in endometrial development and differentiation. With corpus luteum rescue and continued progesterone secretion, the endometrium is transformed into the decidua. With luteolysis and declining luteal progesterone production, events leading to menstruation are initiated (Critchley, 2006; Thiruchelvam, 2013).

In the late premenstrual-phase endometrium, the stroma is invaded by neutrophils to create a pseudoinflammatory appearance. These cells infiltrate primarily on the day or two immediately preceding menses onset. The endometrial stromal and epithelial cells produce interleukin-8 (IL-8), a chemotactic–activating factor for neutrophils (Arici, 1993). Similarly, monocyte chemotactic protein-1 (MCP-1) is synthesized by endometrium and promotes monocyte recruitment (Arici, 1995).

Leukocyte infiltration is considered key to both endometrial extracellular matrix breakdown and repair of the functionalis layer. The term “inflammatory tightrope” refers to the ability of macrophages to assume phenotypes that vary from proinflammatory and phagocytic to immunosuppressive and reparative. These are likely relevant to menstruation, in which tissue breakdown and restoration occur simultaneously (Evans, 2012; Maybin, 2015). Invading leukocytes secrete enzymes that are members of the matrix metalloprotease (MMP) family. These add to the proteases already produced by endometrial stromal cells and effectively initiate matrix degradation. During menses as tissue shedding is completed, microenvironment-regulated changes in macrophage phenotype then promote repair and resolution (Evans, 2012; Thiruchelvam, 2013).

The classic study by Markee (1940) described tissue and vascular alterations in endometrium before menstruation. With endometrial regression, spiral artery coiling becomes sufficiently severe that resistance to blood flow rises to cause endometrial hypoxia. Resultant stasis is the primary cause of endometrial ischemia and tissue degeneration. Intense spiral artery vasoconstriction precedes menstruation and also serves to limit menstrual blood loss.

Prostaglandins play a key role in the events leading to menstruation that include vasoconstriction, myometrial contractions, and upregulation of proinflammatory responses (Abel, 2002). Large amounts of prostaglandins are present in menstrual blood. Painful menstruation is common and likely caused by myometrial contractions and uterine ischemia. This response is believed to be mediated by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)-induced spiral artery vasoconstriction, which render the uppermost endometrial zones hypoxic. The hypoxic environment is a potent inducer of angiogenesis and vascular permeability factors such as VEGF.

Progesterone withdrawal increases expression of cyclooxygenase 2 (COX-2), also called prostaglandin synthase 2, to synthesize prostaglandins. Withdrawal also lowers expression of 15-hydroxyprostaglandin dehydrogenase (PGDH), which degrades prostaglandins (Casey, 1980, 1989). The net result is higher prostaglandin

production by endometrial stromal cells and greater prostaglandin-receptor density on blood vessels and surrounding cells.

Actual menstrual bleeding follows rupture of spiral arterioles and consequent hematoma formation. With a hematoma, the superficial endometrium is distended and ruptures. Subsequently, fissures develop in the adjacent functionalis layer, and blood and tissue fragments are sloughed. Hemorrhage stops with arteriolar constriction. Changes that accompany partial tissue necrosis also serve to seal vessel tips.

The endometrial surface is restored by growth of flanges, or collars, that form the everted free ends of the endometrial glands (Markee, 1940). These flanges rapidly grow in diameter, and epithelial continuity is reestablished by fusion of the edges of these sheets of migrating cells.

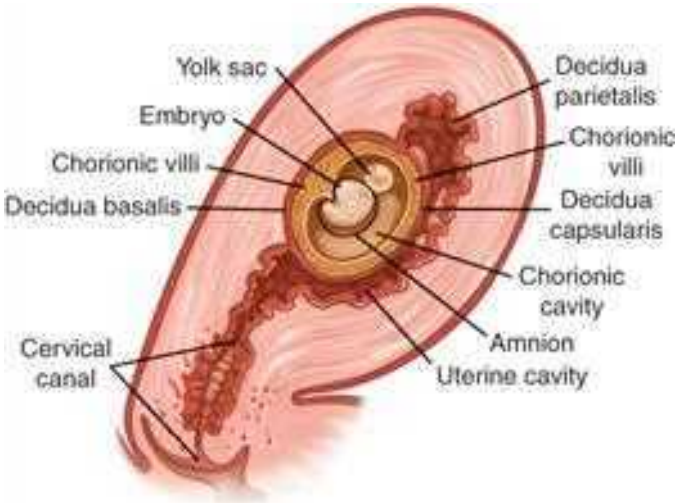
DECIDUA

This is a specialized, highly modified endometrium of pregnancy. It is essential for *hemochorial placentation*, that is, one in which maternal blood contacts trophoblasts. This relationship requires trophoblast invasion, and considerable research has focused on the interaction between decidual cells and invading trophoblasts. *Decidualization*, that is, transformation of proliferating endometrial stromal cells into specialized secretory cells, is dependent on estrogen, progesterone, androgens, and factors secreted by the implanting blastocyst (Gibson, 2016). The decidua produces factors that regulate endometrial receptivity and modulate immune and vascular cell functions within the maternal–fetal microenvironment. The special relationship existing between the decidua and the invading trophoblasts ensures success of the pregnancy semiallograft yet seemingly defies the laws of transplantation immunology.

Decidual Structure

The decidua is classified into three parts based on anatomical location. Decidua directly beneath blastocyst implantation is modified by trophoblast invasion and becomes the *decidua basalis*. The *decidua capsularis* overlies the enlarging blastocyst and initially separates the conceptus from the rest of the uterine cavity (Fig. 5-5). This portion is most prominent during the second month of pregnancy and consists of stromal decidual cells covered by a single layer of flattened epithelial cells. Internally, it contacts the avascular, extraembryonic fetal membrane—the chorion laeve. The remainder of the uterus is lined by *decidua parietalis*. During early pregnancy, there is a space between the decidua capsularis and parietalis because the gestational sac does not fill the entire uterine cavity. The gestation sac is the extraembryonic coelom and also called the chorionic cavity. By 14 to 16 weeks' gestation, the expanding sac has enlarged to completely fill the uterine cavity. The resulting apposition of the decidua capsularis and parietalis creates the *decidua vera*, and the uterine cavity is functionally obliterated.

FIGURE 5-5
Three portions of the decidua—the basalis, capsularis, and parietalis—are illustrated.



In early pregnancy, the decidua begins to thicken, eventually attaining a depth of 5 to 10 mm. With magnification, furrows and numerous small openings, representing the mouths of uterine glands, can be detected. Later in pregnancy, the decidua becomes thinner, presumably because of pressure exerted by the expanding uterine contents.

The decidua parietalis and basalis are composed of three layers. There is a surface or compact zone—*zona compacta*; a middle portion or spongy zone—*zona spongiosa*—with remnants of glands and numerous small blood vessels; and a basal zone—*zona basalis*. The zona compacta and spongiosa together form the *zona functionalis*. The basal zone remains after delivery and gives rise to new endometrium.

In human pregnancy, the decidual reaction is completed only with blastocyst implantation. Predecidual changes, however, commence first during the midluteal phase in endometrial stromal cells adjacent to the spiral arteries and arterioles. Thereafter, they spread in waves throughout the uterine endometrium and then from the implantation site. The endometrial stromal cells enlarge to form polygonal or round decidual cells. The nuclei become vesicular, and the cytoplasm becomes clear, slightly basophilic, and surrounded by a translucent membrane.

As a consequence of implantation, the blood supply to the decidua capsularis is lost as the embryo–fetus grows. Blood supply to the decidua parietalis through spiral arteries persists. These arteries retain a smooth-muscle wall and endothelium and thereby remain responsive to vasoactive agents.

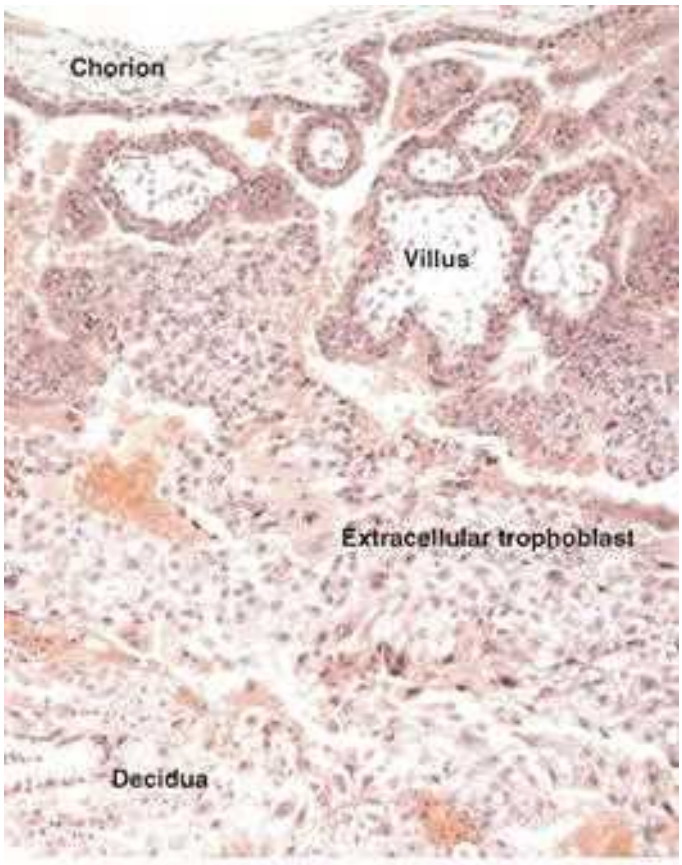
In contrast, the spiral arterial system that supplies the decidua basalis and ultimately the placental intervillous space is altered remarkably. These spiral arterioles and arteries are invaded by trophoblasts, and during this process, the vessel walls in the basalis are destroyed. Only a shell without smooth muscle or endothelial cells remains. Importantly, as a result, these vascular conduits of maternal blood—which become the uteroplacental vessels—are unresponsive to vasoactive agents. Conversely, the fetal chorionic vessels, which transport blood between the placenta and the fetus, contain smooth muscle and thus do respond to vasoactive agents.

Decidual Histology

Early in pregnancy, the zona spongiosa of the decidua consists of large distended glands, often exhibiting marked hyperplasia and separated by minimal stroma. At first, the glands are lined by typical cylindrical uterine epithelium with abundant secretory activity that contributes to blastocyst nourishment. With advanced pregnancy, the glandular elements largely disappear.

The decidua basalis contributes to formation of the placental basal plate (Fig. 5-6). The spongy zone of the decidua basalis consists mainly of arteries and widely dilated veins, and by term, glands have virtually disappeared. Also, the decidua basalis is invaded by many interstitial trophoblasts and trophoblastic giant cells. Although most abundant in the decidua, the giant cells commonly penetrate the upper myometrium. Their number and invasiveness can be so extensive as to resemble choriocarcinoma.

FIGURE 5-6
Section through a junction of chorion, villi, and decidua basalis in early first-trimester pregnancy. (Used with permission from Dr. Kurt Benirschke.)



The *Nitabuch layer* is a zone of fibrinoid degeneration in which invading trophoblasts meet the decidua basalis. If the decidua is defective, as in placenta accreta, the Nitabuch layer is usually absent (Chap. 41, Classification). There is also a more superficial, but inconsistent, deposition of fibrin—*Rohr stria*—at the bottom of the intervillous space and surrounding the anchoring villi. Decidual necrosis is a normal phenomenon in the first and probably second trimesters (McCombs, 1964). Thus, necrotic decidua obtained through curettage after spontaneous abortion in the first trimester should not necessarily be interpreted as either a cause or an effect of the pregnancy loss.

Both decidua types contain numerous cell groups whose composition varies with gestational stage (Loke, 1995). The primary cellular components are the true decidual cells, which differentiated from the endometrial stromal cells, and numerous maternal bone marrow-derived cells. Accumulation of lymphocytes with unique properties at the maternal–fetal interface is essential to evoke tolerance mechanisms that prevent maternal immune rejection of the fetus. These include regulatory T cells, decidual macrophages, and decidual natural killer cells. Collectively, these cells not only provide immunotolerance but also play an important role in trophoblast invasion and vasculogenesis (PrabhuDas, 2015).

Decidual Prolactin

In addition to placental development, the decidua potentially provides other functions. The decidua is the source of prolactin, which is present in enormous amounts in amnionic fluid (Golander, 1978; Riddick, 1979). Decidual prolactin is a product of the same gene that encodes for anterior pituitary prolactin, but the

exact physiological role of decidual prolactin is unknown. Notably, decidual prolactin is not to be confused with placental lactogen (hPL), which is produced only by syncytiotrophoblast.

Prolactin preferentially enters amnionic fluid, and little enters maternal blood. Consequently, prolactin levels in amnionic fluid are extraordinarily high and may reach 10,000 ng/mL at 20 to 24 weeks' gestation (Tyson, 1972). This compares with fetal serum levels of 350 ng/mL and maternal serum levels of 150 to 200 ng/mL. As a result, decidual prolactin is a classic example of paracrine function between maternal and fetal tissues.

IMPLANTATION AND EARLY TROPHOBLAST FORMATION

The fetus is dependent on the placenta for pulmonary, hepatic, and renal functions. These are accomplished through the anatomical relationship of the placenta and its uterine interface. In overview, maternal blood spurts from uteroplacental vessels into the placental intervillous space and bathes the outer syncytiotrophoblast. This allows exchange of gases, nutrients, and other substances with fetal capillary blood within the core of each villus. Thus, fetal and maternal blood does not normally mix in this hemochorial placenta. A paracrine system also links mother and fetus through the anatomical and biochemical juxtaposition of the maternal decidua parietalis and the extraembryonic chorion laeve, which is fetal. This is an extraordinarily important arrangement for communication between fetus and mother and for maternal immunological acceptance of the conceptus (Guzeloglu-Kayisli, 2009).

Fertilization

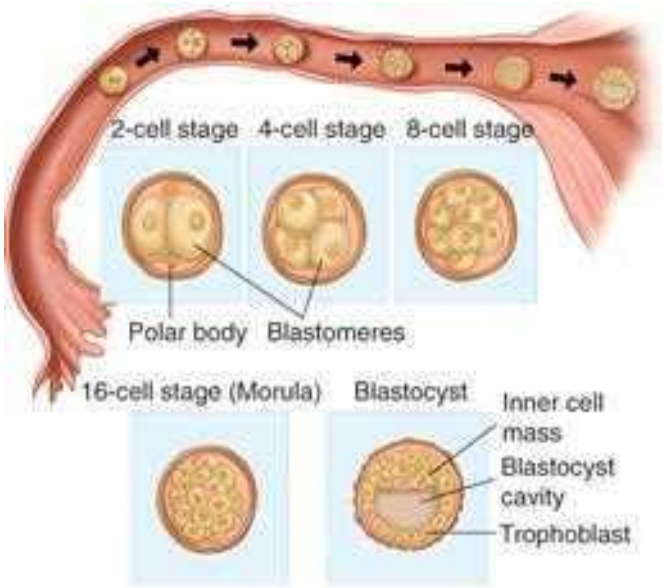
With ovulation, the secondary oocyte and adhered cells of the cumulus–oocyte complex are freed from the ovary. Although technically this mass of cells is released into the peritoneal cavity, the oocyte is quickly engulfed by the fallopian tube infundibulum. Further transport through the tube is accomplished by directional movement of cilia and tubal peristalsis. Fertilization, which normally occurs in the oviduct, must take place within a few hours, and no more than a day after ovulation. Because of this narrow window, spermatozoa must be present in the fallopian tube at the time of oocyte arrival. Almost all pregnancies result when intercourse occurs during the 2 days preceding or on the day of ovulation.

Fertilization is highly complex. Molecular mechanisms allow spermatozoa to pass between follicular cells; through the zona pellucida, which is a thick glycoprotein layer surrounding the oocyte cell membrane; and into the oocyte cytoplasm. Fusion of the two nuclei and intermingling of maternal and paternal chromosomes creates the *zygote*.

Early human development is described by days or weeks postfertilization, that is, postconceptional. By contrast, in most chapters of this book, clinical pregnancy dating is calculated from the first day of the last menstrual period (LMP). Thus, 1 week postfertilization corresponds to approximately 3 weeks from the LMP in women with regular 28-day cycles. As an example, 8 weeks' gestation refers to 8 completed weeks following the LMP.

After fertilization, the zygote—a diploid cell with 46 chromosomes—undergoes cleavage, and zygote cells produced by this division are called *blastomeres* (Fig. 5-7). In the two-cell zygote, the blastomeres and polar body continue to be surrounded by the zona pellucida. The zygote undergoes slow cleavage for 3 days while still remaining in the fallopian tube. As the blastomeres continue to divide, a solid mulberry-like ball of cells—the *morula*—is produced. The morula enters the uterine cavity approximately 3 days after fertilization. Gradual accumulation of fluid between the morula cells leads to formation of the early *blastocyst*.

FIGURE 5-7
Zygote cleavage and blastocyst formation. The morula period begins at the 12- to 16-cell stage and ends when the blastocyst forms, which occurs when there are 50 to 60 blastomeres present. The polar bodies, shown in the 2-cell stage, are small nonfunctional cells that soon degenerate.



Blastocyst

As early as 4 to 5 days after fertilization, the 58-cell blastula differentiates into five embryo-producing cells—the *inner cell mass* (see Fig. 5-7). The remaining 53 outer cells, called the *trophectoderm,* are destined to form *trophoblasts* (Hertig, 1962).

Interestingly, the 107-cell blastocyst is found to be no larger than the earlier cleavage stages, despite the accumulated fluid within the blastocyst cavity. At this stage, the eight formative, embryo-producing cells are surrounded by 99 trophoblastic cells. And, the blastocyst is released from the zona pellucida secondary to secretion of specific proteases from the secretory-phase endometrial glands (O'Sullivan, 2002).

Release from the zona pellucida allows blastocyst-produced cytokines and hormones to directly influence endometrial receptivity (Lindhard, 2002). IL-1α and IL-1β are secreted by the blastocyst, and these cytokines likely directly influence the endometrium. Embryos also have been shown to secrete hCG, which may influence endometrial receptivity (Licht, 2001; Lobo, 2001). The receptive endometrium is thought to respond by producing leukemia inhibitory factor (LIF), follistatin, and colony-stimulating factor-1 (CSF-1). LIF and follistatin activate signaling pathways that collectively inhibit proliferation and promote differentiation of the endometrial epithelia and stroma to enable uterine receptivity (Rosario, 2016b). At the maternal–fetal interface, CSF-1 has proposed immunomodulatory actions and proangiogenic actions that are required for implantation (Rahmati, 2015).

Implantation

Six or 7 days after fertilization, the blastocyst implants into the uterine wall. This process can be divided into three phases: (1) apposition—initial contact of the blastocyst to the uterine wall; (2) adhesion—increased physical contact between the blastocyst and decidua; and (3) invasion—penetration and invasion of syncytiotrophoblast and cytotrophoblasts into the decidua, inner third of the myometrium, and uterine vasculature.

Successful implantation requires a receptive endometrium appropriately primed with estrogen and progesterone by the corpus luteum. Such uterine receptivity is limited to days 20 to 24 of the cycle. Adherence is mediated by cell-surface receptors at the implantation site that interact with blastocyst receptors (Carson, 2002; Lessey, 2002; Lindhard, 2002). If the blastocyst approaches the endometrium after cycle day 24, the potential for adhesion is diminished because antiadhesive glycoprotein synthesis prevents receptor interactions (Navot, 1991).

At the time of its interaction with the endometrium, the blastocyst is composed of 100 to 250 cells. The blastocyst loosely adheres to the decidua by apposition. This most commonly occurs on the upper posterior uterine wall. Attachment of the blastocyst trophectoderm to the decidual surface by apposition and adherence appears to be closely regulated by paracrine interactions between these two tissues.

Successful endometrial blastocyst adhesion involves modification in expression of cellular adhesion molecules (CAMs). The integrins—one of four families of CAMs—are cell-surface receptors that mediate cell adhesion to extracellular matrix proteins (Lessey, 2002). Endometrial integrins are hormonally regulated, and a specific set of integrins is expressed at implantation (Lessey, 1995). Recognition-site blockade of integrins needed for binding will prevent blastocyst attachment (Kaneko, 2013).

Trophoblast Development

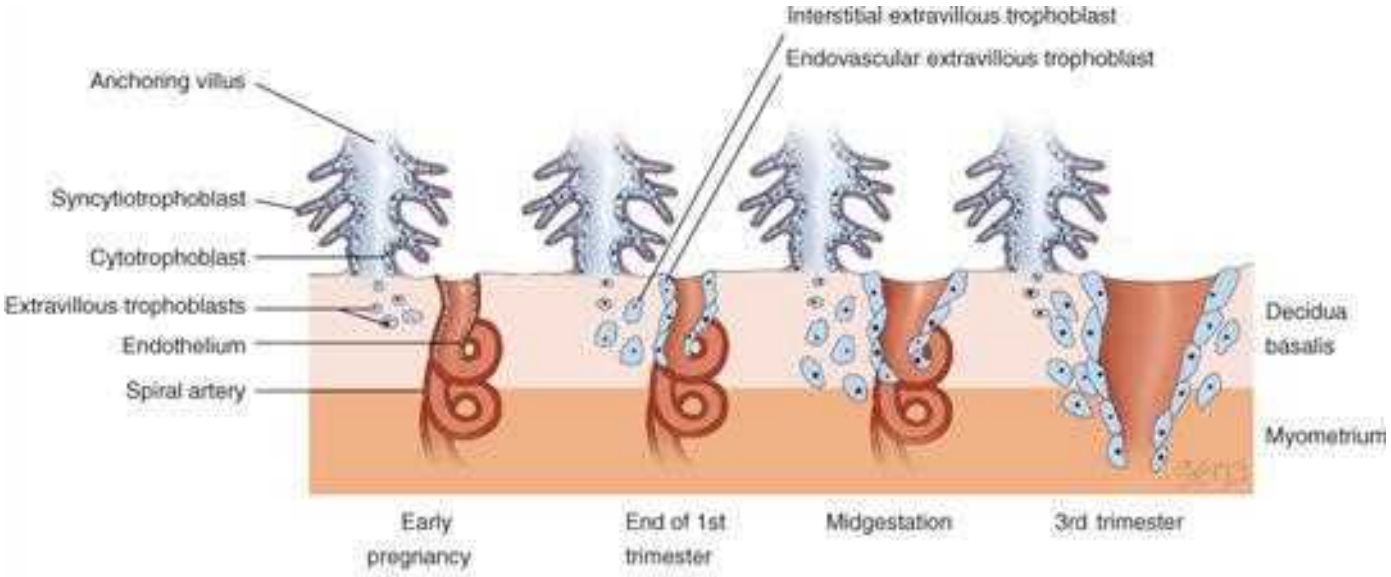
Human placental formation begins with the trophectoderm, which gives rise to a trophoblast cell layer encircling the blastocyst. From then until term, trophoblasts play a critical part at the fetal–maternal interface. Trophoblasts exhibit the most variable structure, function, and developmental pattern of all placental components. Their invasiveness promotes implantation, their nutritional role for the conceptus is reflected in their name, and their endocrine organ function is essential to maternal physiological adaptations and to pregnancy maintenance.

By the eighth day postfertilization, after initial implantation, trophoblasts have differentiated into an outer multinucleated syncytium—primitive *syncytiotrophoblast*, and an inner layer of primitive mononuclear cells—*cytotrophoblasts*. The latter are germinal cells for the syncytium. As cytotrophoblasts proliferate, their cell walls disappear, and the cells fuse to add to the expanding outer layer of syncytiotrophoblast. Each cytotrophoblast has a well-demarcated cell border, a single nucleus, and ability to undergo DNA synthesis and mitosis (Arnholdt, 1991). These are lacking in the syncytiotrophoblast, which provides transport functions of the placenta. It is so named because instead of individual cells, it has an amorphous cytoplasm without cell borders, nuclei that are multiple and diverse in size and shape, and a continuous syncytial lining. This configuration aids transport.

After implantation is complete, trophoblasts further differentiate along two main pathways, giving rise to villous and extravillous trophoblasts. As shown in Figure 5-8, both have distinct functions (Loke, 1995). *Villous trophoblasts* generate chorionic villi, which primarily transport oxygen, nutrients, and other compounds between the fetus and mother. *Extravillous trophoblasts* migrate into the decidua and myometrium and also penetrate maternal vasculature, thus coming into contact with various maternal cell types (Pijnenborg, 1994). Extravillous trophoblasts are further classified as *interstitial trophoblasts* and *endovascular trophoblasts.* The interstitial trophoblasts invade the decidua and eventually penetrate the myometrium to form placental-bed giant cells. These trophoblasts also surround spiral arteries. The endovascular trophoblasts penetrate the spiral artery lumens (Pijnenborg, 1983). These are both discussed in greater detail in subsequent sections.

FIGURE 5-8

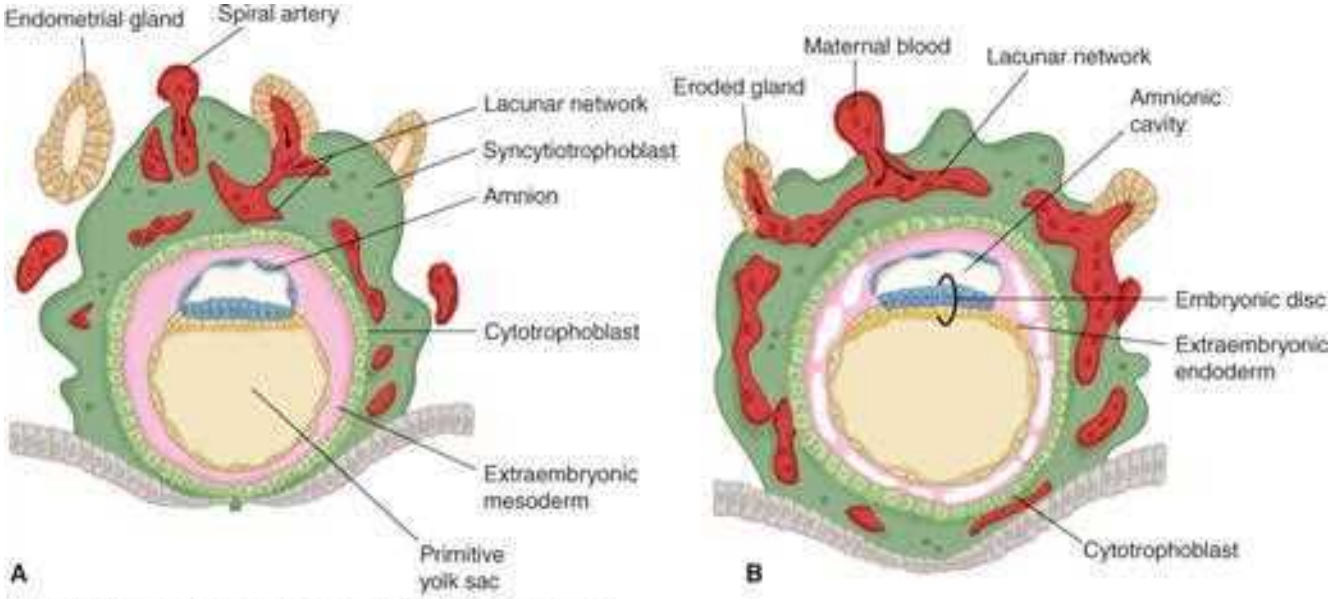
Extravillous trophoblasts are found outside the villus and can be subdivided into endovascular and interstitial categories. Endovascular trophoblasts invade and transform spiral arteries during pregnancy to create low-resistance blood flow that is characteristic of the placenta. Interstitial trophoblasts invade the decidua and surround spiral arteries.



Early Invasion

After gentle erosion between epithelial cells of the surface endometrium, invading trophoblasts burrow deeper. At 9 days of development, the blastocyst wall facing the uterine lumen is a single layer of flattened cells. By the 10th day, the blastocyst becomes totally encased within the endometrium (Fig. 5-9). The blastocyst wall opposite the uterine lumen is thicker and comprises two zones—the trophoblasts and the embryo-forming inner cell mass. As early as 7½ days postfertilization, the inner cell mass or embryonic disc differentiates into a thick plate of primitive ectoderm and an underlying layer of endoderm. Some small cells appear between the embryonic disc and the trophoblasts and enclose a space that will become the amnionic cavity.

FIGURE 5-9
Drawing of sections through implanted blastocysts. **A.** At 10 days. **B.** At 12 days after fertilization. This stage is characterized by the intercommunication of the lacunae filled with maternal blood. Note in **(B)** that large cavities have appeared in the extraembryonic mesoderm, forming the beginning of the extraembryonic coelom. Also note that extraembryonic endodermal cells have begun to form on the inside of the primitive yolk sac. (Redrawn and adapted from Moore KL, Persaud, TV, Torchia, MG (eds): The Developing Human. Clinically Oriented Embryology, 9th edition, Philadelphia, Saunders, 2013.)



Extraembryonic mesenchyme first appears as groups of isolated cells within the blastocyst cavity, and later this mesoderm completely lines the cavity. Spaces form and then fuse within the extraembryonic mesoderm to form the chorionic cavity (extraembryonic coelom). The *chorion* is composed of trophoblasts and mesenchyme. Some mesenchymal cells eventually will condense to form the body stalk. This stalk joins the embryo to the nutrient chorion and later develops into the umbilical cord. The body stalk can be recognized at an early stage at the caudal end of the embryonic disc (Fig. 7-3).

As the embryo enlarges, more maternal decidua basalis is invaded by syncytiotrophoblast. Beginning approximately 12 days after conception, the syncytiotrophoblast is permeated by a system of intercommunicating channels called trophoblastic lacunae. After invasion of superficial decidual capillary walls,

lacunae become filled with maternal blood. At the same time, the decidual reaction intensifies in the surrounding stroma. This is characterized by decidual stromal cell enlargement and glycogen storage.

Chorionic Villi

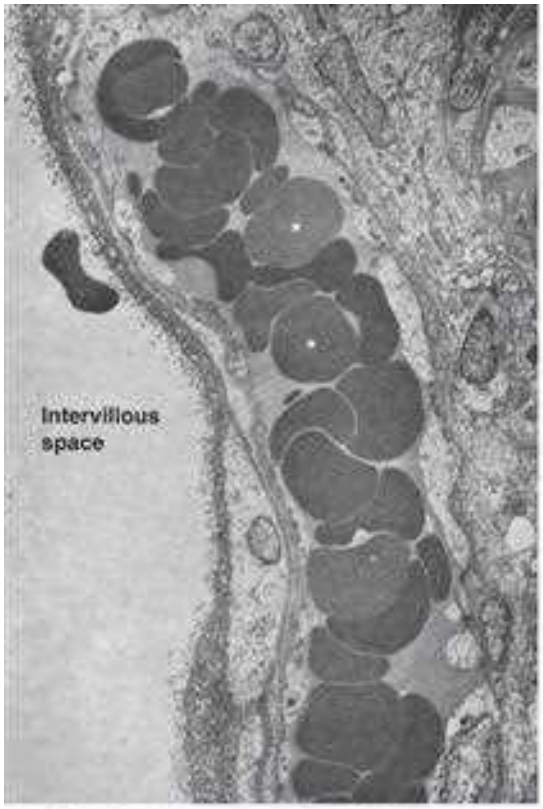
With deeper blastocyst invasion into the decidua, solid primary villi arise from buds of cytotrophoblasts that protrude into the primitive syncytium before 12 days postfertilization. Primary villi are composed of a cytotrophoblast core covered by syncytiotrophoblast. As the lacunae join, a complicated labyrinth is formed that is partitioned by these solid cytotrophoblastic columns. The trophoblast-lined channels form the intervillous space, and the solid cellular columns form the *primary villous stalks*.

Beginning on approximately the 12th day after fertilization, mesenchymal cords derived from extraembryonic mesoderm invade the solid trophoblast columns. These form *secondary villi*. Once angiogenesis begins in the mesenchymal cords, *tertiary villi* are formed. Although maternal venous sinuses are tapped early in implantation, maternal arterial blood does not enter the intervillous space until around day 15. By approximately the 17th day, however, fetal blood vessels are functional, and a placental circulation is established. The fetal–placental circulation is completed when the blood vessels of the embryo are connected with chorionic vessels. In some villi, angiogenesis fails from lack of circulation. They can be seen normally, but the most striking exaggeration of this process is seen with hydatidiform mole (Fig. 20-1).

Villi are covered by an outer layer of syncytiotrophoblast and an inner layer of cytotrophoblasts, which are also known as *Langhans cells*. Cytotrophoblast proliferation at the villous tips produces the trophoblastic cell columns that form anchoring villi. They are not invaded by fetal mesenchyme, and they are anchored to the decidua at the basal plate. Thus, the base of the intervillous space faces the maternal side and consists of cytotrophoblasts from cell columns, the covering shell of syncytiotrophoblast, and maternal decidua of the basal plate. The base of the chorionic plate forms the roof of the intervillous space. It consists of two layers of trophoblasts externally and fibrous mesoderm internally. The “definitive” chorionic plate is formed by 8 to 10 weeks as the amnionic and primary chorionic plate mesenchyme fuse together. This formation is accomplished by expansion of the amnionic sac, which also surrounds the connective stalk and the allantois and joins these structures to form the umbilical cord (Kaufmann, 1992).

Interpretation of the fine structure of the placenta came from electron microscopic studies of Wislocki and Dempsey (1955). There are prominent microvilli on the syncytial surface that correspond to the so-called brush border described by light microscopy. Associated pinocytotic vacuoles and vesicles are related to absorptive and secretory placental functions. Microvilli act to increase surface area in direct contact with maternal blood. This contact between the trophoblast and maternal blood is the defining characteristic of a hemochorial placenta (Fig. 5-10).

FIGURE 5-10
Electron micrograph of term human placenta villus. A villus capillary filled with fetal red blood cells (*asterisks*) is seen in close proximity to the microvilli border. (Reproduced with permission from Boyd JD, Hamilton WJ: The Human Placenta. Cambridge, Heffer, 1970.)



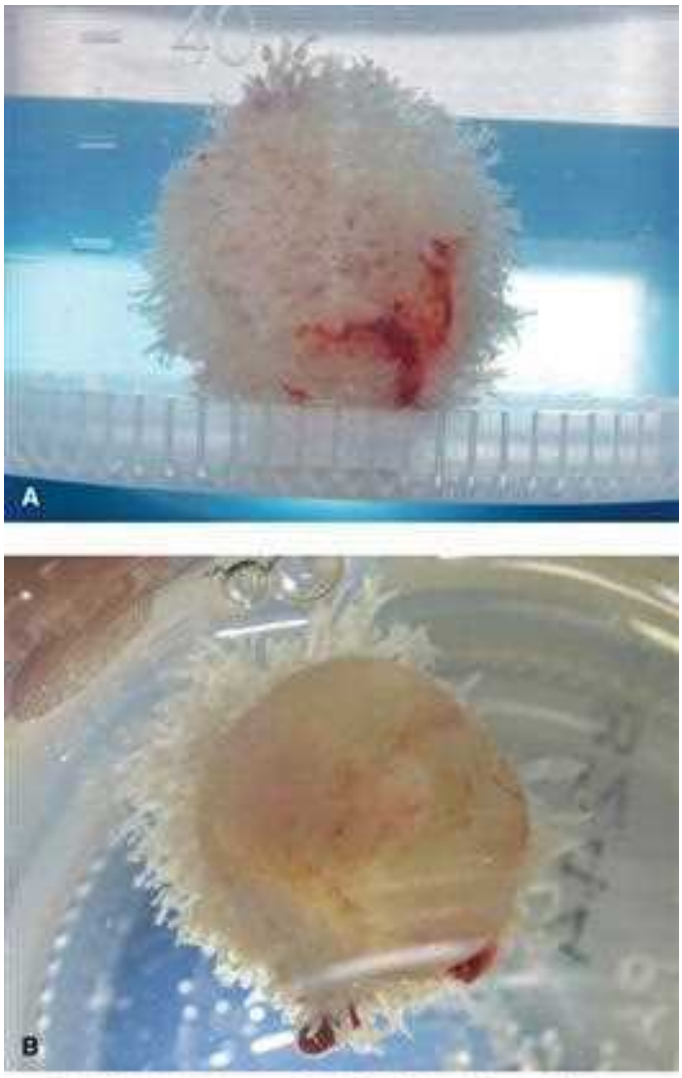
PLACENTA AND CHORION

Chorion Development

In early pregnancy, the villi are distributed over the entire periphery of the chorionic membrane (Fig. 5-11). As the blastocyst with its surrounding trophoblasts grows and expands into the decidua, one pole faces the endometrial cavity. The opposite pole will form the placenta. Here, chorionic villi in contact with the decidua basalis proliferate to form the *chorion frondosum*—or leafy chorion. As growth of embryonic and extraembryonic tissues continues, the blood supply to the chorion facing the endometrial cavity is restricted. Because of this, villi in contact with the decidua capsularis cease to grow and then degenerate. This portion of the chorion becomes the avascular fetal membrane that abuts the decidua parietalis and is called the *chorion laeve*—or smooth chorion. This smooth chorion is composed of cytotrophoblasts and fetal mesodermal mesenchyme.

FIGURE 5-11

Complete abortion specimens. **A.** Initially, the entire chorionic sac is covered with villi, and the embryo within is not visible **B.** With further growth, stretch and pressure prompt partial regression of the villi. Remaining villi form the future placenta, whereas the smooth portion is the chorion.



Until near the end of the third month, the chorion laeve is separated from the amnion by the exocoelomic cavity. Thereafter, they are in intimate contact to form an avascular amniochorion. These two structures are important sites of molecular transfer and metabolic activity. Moreover, they constitute an important paracrine arm of the fetal–maternal communication system.

Regulators of Trophoblast Invasion

Implantation and endometrial decidualization activate a unique population of maternal immune cells that infiltrate the uterus and play critical functions in trophoblast invasion, angiogenesis, spiral artery remodeling, and maternal tolerance to fetal alloantigens. Decidual natural killer cells (dNK) make up 70 percent of decidual leukocytes in the first trimester and are found in direct contact with trophoblasts. In contrast to natural killer cells in peripheral blood, these cells lack cytotoxic functions. They produce specific cytokines and angiogenic factors to regulate invasion of fetal trophoblasts and spiral artery remodeling (Hanna, 2006). These and other unique properties distinguish dNK cells from circulating natural killer cells and from natural killer cells in the endometrium before pregnancy (Fu, 2013; Winger, 2013). dNK cells express both IL-8 and interferon-inducible protein-10, which bind to receptors on invasive trophoblastic cells to promote their decidual invasion toward the spiral arteries. dNK cells also produce proangiogenic factors, including VEGF and placental growth factor (PlGF), which both promote vascular growth in the decidua.

Trophoblasts also secrete specific chemokines that attract the dNK cells to the maternal–fetal interface. Thus, both cell types simultaneously attract each other. Decidual macrophages account for approximately 20 percent of leukocytes in the first trimester and elicit an M2-immunomodulatory phenotype (Williams, 2009). Remember, M1 macrophages are proinflammatory, and M2 macrophages counter proinflammatory responses and promote tissue repair. In addition to a role in angiogenesis and spiral artery remodeling, dNK cells promote phagocytosis of cell debris (Faas, 2017). Concurrent with the critical role of maternal dNK cells and macrophages, T cell subsets aid tolerance toward the allogenic fetus. Regulatory T cells (Tregs) are essential for promoting immune tolerance. Other T cell subsets are present, such as Th1, Th2 and Th17, although their functions are tightly regulated (Ruocco, 2014).

Endometrial Invasion

Extravillous trophoblasts of the first-trimester placenta are highly invasive. This process occurs under low-oxygen conditions, and regulatory factors that are induced under hypoxic conditions are contributory (Soares, 2012). Invasive trophoblasts secrete numerous proteolytic enzymes that digest extracellular matrix and activate proteinases already present in the decidua. Trophoblasts produce urokinase-type plasminogen activator, which converts plasminogen into the broadly acting serine protease, plasmin. This in turn both degrades matrix proteins and activates MMPs. One member of the MMP family, MMP-9, appears to be critical. The timing and extent of trophoblast invasion is regulated by a balanced interplay between pro- and antiinvasive factors.

The relative ability to invade maternal tissue in early pregnancy compared with limited invasiveness in late pregnancy is controlled by autocrine and paracrine trophoblastic and decidual factors. Trophoblasts secrete insulin-like growth factor II that promotes invasion into the decidua. Decidual cells secrete insulin-like growth factor binding-protein type 4, which blocks this autocrine loop.

Low estradiol levels in the first trimester are critical for trophoblast invasion and remodeling of the spiral arteries. Animal studies suggest that the rise in second-trimester estradiol levels suppresses and limits vessel remodeling by reducing trophoblast expression of VEGF and specific integrin receptors (Bonagura, 2012). Namely, extravillous trophoblasts express integrin receptors that recognize the extracellular matrix proteins collagen IV, laminin, and fibronectin. Binding of these matrix proteins and integrin receptors initiates signals to promote trophoblast cell migration and differentiation. However, as pregnancy advances, rising estradiol levels downregulate VEGF and integrin receptor expression. This represses and controls the extent of uterine vessel transformation.

Spiral Artery Invasion

One of the most remarkable features of human placental development is the extensive modification of maternal vasculature by trophoblasts, which are by definition of fetal origin. These events occur in the first half of pregnancy and are considered in detail because of their importance to uteroplacental blood flow. They are also integral to some pathological conditions such as preeclampsia, fetal-growth restriction, and preterm birth. Spiral artery modifications are carried out by two populations of extravillous trophoblasts—endovascular trophoblasts, which penetrate the spiral-artery lumen, and interstitial trophoblasts, which surround the arteries (see Fig. 5-8).

Interstitial trophoblasts constitute a major portion of the placental bed. They penetrate the decidua and adjacent myometrium and aggregate around spiral arteries. Although less defined, their functions may include vessel preparation for endovascular trophoblast invasion.

Endovascular trophoblasts first enter the spiral artery lumens and initially form cellular plugs. They then destroy vascular endothelium via an apoptosis mechanism and invade and modify the vascular media. Thus, fibrinoid material replaces smooth muscle and connective tissue of the vessel media. Spiral arteries later regenerate endothelium. Invading endovascular trophoblasts can extend several centimeters along the vessel lumen, and they must migrate against arterial flow. Of note, invasion by trophoblasts involves only the decidual spiral arteries and not decidual veins.

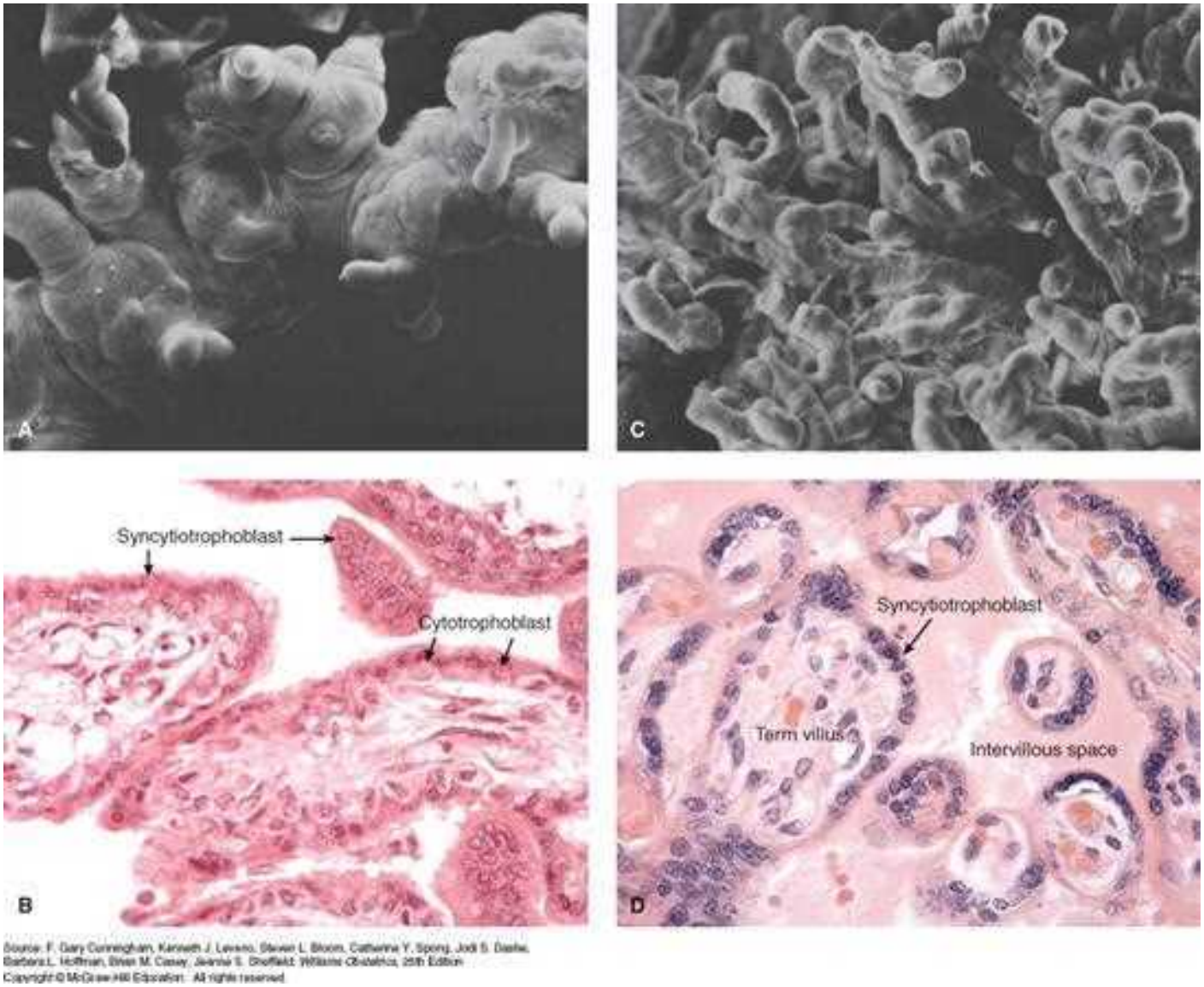
Uteroplacental vessel development proceeds in two waves or stages (Ramsey, 1980). The first occurs before 12 weeks' postfertilization, and spiral arteries are invaded and modified up to the border between the decidua and myometrium. The second wave, between 12 and 16 weeks, involves some invasion of the intramyometrial segments of spiral arteries. Remodeling converts narrow-lumen, muscular spiral arteries into dilated, low-resistance uteroplacental vessels. Molecular mechanisms of these crucial events, their regulation by cytokines, signaling pathways, and their significance in the pathogenesis of preeclampsia and fetal-growth restriction has been reviewed by several authors (Pereira de Sousa, 2017; Xie, 2016; Zhang, 2016).

Approximately 1 month after conception, maternal blood enters the intervillous space in fountain-like bursts from the spiral arteries. Blood is propelled outside of the maternal vessels and sweeps over and directly bathes the syncytiotrophoblast.

Villus Branching

Although certain villi of the chorion frondosum extend from the chorionic plate to the decidua to serve as anchoring villi, most villi arborize and end freely within the intervillous space. As gestation proceeds, the short, thick, early stem villi branch to form progressively finer subdivisions and greater numbers of increasingly smaller villi (Fig. 5-12). Each of the truncal or main stem villi and their ramifications constitutes a placental lobule, or cotyledon. Each lobule is supplied with a single chorionic artery. And each lobule has a single vein, so that lobules constitute the functional units of placental architecture.

FIGURE 5-12
Electron micrographs **(A, C)** and photomicrographs **(B, D)** of early and late human placentas. **A** and **B.** Limited branching of villi is seen in this early placenta. **C** and **D.** With placental maturation, increasing villous arborization is seen, and villous capillaries lie closer to the surface of each villus. (Photomicrographs used with permission from Dr. Kurt Benirschke. Electron micrographs reproduced with permission from King BF, Menton DN: Scanning electron microscopy of human placental villi from early and late in gestation. Am J Obstet Gynecol 122:824, 1975.)



Placental Growth and Maturation

In the first trimester, placental growth is more rapid than that of the fetus. But by approximately 17 weeks' gestation, placental and fetal weights are approximately equal. By term, placental weight is approximately one sixth of fetal weight.

The mature placenta and its variant forms are discussed in detail in Chapter 6 (Shape and Size Variants). Briefly, viewed from the maternal surface, the number of slightly elevated convex areas, called lobes, varies from 10 to 38. Lobes are incompletely separated by grooves of variable depth that overlie placental septa, which arise as upward projections of decidua. The total number of placental lobes remains the same throughout gestation, and individual lobes continue to grow—although less actively in the final weeks (Crawford, 1959). Although grossly visible lobes are commonly referred to as cotyledons, this is not accurate. Correctly used, lobules or cotyledons are the functional units supplied by each main stem villus.

As villi continue to branch and the terminal ramifications become more numerous and smaller, the volume and prominence of cytotrophoblasts decrease. As the syncytium thins, the fetal vessels become more prominent and lie closer to the surface (see Fig. 5-10). The villous stroma also exhibits changes as gestation progresses. In early pregnancy, the branching connective-tissue cells are separated by an abundant loose intercellular matrix. Later, the villous stroma becomes denser, and the cells are more spindly and closely packed.

Another change in the stroma involves the infiltration of *Hofbauer cells*, which are fetal macrophages. These are nearly round with vesicular, often eccentric nuclei and very granular or vacuolated cytoplasm. They grow in number and maturational state throughout pregnancy and appear to be important mediators of protection at the maternal–fetal interface (Johnson, 2012). These macrophages are phagocytic, have an immunosuppressive phenotype, can produce various cytokines, and are capable of paracrine regulation of trophoblastic functions (Cervar, 1999; Reyes, 2017). As discussed further in Chapter 64 (Coronavirus Infections), recent studies suggest that Zika virus can infect Hofbauer cells to allow fetal transmission (Simoni, 2017).

Some of the histological changes that accompany placental growth and maturation improve transport and exchange to meet advancing fetal metabolic requirements. Among these changes are a thinner syncytiotrophoblast, significantly reduced cytotrophoblast number, decreased stroma, and increased number of capillaries with close approximation to the syncytial surface. By 16 weeks' gestation, the apparent continuity of the cytotrophoblasts is lost. At term, villi may be

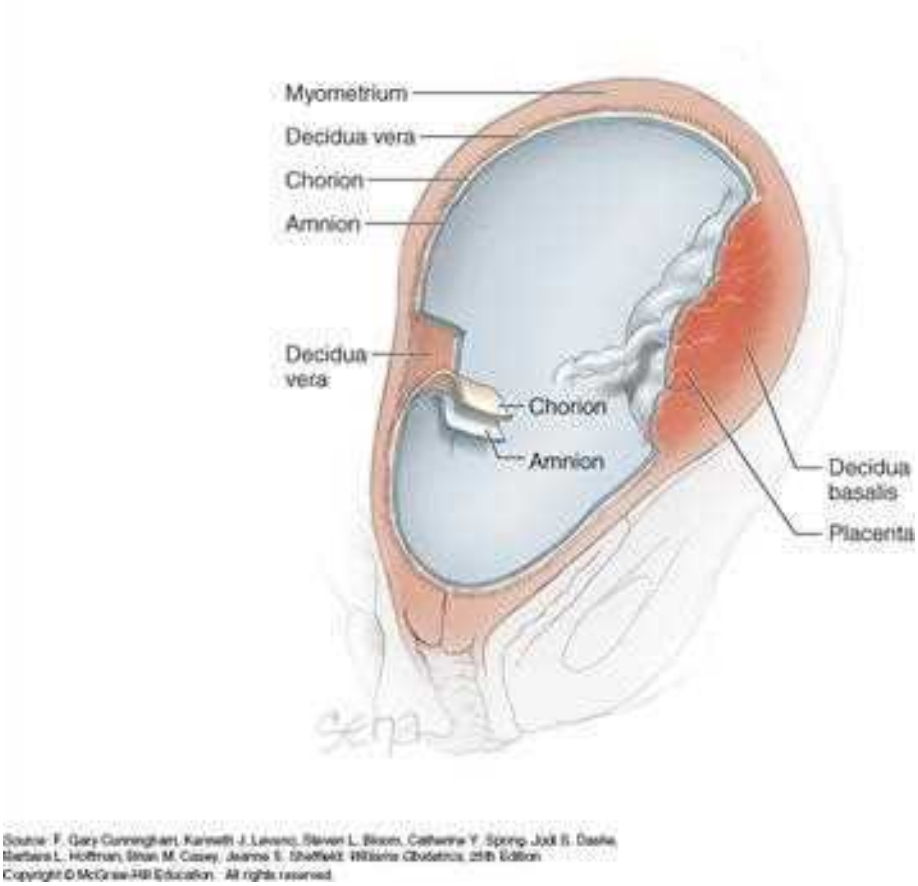
focally reduced to a thin layer of syncytium covering minimal villous connective tissue in which thin-walled fetal capillaries abut the trophoblast and dominate the villi.

There are some changes in placental architecture that can cause decreased placental exchange efficiency if they are substantive. These include thickening of the basal lamina of trophoblast or capillaries, obliteration of certain fetal vessels, greater villous stroma, and fibrin deposition on the villous surface.

Placental Circulation

Because the placenta is functionally an intimate approximation of the fetal capillary bed to maternal blood, its gross anatomy primarily concerns vascular relations. The fetal surface is covered by the transparent amnion, beneath which chorionic vessels course. A section through the placenta includes amnion, chorion, chorionic villi and intervillous space, decidual (basal) plate, and myometrium (Figs. 5-13 and 5-14).

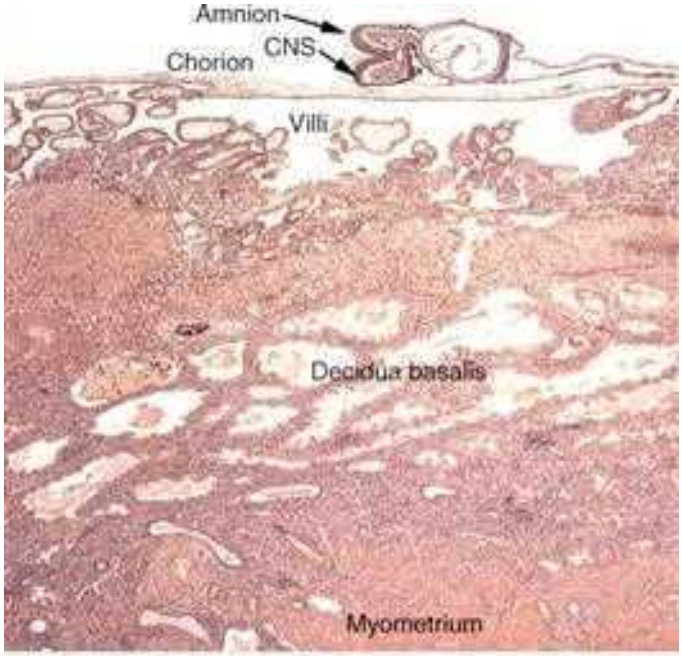
FIGURE 5-13
Uterus showing a normal placenta and its membranes in situ.



Fetal Circulation

Deoxygenated venous-like fetal blood flows to the placenta through the two umbilical arteries. As the cord joins the placenta, these umbilical vessels branch repeatedly beneath the amnion as they run across the chorionic plate. Branching continues within the villi to ultimately form capillary networks in the terminal villous branches. Blood with significantly higher oxygen content returns from the placenta via a single umbilical vein to the fetus.

FIGURE 5-14
Photomicrograph of early implanted blastocyst. Trophoblasts are seen invading the decidua basalis. CNS = central nervous system. (Used with permission from Dr. Kurt Benirschke.)



The branches of the umbilical vessels that traverse along the fetal surface of the placenta in the chorionic plate are referred to as the placental surface or chorionic vessels. These vessels are responsive to vasoactive substances, but anatomically, morphologically, histologically, and functionally, they are unique. Chorionic arteries always cross over chorionic veins. Vessels are most readily recognized by this interesting relationship, but they are difficult to distinguish by histological criteria.

Truncal arteries are perforating branches of the surface arteries that pass through the chorionic plate. Each truncal artery supplies one main stem villus and thus one cotyledon. As the artery penetrates the chorionic plate, its wall loses smooth muscle, and its caliber increases. The loss of muscle continues as the truncal arteries and veins branch into their smaller rami.

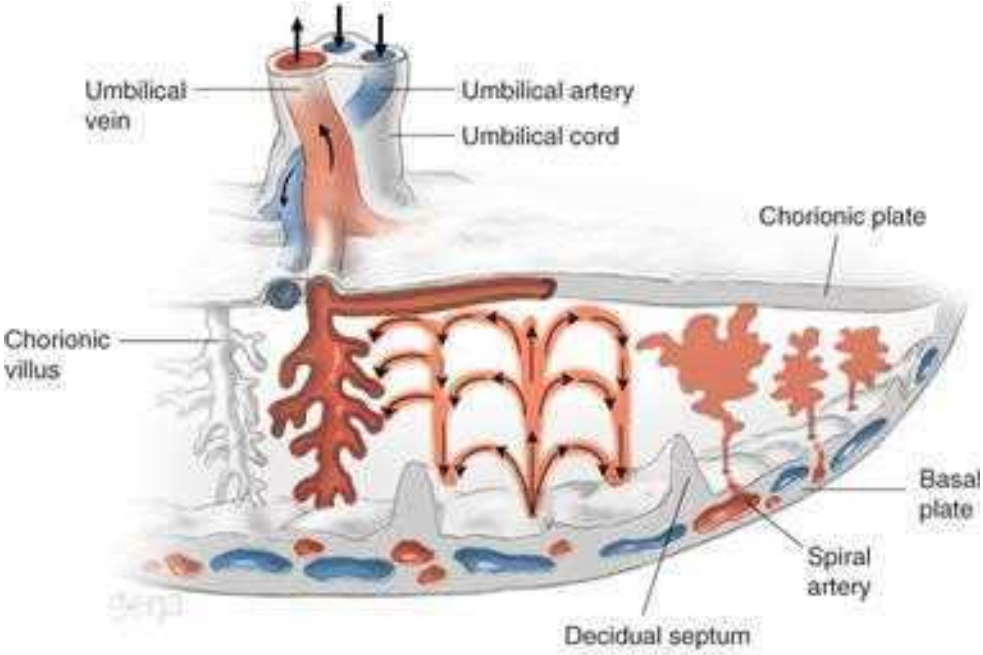
Before 10 weeks' gestation, there is no end-diastolic flow pattern within the umbilical artery at the end of the fetal cardiac cycle (Fisk, 1988; Loquet, 1988). After 10 weeks, however, end-diastolic flow appears and is maintained throughout normal pregnancy. Clinically, these flow patterns are studied with Doppler sonography to assess fetal well-being (Chap. 10, Doppler).

Maternal Circulation

Mechanisms of placental blood flow must allow blood to leave maternal circulation; flow into an amorphous space lined by syncytiotrophoblast, rather than endothelium; and return through maternal veins without producing arteriovenous-like shunts that would prevent maternal blood from remaining in contact with villi long enough for adequate exchange. For this, maternal blood enters through the basal plate and is driven high up toward the chorionic plate by arterial pressure before laterally dispersing (Fig. 5-15). After bathing the external microvillous surface of chorionic villi, maternal blood drains back through venous orifices in the basal plate and enters uterine veins. Thus, maternal blood traverses the placenta randomly without preformed channels. The previously described trophoblast invasion of the spiral arteries creates low-resistance vessels that can accommodate massive increase in uterine perfusion during gestation. Generally, spiral arteries are perpendicular to, but veins are parallel to, the uterine wall. This arrangement aids closure of veins during a uterine contraction and prevents the exit of maternal blood from the intervillous space. The number of arterial openings into the intervillous space is gradually reduced by cytotrophoblastic invasion. There are about 120 spiral arterial entries into the intervillous space at term (Brosens, 1963). These discharge blood in spurts that bathes the adjacent villi (Borell, 1958). After the 30th week, a prominent venous plexus lies between the decidua basalis and myometrium and helps develop the cleavage plane needed for placental separation after delivery.

FIGURE 5-15

Schematic drawing of a section through a full-term placenta. Maternal blood flows into the intervillous spaces in funnel-shaped spurts. Exchanges occur with fetal blood as maternal blood flows around the villi. Inflowing arterial blood pushes venous blood into the endometrial veins, which are scattered over the entire surface of the decidua basalis. Note also that the umbilical arteries carry deoxygenated fetal blood to the placenta and that the umbilical vein carries oxygenated blood to the fetus. Placental lobes are separated from each other by placental (decidual) septa.



Both inflow and outflow are curtailed during uterine contractions. Bleker and associates (1975) used serial sonography during normal labor and found that placental length, thickness, and surface area grew during contractions. They attributed this to distention of the intervillous space by impairment of venous outflow compared with arterial inflow. During contractions, therefore, a somewhat larger volume of blood is available for exchange even though the rate of flow is decreased. Similarly, Doppler velocimetry has shown that diastolic flow velocity in spiral arteries is diminished during uterine contractions. Thus, principal factors regulating intervillous space blood flow are arterial blood pressure, intrauterine pressure, uterine contraction pattern, and factors that act specifically on arterial walls.

Breaks in the Placental "Barrier"

The placenta does not maintain absolute integrity of the fetal and maternal circulations. There are numerous examples of trafficking cells between mother and fetus in both directions. This situation is best exemplified clinically by erythrocyte D-antigen alloimmunization (Chap. 15, Red Cell Alloimmunization). Fetal cell admixtures likely are small in most cases, although rarely the fetus exsanguinates into the maternal circulation.

Fetal cells can also engraft in the mother during pregnancy and can be identified decades later. Fetal lymphocytes, CD34+ mesenchymal stem cells, and endothelial colony-forming cells all reside in maternal blood, bone marrow, or uterine vasculature (Nguyen, 2006; Piper, 2007; Sipos, 2013). Termed *microchimerism*, such residual stem cells have been implicated in the disparate female:male ratio of autoimmune disorders (Greer, 2011; Stevens, 2006). As discussed in Chapter 59 (Systemic Lupus Erythematosus), they are associated with the pathogenesis of lymphocytic thyroiditis, scleroderma, and systemic lupus erythematosus.

Fetal–Maternal Interface

Survival of the semiallogenic fetal graft requires complex interactions between fetal trophoblasts and maternal decidual immune cells. The fetal–maternal interface is not immunologically inert. Rather, it is an active hub of interactions that allows implantation and appropriate placental development and ensures immunotolerance of the fetus. Despite this, a functional immune system must be maintained to protect the mother.

Immunogenicity of the Trophoblasts

Trophoblastic cells are the only fetus-derived cells in direct contact with maternal tissues and blood. Fetal syncytiotrophoblast synthesizes and secretes numerous factors that regulate the immune responses of maternal cells both at the implantation site and systemically.

Human leukocyte antigens (HLAs) are the human analogue of the major histocompatibility complex (MHC) (Hunt, 1992). There are 17 HLA class I genes, including three classic genes, HLA-A, -B, and -C, that encode the major class I (class Ia) transplantation antigens. Three other class I genes, designated HLA-E, -F, and -G, encode class Ib HLA antigens. MHC class I and II antigens are absent from villous trophoblasts, which appear to be immunologically inert at all gestational stages (Weetman, 1999). Invasive extravillous cytotrophoblasts do express MHC class I molecules. Thus, the ability of these cells to bypass transplantation rejection is the focus of considerable study.

Moffett-King (2002) reasoned that normal implantation depends on controlled trophoblastic invasion of maternal decidua and spiral arteries. Such invasion must proceed far enough to provide for normal fetal growth and development, but a mechanism must regulate invasion depth. She suggests that dNK cells combined with unique expression of three specific HLA class I genes in extravillous cytotrophoblasts act in concert to permit and subsequently limit trophoblast invasion.

Class I antigens in extravillous cytotrophoblasts are accounted for by the expression of classic HLA-C and nonclassic class Ib molecules of HLA-E and HLA-G. HLA-G antigen is expressed only in humans, with expression restricted to extravillous cytotrophoblasts contiguous with maternal tissues. Embryos used for in vitro fertilization do not implant if they do not express a soluble HLA-G isoform (Fuzzi, 2002). Thus, HLA-G may be immunologically permissive of the maternal–fetal antigen mismatch (LeBouteiller, 1999). HLA-G has a proposed role in protecting extravillous trophoblasts from immune rejection via modulation of dNK functions

(Apps, 2011; Rajagopalan, 2012). Last, Goldman-Wohl and associates (2000) have provided evidence for abnormal HLA-G expression in extravillous trophoblasts from women with preeclampsia.

Decidual Immune Cells

Natural killer cells are the predominant population of leukocytes present in midluteal phase endometrium and in decidua throughout the first trimester (Johnson, 1999). By term, however, relatively few dNK cells are present in decidua. In first-trimester decidua, dNK cells lie close to extravillous trophoblasts, and there they purportedly serve to regulate invasion. These dNKs have a distinct phenotype characterized by a high surface density of CD56 or neural cell adhesion molecules (Manaster, 2008; Moffett-King, 2002). Their infiltration is increased by progesterone and by stromal cell production of IL-15 and decidual prolactin (Dunn, 2002; Gubbay, 2002). Although dNK cells have the capacity for cytotoxicity, they are not cytotoxic toward fetal trophoblasts. Their cytotoxic potential is prevented by molecular cues from decidual macrophages. In addition, the expression of specific HLA molecules protects against dNK killing. Also, dNK cells function to restrict trophoblast invasiveness to protect the mother.

Of other cell types, *decidual macrophages* are distinct from proinflammatory M1 or antiinflammatory M2 macrophages**.** Decidual macrophages express the complement receptor CD11c at high or low levels: CD11cHI and CD11cLO. These cells function to regulate adaptive T cell responses; control dNK differentiation, activation, and cytotoxicity; and produce antiinflammatory cytokines such as IL-10 to ensure fetal tolerance and inhibition of harmful immune responses.

Dendritic cells are cells that present antigens to T cells. They play an important role in the development of a receptive endometrium for implantation.

Maternal T cells, as part of the adaptive immune response, increase in number and function after encounter with a specific antigen. These cells subsequently retain the ability to respond rapidly in a subsequent encounter with the same antigen. Specific populations of Treg cells persist and can protect against aberrant immune responses. During pregnancy, there is a systemic expansion of maternal Treg cell populations. These cells are FOXP3+ cells with defined fetal specificity. They are immunosuppressive and play a role in fetal tolerance.

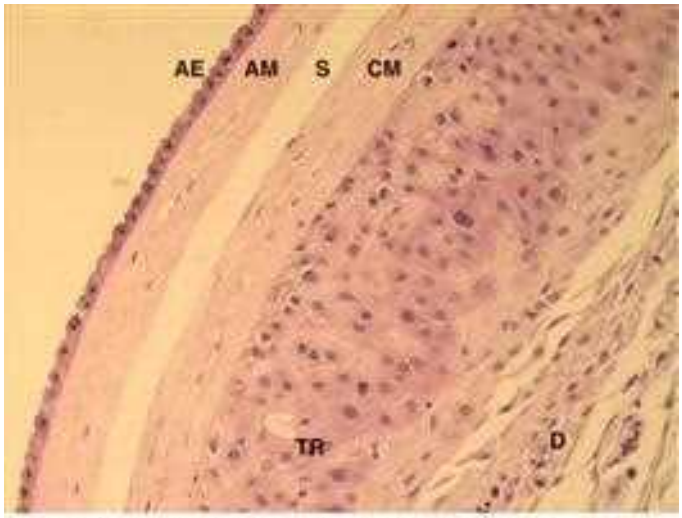
AMNION

At term, the amnion is a tough and tenacious but pliable membrane. This innermost avascular fetal membrane is contiguous with amnionic fluid and plays a role of incredible importance in human pregnancy. The amnion provides almost all tensile strength of the fetal membranes. Thus, its resilience to rupture is vitally important to successful pregnancy outcome. Indeed, preterm rupture of fetal membranes is a major cause of preterm delivery (Chap. 42, Management of Preterm Premature Rupture of Membranes).

Bourne (1962) described five separate amnion layers. The inner surface, which is bathed by amnionic fluid, is an uninterrupted, single layer of cuboidal epithelium (Fig. 5-16). This epithelium is attached firmly to a distinct basement membrane that is connected to an acellular compact layer composed primarily of interstitial collagens. On the outer side of the compact layer, there is a row of fibroblast-like mesenchymal cells, which are widely dispersed at term. There also are a few fetal macrophages in the amnion. The outermost amnion layer is the relatively acellular zona spongiosa, which is contiguous with the second fetal membrane, the chorion laeve. The human amnion lacks smooth muscle cells, nerves, lymphatics, and importantly, blood vessels.

FIGURE 5-16

Photomicrograph of fetal membranes. From left to right: AE = amnion epithelium; AM = amnion mesenchyme; S = zona spongiosa; CM = chorionic mesenchyme; TR = trophoblast; D = decidua. (Used with permission from Dr. Judith R. Head.)



Amnion Development

Early during implantation, a space develops between the embryonic cell mass and adjacent trophoblastic cells (see Fig. 5-9). Small cells that line this inner surface of trophoblasts have been called amniogenic cells—precursors of amnionic epithelium. The amnion is first identifiable on the 7th or 8th day of embryo development. It

is initially a minute vesicle, which then develops into a small sac that covers the dorsal embryo surface. As the amnion enlarges, it gradually engulfs the growing embryo, which prolapses into its cavity (Benirschke, 2012).

Distention of the amnionic sac eventually brings it into contact with the interior surface of the chorion laeve. Apposition of the chorion laeve and amnion near the end of the first trimester then causes an obliteration of the extraembryonic coelom. The amnion and chorion laeve, although slightly adhered, are never intimately connected and can be separated easily. Placental amnion covers the placental surface and thereby is in contact with the adventitial surface of chorionic vessels. Umbilical amnion covers the umbilical cord. With diamnionic-monochorionic placentas, there is no intervening tissue between the fused amnions. In the conjoined portion of membranes of diamnionic-dichorionic twin placentas, amnions are separated by fused chorion laeve.

Amnionic fluid fills this amnionic sac. Until about 34 weeks' gestation, the normally clear fluid increases in volume as pregnancy progresses. After this, the volume declines. At term, amnionic fluid averages 1000 mL, although this may vary widely in normal and especially abnormal conditions. The origin, composition, circulation, and function of amnionic fluid are discussed further in Chapter 11 (Normal Amnionic Fluid Volume).

Amnion Cell Histogenesis

Epithelial cells of the amnion derive from fetal ectoderm of the embryonic disc. They do not arise by delamination from trophoblasts. This is an important consideration from both embryological and functional perspectives. For example, HLA class I gene expression in amnion is more akin to that in embryonic cells than to that in trophoblasts.

The fibroblast-like mesenchymal cell layer of the amnion is likely derived from embryonic mesoderm. Early in human embryogenesis, the amnionic mesenchymal cells lie immediately adjacent to the basal surface of the amnion epithelium. At this time, the amnion surface is a two-cell layer with approximately equal numbers of epithelial and mesenchymal cells. Simultaneously with growth and development, interstitial collagens are deposited between these two cell layers. This marks formation of the amnion compact layer, which separates the two layers of amnion cells.

As the amnionic sac expands, the compactness of the mesenchymal cells is progressively reduced, and they become sparsely distributed. Early in pregnancy, amnionic epithelium replicates at a rate appreciably faster than mesenchymal cells. At term, these cells form a continuous uninterrupted epithelium on the fetal amnionic surface. Conversely, mesenchymal cells are widely dispersed, being connected by a fine lattice network of extracellular matrix with the appearance of long slender fibrils.

Amnion Epithelial Cells

The apical surface of the amnionic epithelium is replete with highly developed microvilli. This structure reflects its function as a major site of transfer between amnionic fluid and amnion. This epithelium is metabolically active, and its cells synthesize tissue inhibitor of MMP-1, prostaglandin E_2 (PGE_2), and fetal fibronectin (fFN) (Rowe, 1997). Although epithelia produce fFN, recent studies suggest that fibronectin functions in the underlying mesenchymal cells. Here, fFN promotes synthesis of MMPs that break down the strength-bearing collagens and enhance prostaglandin synthesis to prompt uterine contractions (Mogami, 2013). This pathway is upregulated in premature rupture of membranes induced by thrombin or infection-induced release of fFN (Chigusa, 2016; Mogami, 2014).

Epithelial cells may respond to signals derived from the fetus or the mother, and they are responsive to various endocrine or paracrine modulators. Examples include oxytocin and vasopressin, both of which increase PGE_2 production in vitro (Moore, 1988). They may also produce cytokines such as IL-8 during labor initiation (Elliott, 2001).

Amnionic epithelium also synthesizes vasoactive peptides, including endothelin and parathyroid hormone-related protein (Economos, 1992; Germain, 1992). The tissue produces brain natriuretic peptide (BNP) and corticotropin-releasing hormone (CRH), which are peptides that invoke smooth-muscle relaxation (Riley, 1991; Warren, 1995). BNP production is positively regulated by mechanical stretch in fetal membranes and is proposed to function in uterine quiescence. Epidermal growth factor, a negative regulator of BNP, is upregulated in the membranes at term and leads to a decline in BNP-regulated uterine quiescence (Carvajal, 2013). It seems reasonable that vasoactive peptides produced in amnion gain access to the adventitial surface of chorionic vessels. Thus, the amnion may be involved in modulating chorionic vessel tone and blood flow. Amnion-derived vasoactive peptides function in both maternal and fetal tissues in diverse physiological processes. After their secretion, these bioactive agents enter amnionic fluid and thereby are available to the fetus by swallowing and inhalation.

Amnion Mesenchymal Cells

Mesenchymal cells of the amnionic fibroblast layer are responsible for other major functions. Synthesis of interstitial collagens that compose the compact layer of the amnion—the major source of its tensile strength—takes place in mesenchymal cells (Casey, 1996). At term the generation of cortisol by 11β-hydroxysteroid dehydrogenase may contribute to membrane rupture via reduction of collagen abundance (Mi, 2017). Mesenchymal cells also synthesize cytokines that include IL-6, IL-8, and MCP-1. Cytokine synthesis rises in response to bacterial toxins and IL-1. This functional capacity of amnion mesenchymal cells is an important consideration in amnionic fluid study of labor-associated accumulation of inflammatory mediators (Garcia-Velasco, 1999). Finally, mesenchymal cells may be a greater source of PGE_2 than epithelial cells, especially in the case of premature membrane rupture (Mogami, 2013; Whittle, 2000).

Tensile Strength

During tests of tensile strength, the decidua and then the chorion laeve give way long before the amnion ruptures. Indeed, the membranes are elastic and can expand to twice normal size during pregnancy (Benirschke, 2012). The amnion tensile strength resides almost exclusively in the compact layer, which is composed of cross-linked interstitial collagens I and III and lesser amounts of collagens V and VI.

Collagens are the primary macromolecules of most connective tissues. Collagen I is the major interstitial collagen in tissues characterized by great tensile strength, such as bone and tendon. In other tissues, collagen III is believed to contribute to tissue integrity and provides both tissue extensibility and tensile strength. For

example, the ratio of collagen III to collagen I in the walls of a number of highly extensible tissues—amnionic sac, blood vessels, urinary bladder, bile ducts, intestine, and gravid uterus—is greater than that in nonelastic tissues (Jeffrey, 1991).

Amnion tensile strength is regulated in part by fibrillar collagen assembly. This process is influenced by the interaction fibrils with proteoglycans such as decorin and biglycan (Chap. 21, Cervical Ripening). Reduction of these proteoglycans is reported to perturb fetal membrane function (Horgan, 2014; Wu, 2014). Fetal membranes overlying the cervix have a regional shift in gene expression and lymphocyte activation that set in motion an inflammatory cascade (Marcellin, 2017). This change may contribute to tissue remodeling and loss of tensile strength in the amnion (Moore, 2009).

Metabolic Functions

The amnion is metabolically active, is involved in solute and water transport for amnionic fluid homeostasis, and produces an impressive array of bioactive compounds. The amnion is responsive both acutely and chronically to mechanical stretch, which alters amnionic gene expression (Carvajal, 2013; Nemeth, 2000). This in turn may trigger both autocrine and paracrine responses that include production of MMPs, IL-8, and collagenase (Bryant-Greenwood, 1998; Mogami, 2013). Such factors may modulate changes in membrane properties during labor.

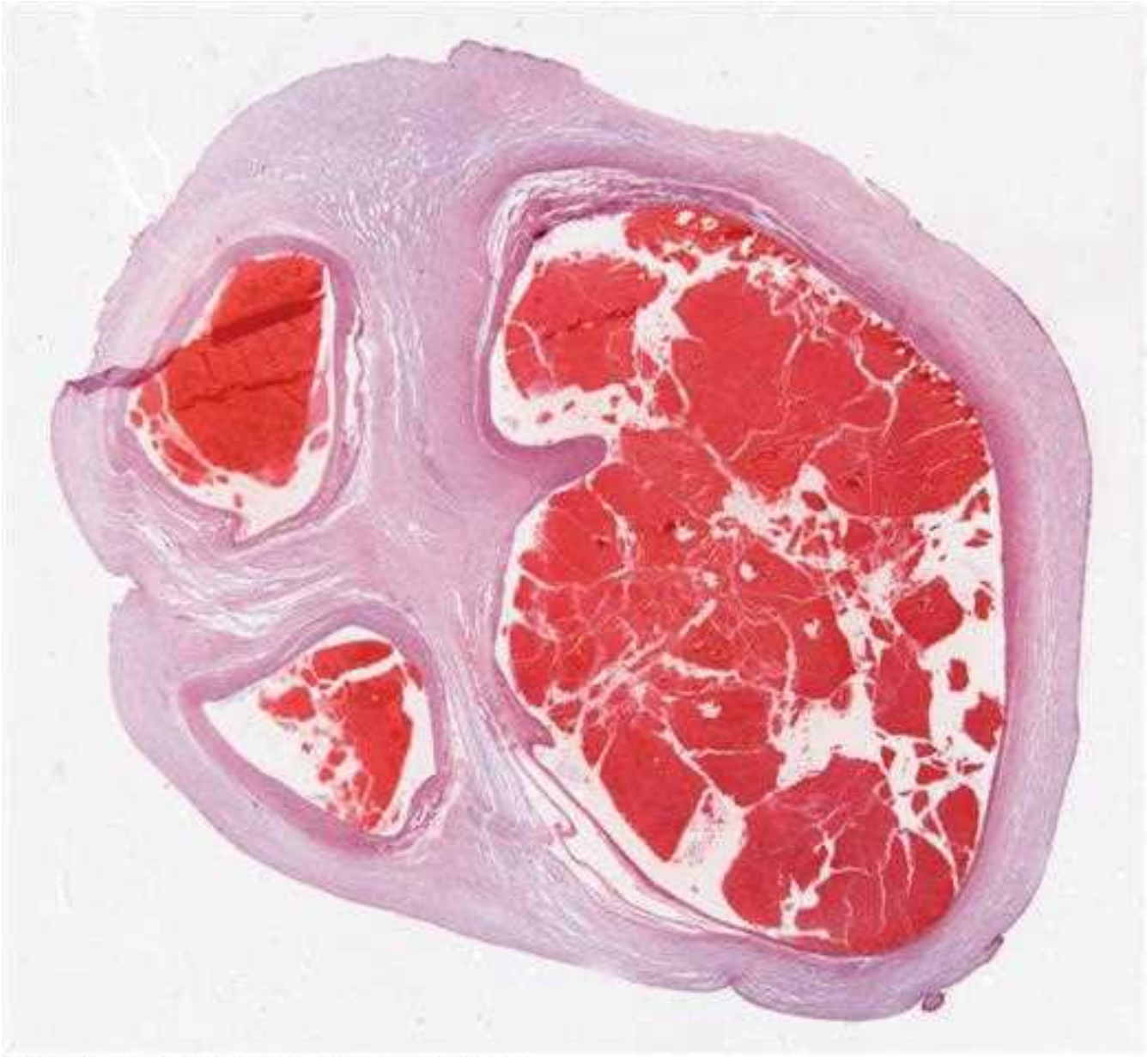
UMBILICAL CORD

The yolk sac and the umbilical vesicle into which it develops are prominent early in pregnancy. At first, the embryo is a flattened disc interposed between amnion and yolk sac (see Fig. 5-9). Its dorsal surface grows faster than the ventral surface, in association with the elongation of its neural tube. Thus, the embryo bulges into the amnionic sac, and the dorsal part of the yolk sac is incorporated into the embryo body to form the gut. The allantois projects into the base of the body stalk from the caudal wall of the yolk sac and later, from the anterior wall of the hindgut.

As pregnancy advances, the yolk sac becomes smaller and its pedicle relatively longer. By the middle of the third month, the expanding amnion obliterates the extraembryonic coelom, fuses with the chorion laeve, and covers the bulging placental disc and the lateral surface of the body stalk. The latter is then called the umbilical cord—or funis. A more detailed description of this cord and potential abnormalities is found in Chapter 6 (Umbilical Cord).

The cord at term normally has two arteries and one vein (Fig. 5-17). The right umbilical vein usually disappears early during fetal development, leaving only the original left vein.

FIGURE 5-17
Cross-section of umbilical cord. The large umbilical vein carries oxygenated blood to the fetus *(right)*. To its left are the two smaller umbilical arteries, carrying deoxygenated blood from the fetus to the placenta. (Used with permission from Dr. Mandolin S. Ziadie.)



The umbilical cord extends from the fetal umbilicus to the fetal surface of the placenta, that is, the chorionic plate. Blood flows from the umbilical vein toward the fetus. Blood then takes a path of least resistance via two routes within the fetus. One is the ductus venosus, which empties directly into the inferior vena cava (Fig. 7-9). The other route consists of numerous smaller openings into the hepatic circulation. Blood from the liver flows into the inferior vena cava via the hepatic vein. Resistance in the ductus venosus is controlled by a sphincter that is situated at the origin of the ductus at the umbilical recess and is innervated by a vagus nerve branch.

Blood exits the fetus via the two umbilical arteries. These are anterior branches of the internal iliac artery and become obliterated after birth to form the medial umbilical ligaments.

PLACENTAL HORMONES

The production of steroid and protein hormones by human trophoblasts is greater in amount and diversity than that of any single endocrine tissue in all of mammalian physiology. A compendium of average production rates for various steroid hormones in nonpregnant and in near-term pregnant women is given in Table 5-1. It is apparent that alterations in steroid hormone production that accompany normal human pregnancy are incredible. The human placenta also synthesizes an enormous amount of protein and peptide hormones, summarized in Table 5-2. Another remarkable feature is the successful physiological adaptations of pregnant women to the unique endocrine milieu, and this is discussed throughout Chapter 4 (Reproductive Tract).

TABLE 5-1

Steroid Production Rates in Nonpregnant and Near-Term Pregnant Women

	Production Rates (mg/24 hr)	
Steroid[a]	**Nonpregnant**	**Pregnant**
Estradiol-17β	0.1–0.6	15–20
Estriol	0.02–0.1	50–150
Progesterone	0.1–40	250–600
Aldosterone	0.05–0.1	0.250–0.600
Deoxycorticosterone	0.05–0.5	1–12
Cortisol	10–30	10–20

[a]Estrogens and progesterone are produced by placenta. Aldosterone is produced by the maternal adrenal in response to the stimulus of angiotensin II. Deoxycorticosterone is produced in extraglandular tissue sites by way of the 21-hydroxylation of plasma progesterone. Cortisol production during pregnancy is not increased, even though the blood levels are elevated because of decreased clearance caused by increased cortisol-binding globulin.

TABLE 5-2

Protein Hormones Produced by the Human Placenta

Hormone	Primary Non-placental Site of Expression	Shares Structural or Function Similarity	Functions
Human chorionic gonadotropin (hCG)	—	LH, FSH, TSH	Maintains corpus luteum function Regulates fetal testis testosterone secretion Stimulates maternal thyroid
Placental lactogen (PL)	—	GH, prolactin	Aids maternal adaptation to fetal energy requirements
Adrenocorticotropin (ACTH)	Hypothalamus	—	
Corticotropin-releasing hormone (CRH)	Hypothalamus	—	Relaxes smooth-muscle; initiates parturition? Promotes fetal and maternal glucocorticoid production
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	—	Regulates trophoblast hCG production
Thyrotropin (TRH)	Hypothalamus		Unknown
Growth hormone- releasing hormone (GHRH)	Hypothalamus	—	Unknown
Growth hormone variant (hGH-V)	—	GH variant not found in pituitary	Potentially mediates pregnancy insulin resistance
Neuropeptide Y	Brain		Potential regulates CRH release by trophoblasts
Parathyroid-releasing protein (PTH-rp)	—		Regulates transfer of calcium and other solutes; regulates fetal mineral homeostasis
Inhibin	Ovary/testis		Potentially inhibits FSH-mediated ovulation; regulates hCG synthesis
Activin	Ovary/testis		Regulates placental GnRH synthesis

GH = growth hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

Human Chorionic Gonadotropin

Biosynthesis

Chorionic gonadotropin is a glycoprotein with biological activity similar to that of LH, and both act via the same LH-hCG receptor. hCG has with a molecular weight of 36,000 to 40,000 Da and has the highest carbohydrate content of any human hormone—30 percent. The carbohydrate component, and especially the terminal sialic acid, protects the molecule from catabolism. As a result, the 36-hour plasma half-life of intact hCG is much longer than the 2 hours for LH. The hCG molecule is composed of two dissimilar subunits termed α and β subunits. These are noncovalently linked and are held together by electrostatic and hydrophobic forces. Isolated subunits are unable to bind the LH-hCG receptor and thus lack biological activity.

hCG is produced almost exclusively in the placenta, but low levels are synthesized in the fetal kidney. Other fetal tissues produce either the β-subunit or intact hCG molecule (McGregor, 1981, 1983).

The hCG hormone is structurally related to three other glycoprotein hormones—LH, FSH, and TSH. All four glycoproteins share a common α-subunit. However, each of their β-subunits, although sharing certain similarities, is characterized by a distinctly different amino acid sequence.

Synthesis of the α- and β-chains of hCG is regulated separately. A single gene located on chromosome 6 encodes the α-subunit. Seven genes on chromosome 19 encode for the β-hCG–β-LH family of subunits. Six genes code for β-hCG and one for β-LH (Miller-Lindholm, 1997). Both subunits are synthesized as larger precursors, which are then cleaved by endopeptidases. Intact hCG is then assembled and rapidly released by secretory granule exocytosis (Morrish, 1987). There are multiple forms of hCG in maternal plasma and urine that vary enormously in bioactivity and immunoreactivity. Some result from enzymatic degradation, and others from modifications during molecular synthesis and processing.

Before 5 weeks, hCG is expressed both in the syncytiotrophoblast and in cytotrophoblasts (Maruo, 1992). Later, in the first trimester when maternal serum levels peak, hCG is produced almost solely in the syncytiotrophoblast (Beck, 1986; Kurman, 1984). At this time, mRNA concentrations of both α- and β-subunits in the syncytiotrophoblast are greater than at term (Hoshina, 1982). This may be an important consideration when hCG is used as a screening procedure to identify abnormal fetuses.

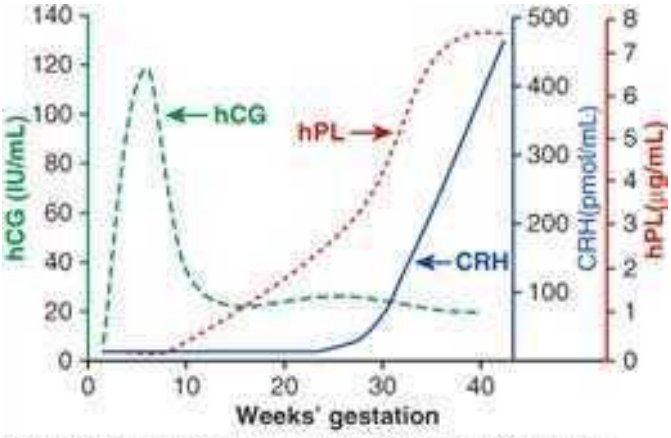
Circulating free levels of β-subunit are low to undetectable throughout pregnancy. In part, this is the result of its rate-limiting synthesis. Free α-subunits that do not combine with the β-subunit are found in placental tissue and maternal plasma. Levels of the α-subunit rise gradually and steadily until they plateau at approximately 36 weeks' gestation. At this time, they account for 30 to 50 percent of hormone (Cole, 1997). Thus, α-hCG secretion roughly corresponds to placental mass, whereas secretion of complete hCG molecules is maximal at 8 to 10 weeks.

Concentrations in Serum and Urine

The combined hCG molecule is detectable in plasma of pregnant women 7 to 9 days after the midcycle surge of LH that precedes ovulation. Thus, hCG likely enters maternal blood at the time of blastocyst implantation. Plasma levels rise rapidly, doubling every 2 days in the first trimester (Fig. 5-18). Appreciable fluctuations in levels for a given patient are observed on the same day.

FIGURE 5-18

Distinct profiles for the concentrations of human chorionic gonadotropin (hCG), human placental lactogen (hPL), and corticotropin-releasing hormone (CRH) in serum of women throughout normal pregnancy.



Intact hCG circulates as multiple highly related isoforms with variable cross-reactivity between commercial assays. Thus, calculated serum hCG levels can vary considerably among the more than a hundred available assays. This emphasizes the need to use the same assay type when clinically measuring serial hCG levels. Peak maternal plasma levels reach approximately 50,000 to 100,000 mIU/mL between the 60th and 80th days after menses. At 10 to 12 weeks' gestation, plasma levels begin to decline, and a nadir is reached by approximately 16 weeks. Plasma levels are maintained at this lower level for the remainder of pregnancy.

The pattern of hCG appearance in fetal blood is similar to that in the mother. Fetal plasma levels, however, are only about 3 percent of those in maternal plasma. Amnionic fluid hCG concentration early in pregnancy is similar to that in maternal plasma. As pregnancy progresses, hCG concentration in amnionic fluid declines, and near term the levels are approximately 20 percent of those in maternal plasma.

Maternal urine contains the same variety of hCG degradation products as maternal plasma. The principal urinary form is the terminal product of hCG degradation, namely, the β-core fragment. Concentrations of this fragment follow the same general pattern as that in maternal plasma, peaking at approximately 10 weeks' gestation. Importantly, the so-called β-subunit antibody used in most pregnancy tests reacts with both intact hCG—the major form in the plasma, and with fragments of hCG—the major forms found in urine.

hCG Regulation

Placental gonadotropin-releasing hormone (GnRH) is likely involved in the regulation of hCG formation. Both GnRH and its receptor are expressed by cytotrophoblasts and by the syncytiotrophoblast (Wolfahrt, 1998). GnRH administration elevates circulating hCG levels, and cultured trophoblasts respond to GnRH treatment and raise hCG secretion (Iwashita, 1993; Siler-Khodr, 1981). Pituitary GnRH production also is regulated by inhibin and activin. In cultured placental cells, activin stimulates and inhibin inhibits GnRH and hCG production (Petraglia, 1989; Steele, 1993).

Renal clearance of hCG accounts for 30 percent of its metabolic clearance. The remainder is likely cleared by metabolism in the liver (Wehmann, 1980). Clearances of β- and α-subunits are approximately 10- and 30-fold, respectively, greater than that of intact hCG. In pregnancies complicated by chronic renal disease, hCG clearance can be markedly decreased.

Biological Functions

Both hCG subunits are required for binding to the LH-hCG receptor in the corpus luteum and the fetal testis. LH-hCG receptors are present in various other tissues, but their roles there are less defined.

The best-known biological function of hCG is the so-called rescue and maintenance of corpus luteum function—that is, continued progesterone production. This is only an incomplete explanation for the physiological function of hCG in pregnancy. For example, maximum plasma hCG concentrations are attained well after hCG-

stimulated corpus luteum secretion of progesterone has ceased. Specifically, luteal progesterone synthesis begins to decline at about 6 weeks despite continued and increasing hCG production.

A second hCG role is stimulation of fetal testicular testosterone secretion. This is maximum approximately when hCG levels peak. Thus, at a critical time in male sexual differentiation, hCG enters fetal plasma from the syncytiotrophoblast. In the fetus, it acts as an LH surrogate to stimulate Leydig cell replication and testosterone synthesis to promote male sexual differentiation (Chap. 3, Embryology of the Gonads). Before approximately 110 days, there is no vascularization of the fetal anterior pituitary from the hypothalamus. Thus, pituitary LH secretion is minimal, and hCG acts as LH before this time. Thereafter, as hCG levels fall, pituitary LH maintains modest testicular stimulation.

The maternal thyroid gland is also stimulated by large quantities of hCG. In some women with gestational trophoblastic disease, biochemical and clinical evidence of hyperthyroidism sometimes develops (Chap. 20, Diagnosis). This once was attributed to formation of chorionic thyrotropins by neoplastic trophoblasts. It was subsequently shown, however, that some forms of hCG bind to TSH receptors on thyrocytes (Hershman, 1999). And, treatment of men with exogenous hCG increases thyroid activity. The thyroid-stimulatory activity in plasma of first-trimester pregnant women varies appreciably from sample to sample. Modifications of hCG oligosaccharides likely are important in the capacity of hCG to stimulate thyroid function. For example, acidic isoforms stimulate thyroid activity, and some more basic isoforms stimulate iodine uptake (Kraiem, 1994; Tsuruta, 1995; Yoshimura, 1994). Finally, the LH-hCG receptor is expressed by thyrocytes, which suggests that hCG stimulates thyroid activity via the LH-hCG receptor as well as by the TSH receptor (Tomer, 1992).

Other hCG functions include promotion of relaxin secretion by the corpus luteum (Duffy, 1996). LH-hCG receptors are found in myometrium and in uterine vascular tissue. It has been hypothesized that hCG may promote uterine vascular vasodilatation and myometrial smooth muscle relaxation (Kurtzman, 2001). Chorionic gonadotropin also regulates expansion of dNK cell numbers during early stages of placentation, thus ensuring appropriate establishment of pregnancy (Kane, 2009).

Abnormally High or Low Levels

There are several clinical circumstances in which substantively higher maternal plasma hCG levels are found. Some examples are multifetal pregnancy, erythroblastosis fetalis associated with fetal hemolytic anemia, and gestational trophoblastic disease. Relatively higher hCG levels may be found in women carrying a fetus with Down syndrome. This observation is used in biochemical screening tests (Chap. 14, Traditional Aneuploidy Screening Tests). The reason for the elevation is not clear, but reduced placental maturity has been speculated. Various malignant tumors also produce hCG, sometimes in large amounts—especially trophoblastic neoplasms (Chaps. 9 (Initial Prenatal Evaluation) and 20, Diagnosis).

Relatively lower hCG plasma levels are found in women with early pregnancy wastage, including ectopic pregnancy (Chap. 19, Multimodality Diagnosis). hCG is produced in very small amounts in normal tissues of men and nonpregnant women, perhaps primarily in the anterior pituitary gland. Nonetheless, the detection of hCG in blood or urine almost always indicates pregnancy (Chap. 9, Diagnosis of Pregnancy).

Human Placental Lactogen

Biosynthesis

This is a single, nonglycosylated polypeptide chain with a molecular weight of 22,279 Da. The sequences of hPL and of human growth hormone (hGH) are strikingly similar, with 96-percent homology. Also, hPL is structurally similar to human prolactin (hPRL), with a 67-percent amino acid sequence similarity. Because of these similarities, it was called human placental lactogen or chorionic growth hormone. Currently, human placental lactogen is used by most.

There are five genes in the growth hormone–placental lactogen gene cluster that are linked and located on chromosome 17. hPL is concentrated in syncytiotrophoblast, but similar to hCG, hPL is demonstrated in cytotrophoblasts before 6 weeks (Grumbach, 1964; Maruo, 1992). Within 5 to 10 days after conception, hPL is demonstrable in the placenta and can be detected in maternal serum as early as 3 weeks. Levels of mRNA for hPL in syncytiotrophoblast remain relatively constant throughout pregnancy. This finding supports the idea that the hPL secretion rate is proportional to placental mass. Levels rise steadily until 34 to 36 weeks' gestation. The hPL production rate near term—approximately 1 g/d—is by far the greatest of any known hormone in humans. The half-life of hPL in maternal plasma is between 10 and 30 minutes (Walker, 1991). In late pregnancy, maternal serum concentrations reach levels of 5 to 15 µg/mL (see Fig. 5-18).

Very little hPL is detected in fetal blood or in the urine of the mother or newborn. Amnionic fluid levels are somewhat lower than in maternal plasma. hPL is secreted primarily into the maternal circulation, with only very small amounts in cord blood. Thus, its role in pregnancy is believed to be mediated through actions in maternal rather than in fetal tissues. Nonetheless, interest continues for the possibility that hPL serves select functions in fetal growth.

Metabolic Actions

hPL has putative actions in several important metabolic processes. First, hPL promotes maternal lipolysis with increased circulating free fatty acid levels. This provides an energy source for maternal metabolism and fetal nutrition. In vitro studies suggest that hPL inhibits leptin secretion by term syncytiotrophoblast (Coya, 2005). Prolonged maternal starvation in the first half of pregnancy leads to higher hPL plasma concentrations.

Second, hPL may aid maternal adaptation to fetal energy requirements. For example, increased maternal insulin resistance ensures nutrient flow to the fetus. It also favors protein synthesis and provides a readily available amino acid source to the fetus. To counterbalance the greater insulin resistance and prevent maternal hyperglycemia, maternal insulin levels are increased. Both hPL and prolactin signal through the prolactin receptor to increase maternal beta cell proliferation to augment insulin secretion (Georgia, 2010). In animals, prolactin and hPL upregulate serotonin synthesis, which increases beta cell proliferation (Kim, 2010). Short-term changes in plasma glucose or insulin, however, have relatively little effect on plasma hPL levels. In vitro studies of syncytiotrophoblast suggest that hPL synthesis is stimulated by insulin and insulin-like growth factor-1 and inhibited by PGE_2 and $PGF_{2\alpha}$ (Bhaumick, 1987; Genbacev, 1977).

Last, hPL is a potent angiogenic hormone. It may serve an important function in fetal vasculature formation (Corbacho, 2002).

Other Placental Protein Hormones

The placenta has a remarkable capacity to synthesize numerous peptide hormones, including some that are analogous or related to hypothalamic and pituitary hormones. In contrast to their counterparts, some of these placental peptide/protein hormones are not subject to feedback inhibition.

Hypothalamic-Like Releasing Hormones

The known hypothalamic-releasing or -inhibiting hormones include GnRH, CRH, thyrotropin-releasing hormone (TRH), growth hormone-releasing hormone, and somatostatin. For each, there is an analogous hormone produced in the human placenta (Petraglia, 1992; Siler-Khodr, 1988).

GnRH in the placenta shows its highest expression in the first trimester (Siler-Khodr, 1978, 1988). Interestingly, it is found in cytotrophoblasts, but not syncytiotrophoblast. Placenta-derived GnRH functions to regulate trophoblast hCG production and extravillous trophoblast invasion via regulation of MMP-2 and MMP-9 (Peng, 2016). Placenta-derived GnRH is also the likely cause of elevated maternal GnRH levels in pregnancy (Siler-Khodr, 1984).

CRH is a member of a larger family of CRH-related peptides that includes CRH and urocortins (Dautzenberg, 2002). Maternal serum CRH levels increase from 5 to 10 pmol/L in the nonpregnant woman to approximately 100 pmol/L in the early third trimester of pregnancy and to almost 500 pmol/L abruptly during the last 5 to 6 weeks (see Fig. 5-18). Urocortin also is produced by the placenta and secreted into the maternal circulation, but at much lower levels than seen for CRH (Florio, 2002). After labor begins, maternal plasma CRH levels rise even further (Petraglia, 1989, 1990).

The biological function of CRH synthesized in the placenta, membranes, and decidua has been somewhat defined. CRH receptors are present in many tissues including placenta. Trophoblast, amniochorion, and decidua express both CRH-R1 and CRH-R2 receptors and several variant receptors (Florio, 2000). Both CRH and urocortin enhance trophoblast secretion of adrenocorticotropic hormone (ACTH), supporting an autocrine-paracrine role (Petraglia, 1999). Large amounts of trophoblast CRH enter maternal blood.

Other proposed biological roles include induction of smooth-muscle relaxation in vascular and myometrial tissue and immunosuppression. The physiological reverse, however, induction of myometrial contractions, has been proposed for the rising CRH levels seen near term. One hypothesis suggests that CRH may be involved with parturition initiation (Wadhwa, 1998). Some evidence suggests that urocortin 2 expression is induced at term and induces expression of proinflammatory markers and prostaglandin F receptor expression in the placenta and myometrium (Voltolini, 2015). Prostaglandin formation in the placenta, amnion, chorion laeve, and decidua is increased with CRH treatment (Jones, 1989b). These observations further support a potential action in parturition timing.

Glucocorticoids act in the hypothalamus to inhibit CRH release, but in the trophoblast, glucocorticoids stimulate CRH gene expression (Jones, 1989a; Robinson, 1988). Thus, there may be a novel positive feedback loop in the placenta by which placental CRH stimulates placental ACTH to stimulate fetal and maternal adrenal glucocorticoid production with subsequent stimulation of placental CRH expression (Nicholson, 2001; Riley, 1991).

G*rowth hormone-releasing hormone* has an unknown role (Berry, 1992). Ghrelin is another regulator of hGH secretion that is produced by placental tissue (Horvath, 2001). Trophoblast ghrelin expression peaks at midpregnancy and is a paracrine regulator of differentiation or is a potential regulator of human growth hormone variant production, described next (Fuglsang, 2005; Gualillo, 2001).

Pituitary-Like Hormones

ACTH, lipotropin, and β-endorphin, which are all proteolytic products of pro-opiomelanocortin, are recovered from placental extracts (Genazzani, 1975; Odagiri, 1979). The physiological action of placental ACTH is unclear. As discussed, placental CRH stimulates synthesis and release of chorionic ACTH.

A *human growth hormone variant (hGH-V)* that is not expressed in the pituitary is expressed in the placenta. The gene encoding hGH-V is located in the hGH–hPL gene cluster on chromosome 17. Sometimes referred to as placental growth hormone, hGH-V is a 191-amino-acid protein that differs in 15 amino acid positions from the sequence for hGH. Although hGH-V retains growth-promoting and antilipogenic functions similar to those of hGH, it has reduced diabetogenic and lactogenic functions relative to hGH (Vickers, 2009). Placental hGH-V presumably is synthesized in the syncytiotrophoblast. It is believed that hGH-V is present in maternal plasma by 21 to 26 weeks' gestation, rises in concentration until approximately 36 weeks, and remains relatively constant thereafter. There is a correlation between the levels of hGH-V in maternal plasma and those of insulin-like growth factor-1. Also, hGH-V secretion by trophoblast in vitro is inhibited by glucose in a dose-dependent manner (Patel, 1995). Overexpression of hGH-V in mice causes severe insulin resistance, making it a likely candidate to mediate insulin resistance of pregnancy (Liao, 2016).

Relaxin

Expression of relaxin has been demonstrated in human corpus luteum, decidua, and placenta (Bogic, 1995). This peptide is synthesized as a single, 105-amino-acid preprorelaxin molecule that is cleaved to A and B molecules. Relaxin is structurally similar to insulin and insulin-like growth factor. Two of the three relaxin genes—*H2* and *H3*—are transcribed in the corpus luteum (Bathgate, 2002; Hudson, 1983, 1984). Decidua, placenta, and membranes express *H1* and *H2* (Hansell, 1991).

The rise in maternal circulating relaxin levels seen in early pregnancy is attributed to corpus luteum secretion, and levels parallel those of hCG. Relaxin, along with rising progesterone levels, may act on myometrium to promote relaxation and the quiescence of early pregnancy (Chap. 21, Decidua). In addition, the production of relaxin and relaxin-like factors within the placenta and fetal membranes may play an autocrine-paracrine role in postpartum regulation of extracellular matrix remodeling (Qin, 1997a,b). One important relaxin function is enhancement of the glomerular filtration rate (Chap. 4, Renal Function Tests).

Parathyroid Hormone-Related Protein

In pregnancy, circulating parathyroid hormone-related protein (PTH-rP) levels are significantly elevated within maternal but not fetal circulation (Bertelloni, 1994; Saxe, 1997). Many functions of this hormone have been proposed. PTH-rP synthesis is found in several normal adult tissues, especially in reproductive organs that include myometrium, endometrium, corpus luteum, and lactating mammary tissue. PTH-rP is not produced in the parathyroid glands of normal adults. Placenta-derived PTH-rP may have an important function to regulate genes involved in transfer of calcium and other solutes. It also contributes to fetal mineral homeostasis in bone, amnionic fluid, and the fetal circulation (Simmonds, 2010).

Leptin

This hormone is normally secreted by adipocytes. It functions as an antiobesity hormone that decreases food intake through its hypothalamic receptor. It also regulates bone growth and immune function (Cock, 2003; La Cava, 2004). In the placenta, leptin is synthesized by both cytotrophoblasts and syncytiotrophoblast (Henson, 2002). Relative contributions of leptin from maternal adipose tissue versus placenta are currently not well defined, although recent evidence highlights a key regulatory role of placental leptin in placental amino acid transport and fetal growth (Rosario, 2016a). Maternal serum levels are significantly higher than those in nonpregnant women. Fetal leptin levels correlate positively with birthweight and likely function in fetal development and growth. Studies suggest that reductions in leptin availability contribute to adverse fetal metabolic programing in intrauterine growth-restricted offspring (Nusken, 2016).

Neuropeptide Y

This 36-amino-acid peptide is widely distributed in brain. It also is found in sympathetic neurons innervating the cardiovascular, respiratory, gastrointestinal, and genitourinary systems. Neuropeptide Y has been isolated from the placenta and localized in cytotrophoblasts (Petraglia, 1989). Trophoblasts possess neuropeptide Y receptors, and treatment of these with neuropeptide Y causes CRH release (Robidoux, 2000).

Inhibin and Activin

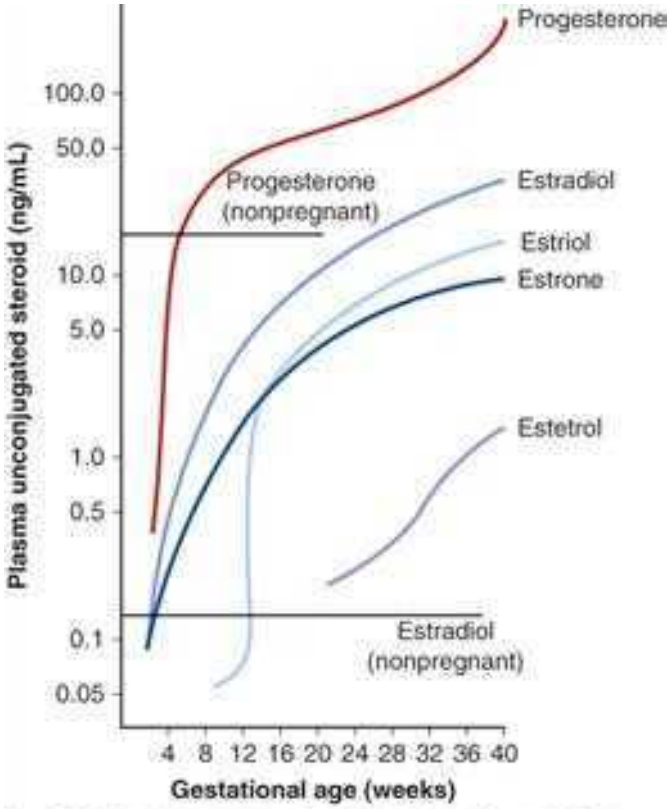
These glycoprotein hormones are expressed in male and female reproductive tissues and belong to the transforming growth factor-β family (Jones, 2006). Inhibin is a heterodimer made up of one α-subunit and one of two distinct β-subunits, either βA or βB. This yields either inhibin A or inhibin B, respectively. Activin is formed by the combination of the two β-subunits. Activin, inhibin, and their respective receptors are expressed in the placenta. Both activin and inhibin A have proposed functions during cytotrophoblast fusion into the syncytiotrophoblast (Debiève, 2000; Jones, 2006). Activin also stimulates production of placental hormones such as hCG, hPL, progesterone, and estrogen (Luo, 2002; Morrish, 1991; Petraglia, 1989; Song, 1996). Inhibin A opposes activin action in the placenta to inhibit production of hCG and steroidogenesis (Petraglia, 1989). Abnormal levels of inhibin or activin correlate with placental pathologies. For example, elevation in inhibin A levels in the second trimester is indicative of fetal Down syndrome. Further, low inhibin levels early in pregnancy may indicate pregnancy failure (Prakash, 2005; Wallace, 1996). Elevations in circulating inhibin and activin levels are reported in women with preeclampsia (Bersinger, 2003).

Placental Progesterone Production

After 6 to 7 weeks' gestation, little progesterone is produced in the ovary (Diczfalusy, 1961). Surgical removal of the corpus luteum or even bilateral oophorectomy during the 7th to 10th week does not decrease excretion rates of urinary pregnanediol, the principal urinary metabolite of progesterone. Before this time, however, corpus luteum removal will result in spontaneous abortion unless an exogenous progestin is given (Chap. 63, Diagnosis). After approximately 8 weeks, the placenta assumes progesterone secretion, resulting in a gradual increase in maternal serum levels throughout pregnancy (Fig. 5-19). By term, these levels are 10 to 5000 times those found in nonpregnant women, depending on the stage of the ovarian cycle.

FIGURE 5-19

Plasma levels of progesterone, estradiol, estrone, estetrol, and estriol in women during the course of gestation. (Modified and redrawn with permission from Mesiano S: The endocrinology of human pregnancy and fetoplacental neuroendocrine development. In Strauss JF, Barbieri RL (eds) Yen and Jaffe's Reproductive Endocrinology: Physiology, Pathophysiology, and Clinical Management, 6th ed. Philadephia, Saunders, 2009.)



The daily production rate of progesterone in late, normal, singleton pregnancies approximates 250 mg. In multifetal pregnancies, the daily production rate may exceed 600 mg. Progesterone is synthesized from cholesterol in a two-step enzymatic reaction. First, cholesterol is converted to pregnenolone within the

mitochondria, in a reaction catalyzed by cytochrome P450 cholesterol side-chain cleavage enzyme. Pregnenolone leaves the mitochondria and is converted to progesterone in the endoplasmic reticulum by 3β-hydroxysteroid dehydrogenase. Progesterone is released immediately through a process of diffusion.

Although the placenta produces a prodigious amount of progesterone, the syncytiotrophoblast has a limited capacity for cholesterol biosynthesis. Radiolabeled acetate is incorporated into cholesterol by placental tissue at a slow rate. The rate-limiting enzyme in cholesterol biosynthesis is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Because of this, the placenta must rely on an exogenous source, that is, maternal cholesterol, for progesterone formation. The trophoblast preferentially uses LDL cholesterol for progesterone biosynthesis (Simpson, 1979, 1980). This mechanism differs from placental production of estrogens, which relies principally on fetal adrenal precursors.

Although there is a relationship between fetal well-being and placental estrogen production, this is not the case for placental progesterone. Thus, placental endocrine function, including the formation of protein hormones such as hCG and progesterone biosynthesis, may persist for weeks after fetal demise.

The metabolic clearance rate of progesterone in pregnant women is similar to that found in men and nonpregnant women. During pregnancy, the plasma concentration of 5α-dihydroprogesterone disproportionately rises due to synthesis in syncytiotrophoblast from both placenta-produced progesterone and fetus-derived precursor (Dombroski, 1997). Thus, the concentration ratio of this progesterone metabolite to progesterone is elevated in pregnancy. The mechanisms for this are not defined completely. Progesterone also is converted to the potent mineralocorticoid deoxycorticosterone in pregnant women and in the fetus. The concentration of deoxycorticosterone is strikingly higher in both maternal and fetal compartments (see Table 5-1). The extraadrenal formation of deoxycorticosterone from circulating progesterone accounts for most of its production in pregnancy (Casey, 1982a,b).

Placental Estrogen Production

During the first 2 to 4 weeks of pregnancy, rising hCG levels maintain production of estradiol in the maternal corpus luteum. Production of both progesterone and estrogens in the maternal ovaries drops significantly by the 7th week of pregnancy. At this time, there is a luteal–placental transition. By the 7th week, more than half of estrogen entering maternal circulation is produced in the placenta (MacDonald, 1965a; Siiteri, 1963, 1966). Subsequently, the placenta produces a continually increasing magnitude of estrogen. Near term, normal human pregnancy is a hyperestrogenic state, and syncytiotrophoblast is producing estrogen in amounts equivalent to that produced in 1 day by the ovaries of no fewer than 1000 ovulatory women. This hyperestrogenic state terminates abruptly after delivery of the placenta.

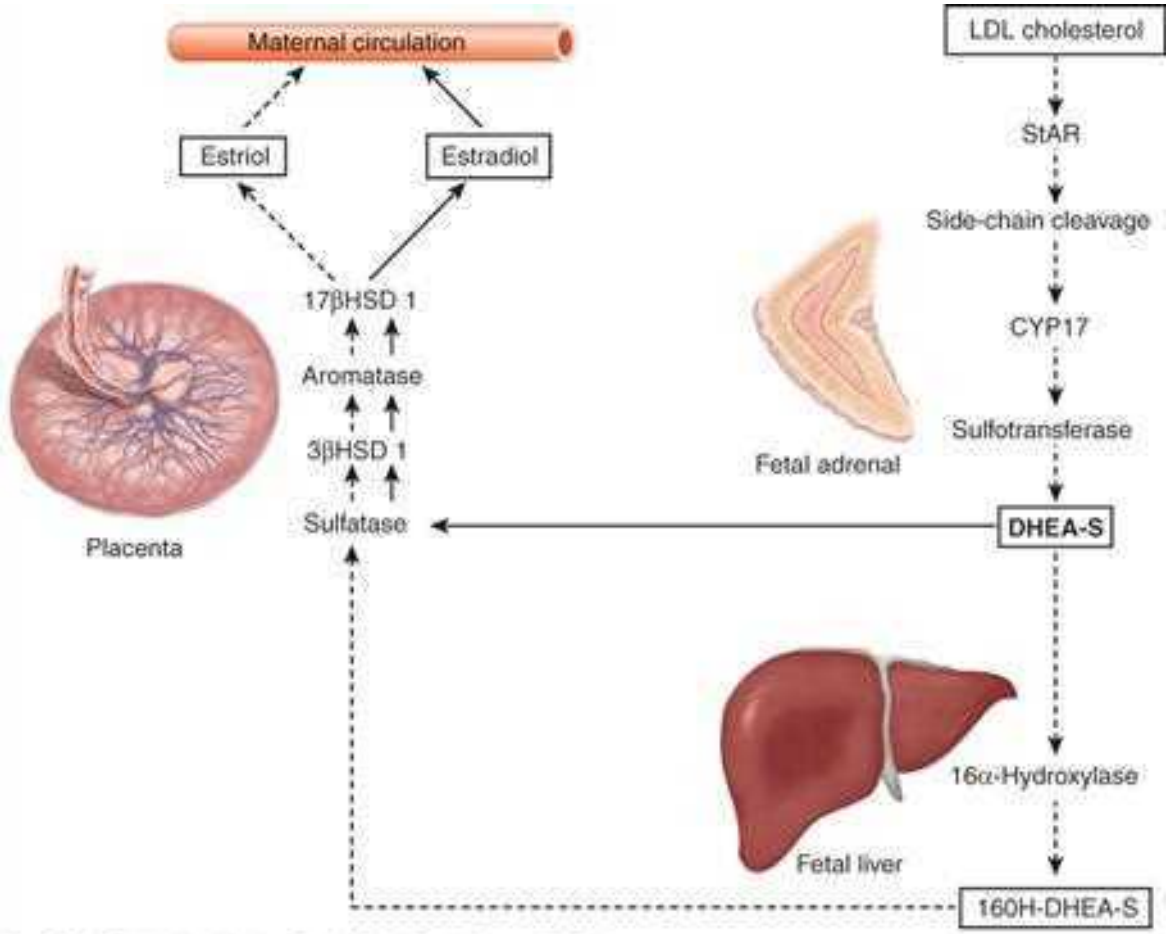
Biosynthesis

In human trophoblast, neither cholesterol nor, in turn, progesterone can serve as precursor for estrogen biosynthesis. This is because *steroid 17α-hydroxylase/17,20-lyase (CYP17A1)* is not expressed in the human placenta. This essential enzyme converts 17-OH progesterone (a C_{21} steroid) to androstenedione, which is a C_{19} steroid and an estrogen precursor. Consequently, the conversion of C_{21} steroids to C_{19} steroids is not possible.

However, dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are also C_{19} steroids and are produced by maternal and fetal adrenal glands. These two steroids can serve as estrogen precursors (Fig. 5-20). Ryan (1959a) found that the placenta had an exceptionally high capacity to convert appropriate C_{19} steroids to estrone and estradiol. The conversion of DHEA-S to estradiol requires placental expression of four key enzymes that are located principally in syncytiotrophoblast (Bonenfant, 2000; Salido, 1990). First, the placenta expresses high levels of steroid sulfatase (STS), which converts the conjugated DHEA-S to DHEA. DHEA is then acted upon by 3β-hydroxysteroid dehydrogenase type 1 (3βHSD) to produce androstenedione. Cytochrome P450 aromatase (CYP19) then converts androstenedione to estrone, which is then converted to estradiol by 17β-hydroxysteroid dehydrogenase type 1 (17βHSD1).

FIGURE 5-20

Schematic presentation of estrogen biosynthesis in the human placenta. Dehydroepiandrosterone sulfate (DHEAS), secreted in prodigious amounts by the fetal adrenal glands, is converted to 16α-hydroxydehydroepiandrosterone sulfate (16αOHDHEAS) in the fetal liver. These steroids, DHEAS and 16αOHDHEAS, are converted in the placenta to estrogens, that is, 17β-estradiol (E_2) and estriol (E_3). Near term, half of E_2 is derived from fetal adrenal DHEAS and half from maternal DHEAS. On the other hand, 90 percent of E_3 in the placenta arises from fetal 16αOHDHEAS and only 10 percent from all other sources.



DHEA-S is the major precursor of estrogens in pregnancy (Baulieu, 1963; Siiteri, 1963). However, maternal adrenal glands do not produce sufficient amounts of DHEA-S to account for more than a fraction of total placental estrogen biosynthesis. The fetal adrenal glands are quantitatively the most important source of placental estrogen precursors in human pregnancy. Thus, estrogen production during pregnancy reflects the unique interactions among fetal adrenal glands, fetal liver, placenta, and maternal adrenal glands.

Directional Secretion

More than 90 percent of estradiol and estriol formed in syncytiotrophoblast enters maternal plasma (Gurpide, 1966). And, 85 percent or more of placental progesterone enters maternal plasma, and little maternal progesterone crosses the placenta to the fetus (Gurpide, 1972).

This directional movement of newly formed steroid into the maternal circulation stems from basic characteristics of hemochorioendothelial placentation. In this system, steroids secreted from syncytiotrophoblast can enter maternal blood directly. Steroids that leave the syncytium do not enter fetal blood directly. They must first traverse the cytotrophoblast layer and then enter the stroma of the villous core and then fetal capillaries. From either of these spaces, steroids can reenter the syncytium. The net result of this hemochorial arrangement is that entry of steroids into the maternal circulation is substantially greater than that into fetal blood.

FETAL ADRENAL GLAND–PLACENTAL INTERACTIONS

Morphologically, functionally, and physiologically, the fetal adrenal glands are remarkable. At term, the fetal adrenal glands weigh the same as those of the adult. More than 85 percent of the fetal gland is composed of a unique fetal zone, which has a great capacity for steroid biosynthesis. Daily steroid production of fetal adrenal glands near term is 100 to 200 mg/d. This compares with resting adult steroid secretion of 30 to 40 mg/d.

The fetal zone is lost in the first year of life and is not present in the adult. In addition to ACTH, fetal adrenal gland growth is influenced by factors secreted by the placenta. This is exemplified by the continued growth of the fetal glands throughout gestation and by rapid involution immediately after birth and placental delivery.

Placental Estriol Synthesis

Estradiol is the primary placental estrogen product at term. In addition, significant levels of *estriol* and *estetrol* are found in the maternal circulation, and levels also rise, particularly late in gestation (see Fig. 5-19). These hydroxylated forms of estrogen derive from the placenta using substrates formed by the combined efforts of the fetal adrenal gland and fetal liver. For this, high levels of fetal hepatic 16α-hydroxylase act on adrenal-derived steroids. Ryan (1959b) and MacDonald and Siiteri (1965b) found that 16α-hydroxylated C_{19} steroids, particularly 16α-hydroxydehydroepiandrosterone (16-OHDHEA), were converted to estriol by placental tissue.

Thus, the disproportionate increase in estriol formation during pregnancy is accounted for by placental synthesis of estriol principally from plasma-borne 16-OHDHEA-sulfate. Near term, the fetus is the source of 90 percent of placental estriol and estetrol precursors in normal human pregnancy.

Maternal estriol and estetrol are produced almost solely by fetal steroid precursors. Thus, in the past, levels of these steroids were used as an indicator of fetal well-being. However, the low sensitivity and specificity of such tests have caused them to be discarded.

Fetal Adrenal Steroid Precursor

The precursor for fetal adrenal steroidogenesis is cholesterol. The steroid biosynthesis rate in the fetal gland is so great that its steroidogenesis alone is equivalent to a fourth of the total daily LDL cholesterol turnover in adults. Fetal adrenal glands synthesize cholesterol from acetate. All enzymes involved in cholesterol biosynthesis are elevated compared with those of the adult adrenal gland (Rainey, 2001). Thus, the de novo cholesterol synthesis rate by fetal adrenal tissue is extremely high. Even so, it is insufficient to account for the steroids produced by fetal adrenal glands. Therefore, cholesterol must be assimilated from the fetal circulation and mainly from LDL (Carr, 1980, 1981b, 1982; Simpson, 1979).

Most fetal plasma cholesterol arises by de novo synthesis in the fetal liver (Carr, 1984). The low LDL cholesterol level in fetal plasma is not the consequence of impaired fetal LDL synthesis, but instead results from the rapid use of LDL by the fetal adrenal glands for steroidogenesis (Parker, 1980, 1983).

Fetal Conditions Affecting Estrogen Production

Several fetal disorders alter the availability of substrate for placental steroid synthesis and thus highlight the interdependence of fetal development and placental function.

Fetal demise is followed by a striking reduction in urinary estrogen levels. Similarly, after ligation of the umbilical cord with the fetus and placenta left in situ, placental estrogen production declines markedly (Cassmer, 1959). However, as previously discussed, placental progesterone production is maintained. In sum, an important source of precursors of placental estrogen—but not progesterone—biosynthesis is eliminated with fetal death.

Anencephalic fetuses have markedly atrophic adrenal glands. This stems from absent hypothalamic-pituitary function, which precludes adrenal stimulation by ACTH. With absence of the adrenal cortex fetal zone, the placental formation of estrogen—especially estriol—is severely limited because of diminished availability of C_{19} steroid precursors. Indeed, urinary estrogen levels in women pregnant with an anencephalic fetus are only about 10 percent of those found in normal pregnancy (Frandsen, 1961). With an anencephalic fetus, almost all estrogens produced arise from placental use of maternal plasma DHEA-S.

Fetal adrenal cortical hypoplasia occurs in perhaps 1 in 12,500 births (McCabe, 2001). Estrogen production in these pregnancies is limited, which suggests the absence of C_{19} precursors.

Fetal–placental sulfatase deficiency is associated with very low estrogen levels in otherwise normal pregnancies (France, 1969). Namely, sulfatase deficiency precludes the hydrolysis of C_{19} steroid sulfates, the first enzymatic step in the placental use of these circulating prehormones for estrogen biosynthesis. This deficiency is an X-linked disorder, and thus all affected fetuses are male. Its estimated frequency is 1 in 2000 to 5000 births and is associated with delayed labor onset. It also is associated with the development of ichthyosis in affected males later in life (Bradshaw, 1986).

Fetal–placental aromatase deficiency is a rare autosomal recessive disorder in which individuals cannot synthesize endogenous estrogens (Grumbach, 2011; Simpson, 2000). To recall, fetal adrenal DHEA-S is converted in the placenta to androstenedione, but in cases of placental aromatase deficiency, androstenedione cannot be converted to estradiol. Rather, androgen metabolites of DHEA produced in the placenta, including androstenedione and some testosterone, are secreted into the maternal or fetal circulation, or both. This can cause virilization of the mother and the female fetus (Belgorosky, 2009; Harada, 1992; Shozu, 1991).

Trisomy 21—Down syndrome screening searches for abnormal levels of hCG, alpha-fetoprotein, and other analytes (Chap. 14, Traditional Aneuploidy Screening Tests). It was discovered that serum unconjugated estriol levels were low in women with Down syndrome fetuses (Benn, 2002). The likely reason for this is inadequate formation of C_{19} steroids in the adrenal glands of these trisomic fetuses.

Fetal erythroblastosis in some cases of severe fetal D-antigen alloimmunization can lead to elevated maternal plasma estrogen levels. A suspected cause is the greater placental mass from hypertrophy, which can be seen with such fetal hemolytic anemia (Chap. 15, Fetal Anemia).

Maternal Conditions Affecting Estrogen Production

Glucocorticoid treatment can cause a striking reduction in placental estrogen formation. Glucocorticoids inhibit ACTH secretion from the maternal and fetal pituitary glands. This diminishes maternal and fetal adrenal secretion of the placental estrogen precursor DHEA-S.

With *Addison disease,* pregnant women show lower estrogen levels, principally estrone and estradiol levels (Baulieu, 1956). The fetal adrenal contribution to estriol synthesis, particularly in later pregnancy, is quantitatively much more important.

Maternal *androgen-producing tumors* can present the placenta with elevated androgen levels. Fortunately, placenta is extraordinary efficient in the aromatization of C_{19} steroids. For example, Edman and associates (1981) found that virtually all androstenedione entering the intervillous space is taken up by syncytiotrophoblast and converted to estradiol. None of this C_{19} steroid enters the fetus. Second, a female fetus is rarely virilized if there is a maternal androgen-secreting tumor. The placenta efficiently converts aromatizable C_{19} steroids, including testosterone, to estrogens, thus precluding transplacental passage. Indeed, virilized female fetuses of women with an androgen-producing tumor may be cases in which a nonaromatizable C_{19} steroid androgen is produced by the tumor—for example, 5α-dihydrotestosterone. Another explanation is that testosterone is produced very early in pregnancy in amounts that exceed the placental aromatase capacity at that time.

Complete hydatidiform mole and *gestational trophoblastic neoplasias* lack a fetus and also a fetal adrenal source of C_{19} steroid precursors for trophoblast estrogen biosynthesis. Consequently, placental estrogen formation is limited to the use of C_{19} steroids from the maternal plasma, and therefore estradiol is principally produced (MacDonald, 1964, 1966).

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CHAPTER 6: Placental Abnormalities

The placenta, as a rule, presents more or less rounded outlines, but now and again when inserted in the neighbourhood of the internal os it may take on a horseshoe-like appearance, its two branches running partially around the orifice.

—J. Whitridge Williams (1903)

INTRODUCTION

The placenta is a fantastic organ in its own right. As discussed in Chapter 5 (Blastocyst), it provides the indispensable interface between mother and fetus. Indeed, placental anatomy, physiology, and molecular structure remain some of the most intriguing and understudied topics in obstetrics.

Although a placental examination by the obstetrician is recommended, by consensus, routine pathological examination is not mandatory. Indeed, specific conditions that merit submission for detailed inspection are still debated. By way of example, the College of American Pathologists has recommended placental examination for an extensive list of indications (Langston, 1997). Data, however, are insufficient to support all of these. At minimum, the placenta and cord should be inspected in the delivery room. The decision to request pathological examination should be based on clinical and placental findings (Redline, 2008; Roberts, 2008). Listed in Table 6-1 are some of the indications at Parkland Hospital for placental anatomical and histopathological examination.

TABLE 6-1

Some Indications for Placental Pathological Examination[a]

Maternal Indications
Abruption
Antepartum infection with fetal risks
Anti-CDE alloimmunization
Cesarean hysterectomy
Oligohydramnios or hydramnios
Peripartum fever or infection
Preterm delivery
Postterm delivery
Severe trauma
Suspected placental injury
Systemic disorders with known effects
Thick or viscid meconium
Unexplained late pregnancy bleeding
Unexplained or recurrent pregnancy complications
Fetal and Neonatal Indications
Admission to an acute care nursery
Birth weight ≤10th or ≥95th percentile
Fetal anemia
Fetal or neonatal compromise
Neonatal seizures
Hydrops fetalis
Infection or sepsis
Major anomalies or abnormal karyotype
Multifetal gestation
Stillbirth or neonatal death
Vanishing twin beyond the first trimester
Placental Indications
Gross lesions
Marginal or velamentous cord insertion
Markedly abnormal placental shape or size
Markedly adhered placenta
Term cord <32 cm or >100 cm
Umbilical cord lesions

[a]Indications are organized alphabetically.

NORMAL PLACENTA

At term, the typical placenta weighs 470 g, is round to oval with a 22-cm diameter, and has a central thickness of 2.5 cm (Benirschke, 2012). It is composed of a placental disc, extraplacental membranes, and three-vessel umbilical cord. The disc surface that lies against the uterine wall is the *basal plate*, which is divided by clefts into portions—termed cotyledons. The fetal surface is the *chorionic plate*, into which the umbilical cord inserts, typically in the center. Large fetal vessels that originate from the cord vessels then spread and branch across the chorionic plate before entering stem villi of the placenta parenchyma. In tracing these, fetal arteries almost invariably cross over veins. The chorionic plate and its vessels are covered by thin amnion, which can be easily peeled away from a postdelivery specimen.

As recommended by the American Institute of Ultrasound in Medicine (2013), placental location and relationship to the internal cervical os are recorded during prenatal sonographic examinations. As visualized ultrasonically, the normal placenta is homogenous and 2 to 4 cm thick, lies against the myometrium, and indents into the amnionic sac. The retroplacental space is a hypoechoic area that separates the myometrium from the basal plate and measures less than 1 to 2 cm. The umbilical cord is also imaged, its fetal and placental insertion sites examined, and its vessels counted.

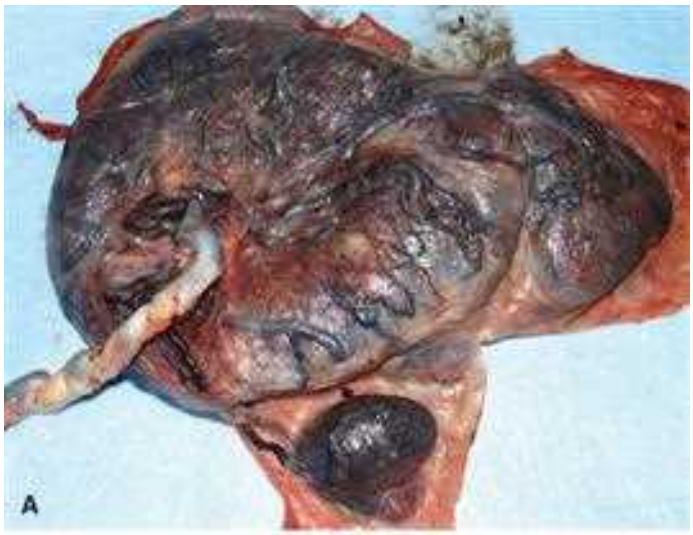
Many placental lesions can be identified grossly or sonographically, but other abnormalities require histopathological examination for clarification. A detailed description of these is beyond the scope of this chapter, and interested readers are referred to textbooks by Benirschke (2012), Fox (2007), and Faye-Petersen (2006) and their colleagues. Moreover, the placenta accrete syndrome and gestational trophoblastic disease are presented in detail in Chapters 20 and 41, respectively.

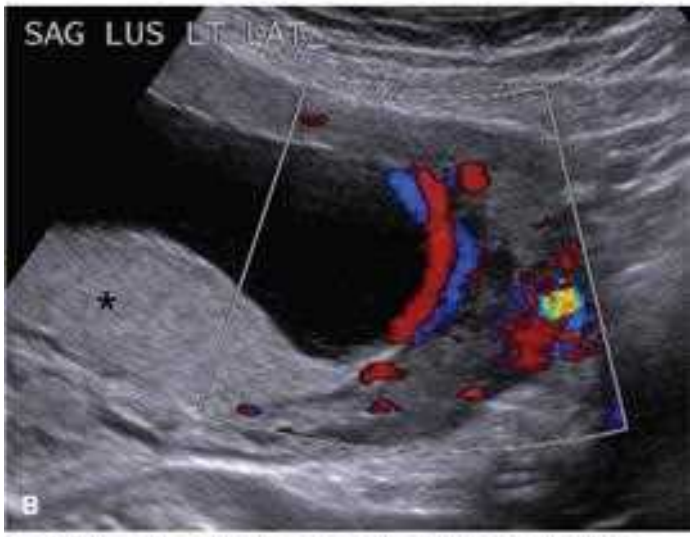
SHAPE AND SIZE VARIANTS

Of variants, placentas may infrequently form as separate, nearly equally sized discs. This *bilobate placenta* may also be called bipartite placenta or placenta duplex. In these, the cord inserts between the two placental lobes—either into a connecting chorionic bridge or into intervening membranes. A placenta containing three or more equivalently sized lobes is rare and termed *multilobate*. Unlike this equal distribution, one or more disparately smaller accessory lobes —*succenturiate lobes*—may develop in the membranes at a distance from the main placenta (Fig. 6-1). These lobes have vessels that course through the membranes. Of clinical importance, if these vessels overlie the cervix to create a vasa previa, dangerous fetal hemorrhage can follow vessel laceration (Remnants and Cysts). An accessory lobe can also be retained in the uterus after delivery to cause postpartum uterine atony and hemorrhage or later endometritis.

FIGURE 6-1

Succenturiate lobe. **A.** Vessels extend from the main placental disc to supply the small round succenturiate lobe located beneath it. (Used with permission from Dr. Jaya George.) **B.** Sonographic imaging with color Doppler shows the main placental disc implanted posteriorly (*asterisk*). The succenturiate lobe is located on the anterior uterine wall across the amnionic cavity. Vessels are identified as the long red and blue crossing tubular structures that travel within the membranes to connect these two portions of placenta.





Rarely, the placental surface area varies from the norm. With placenta membranacea, villi cover all or nearly all the uterine cavity. This may occasionally give rise to serious hemorrhage because of associated placenta previa or accreta (Greenberg, 1991; Pereira, 2013). A ring-shaped placenta may be a variant of placenta membranacea. This placenta is annular, and a partial or complete ring of placental tissue is present. These abnormalities appear to be associated with a greater likelihood of antepartum and postpartum bleeding and fetal-growth restriction (Faye-Petersen, 2006; Steemers, 1995). With placenta fenestrata, the central

portion of a placental disc is missing. In some instances, there is an actual hole in the placenta, but more often, the defect involves only villous tissue, and the chorionic plate remains intact. Clinically, it may erroneously prompt a search for a retained placental cotyledon.

During pregnancy, the normal placenta increases its thickness at a rate of approximately 1 mm per week. Although not measured as a component of routine sonographic evaluation, this thickness typically does not exceed 40 mm (Hoddick, 1985). *Placentomegaly* defines those thicker than 40 mm and commonly results from striking villous enlargement. This may be secondary to maternal diabetes or severe maternal anemia, or to fetal hydrops, anemia, or infection caused by syphilis, toxoplasmosis, parvovirus, or cytomegalovirus. In these conditions, the placenta is homogeneously thickened. Less commonly with placentomegaly, fetal parts are present, but villi are edematous and appear as small placental cysts, such as in cases of partial mole (Chap. 20, Diagnosis). Cystic vesicles are also seen with *placental mesenchymal dysplasia*. Vesicles in this rare condition correspond to enlarged stem villi, but unlike molar pregnancy, trophoblast proliferation is not excessive (Woo, 2011).

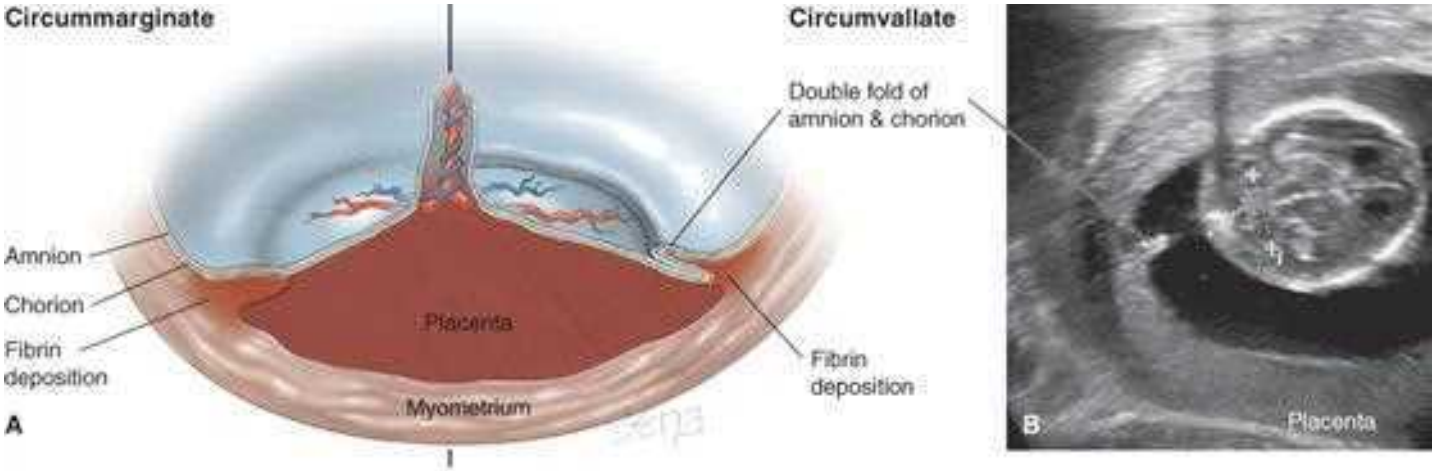
Rather than villous enlargement, placentomegaly often may result from collections of blood or fibrin, which impart heterogeneity to the placenta. Examples of this are discussed in Maternal Blood Flow Disruption and include massive perivillous fibrin deposition, intervillous or subchorionic thromboses, and large retroplacental hematomas.

EXTRACHORIAL PLACENTATION

The chorionic plate normally extends to the periphery of the placenta and has a diameter similar to that of the basal plate. With extrachorial placentation, however, the chorionic plate fails to extend to this periphery and leads to a chorionic plate that is smaller than the basal plate (Fig. 6-2). Circummarginate and circumvallate placentas are the two types. In a *circummarginate placenta*, fibrin and old hemorrhage lie between the placenta and the overlying sheer amniochorion. In contrast, with a *circumvallate placenta*, the chorion periphery is a thickened, opaque, gray-white circular ridge composed of a double fold of chorion and amnion. Sonographically, the double fold can be seen as a thick, linear band of echoes extending from one placental edge to the other. On cross section, however, it appears as two "shelves," with each lying above an opposing placental margin (see Fig. 6-2). This anatomy can help differentiate this shelf from amnionic bands and amnionic sheets, which are described in Amniochorion.

FIGURE 6-2

A. In this illustration, circummarginate (*left*) and circumvallate (*right*) varieties of extrachorial placentation are shown. A circummarginate placenta is covered by a single layer of amniochorion. **B.** This transabdominal gray-scale sonographic image shows a circumvallate placenta. The double fold of amnion and chorion creates a broad, opaque white ring and ridge on the fetal surface.



In relatively small observational studies of circumvallate placenta diagnosed postpartum, it was associated with increased risk for antepartum bleeding, abruption, fetal demise, and preterm birth (Lademacher, 1981; Suzuki, 2008; Taniguchi, 2014). In a prospective sonographic investigation of 17 cases, however, Shen and associates (2007a) found most circumvallate placentas to be transient. Persistent cases were benign. In general, most otherwise uncomplicated pregnancies with either type of extrachorial placentation have normal outcomes, and no increased surveillance is usually required.

CIRCULATORY DISTURBANCES

Functionally, placental perfusion disorders can be grouped into: (1) those in which maternal blood flow to or within the intervillous space is disrupted, and (2) those with disturbed fetal blood flow through the villi. These lesions are frequently identified in the normal, mature placenta. Although they can limit maximal placental blood flow, functional reserve within the placental prevents harm in most cases. Indeed, some estimate that up to 30 percent of placental villi can be lost without untoward fetal effects (Fox, 2007). If extensive, however, these lesions can profoundly limit fetal growth.

Lesions that disrupt perfusion are frequently seen grossly or sonographically, whereas smaller lesions are seen only histologically. With sonography, many of these, such as subchorionic fibrin deposition, perivillous fibrin deposition, and intervillous thrombosis, appear as focal sonolucencies within the placenta. Importantly, in the absence of maternal or fetal complications, isolated placental sonolucencies are considered incidental findings.

Maternal Blood Flow Disruption

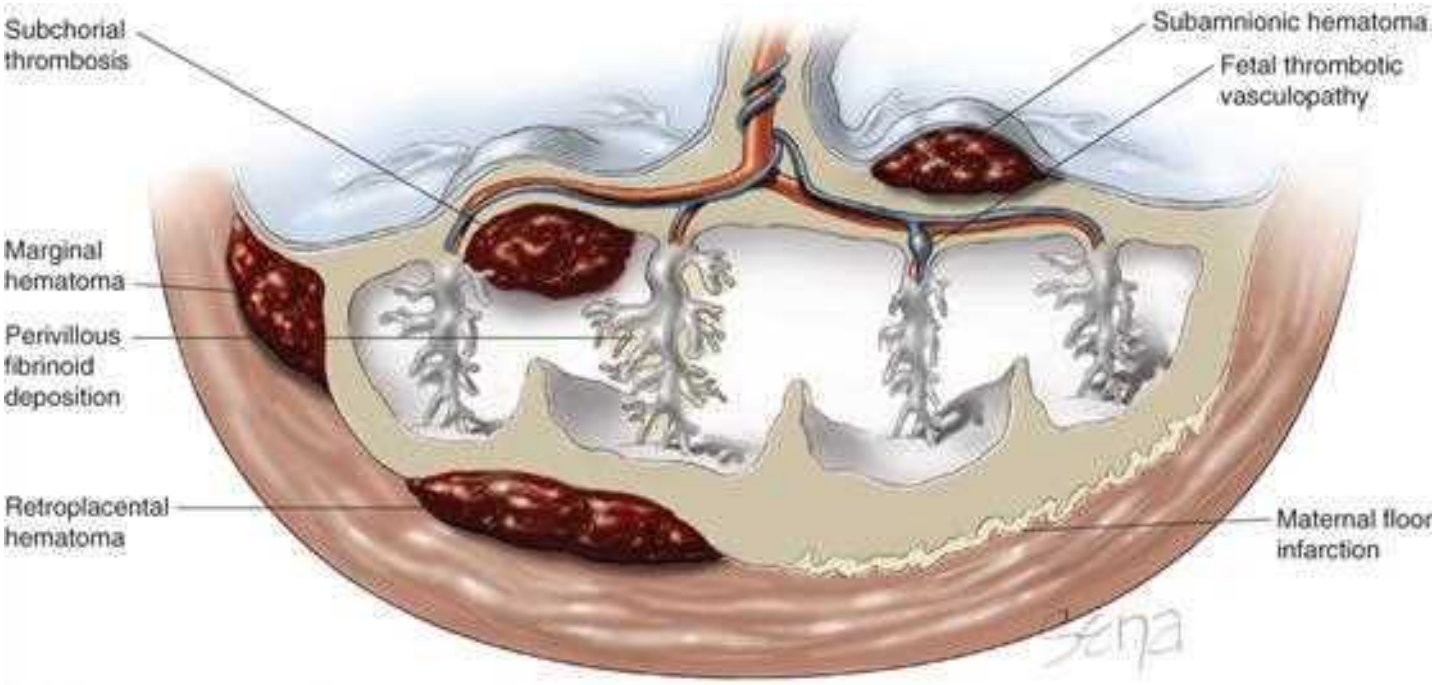
Subchorionic Fibrin Deposition

These collections are caused by slowing of maternal blood flow within the intervillous space. In the portion of this space near the chorionic plate, blood stasis is prominent and leads to subsequent fibrin deposition. In viewing the placental fetal surface, subchorionic lesions are commonly seen as white or yellow, firm, round, elevated plaques just beneath the chorionic plate.

Perivillous Fibrin Deposition

Stasis of maternal blood flow around an individual villus also results in fibrin deposition and can lead to diminished villous oxygenation and necrosis of syncytiotrophoblast (Fig. 6-3). These small yellow-white placental nodules are grossly visible within the parenchyma of a sectioned placenta. Within limits, these reflect normal placental aging.

FIGURE 6-3
Potential sites of maternally and fetally related placental circulatory disturbances. (Adapted from Faye-Petersen, 2006.)



Maternal Floor Infarction

This extreme variant of perivillous fibrin deposition is a dense fibrinoid layer within the placental basal plate and is erroneously termed an infarction. *Maternal floor infarction* has a thick, yellow or white, firm corrugated surface that impedes normal maternal blood flow into the intervillous space. In specific cases that extend beyond the basal plate to entrap villi and obliterate the intervillous space, the term *massive perivillous fibrin deposition* is used. The etiopathogenesis is unclear, but maternal auto- or alloimmunity appears contributory (Faye-Peterson, 2017; Romero, 2013). Antiphospholipid antibody syndrome and angiogenic factors involved with preeclampsia have also been implicated (Sebire, 2002, 2003; Whitten, 2013).

These lesions are not reliably imaged with prenatal sonography, but they may create a thicker basal plate. Affected pregnancies are associated with miscarriage, fetal-growth restriction, preterm delivery, and stillbirth (Andres, 1990; Mandsager, 1994). Importantly, these adverse outcomes can recur in subsequent pregnancies.

Intervillous Thrombus

This is a collection of coagulated maternal blood normally found in the intervillous space mixed with fetal blood from a break in a villus. Grossly, these round or oval collections vary in size up to several centimeters. They appear red if recent or white-yellow if older, and they develop at any placental depth. Intervillous thrombi are common and typically not associated with adverse fetal sequelae. Because there is potential for a communication between maternal and fetal circulations, large lesions can cause elevated maternal serum alpha-fetoprotein levels (Salafia, 1988).

Infarction

Chorionic villi themselves receive oxygen solely from maternal circulation supplied to the intervillous space. Any uteroplacental disease that diminishes or obstructs this supply can result in infarction of an individual villus. These are common lesions in mature placentas and are benign in limited numbers. If

numerous, however, placental insufficiency can develop. When they are thick, centrally located, and randomly distributed, they may be associated with preeclampsia or lupus anticoagulant.

Hematoma

As depicted in Figure 6-3, the maternal-placental-fetal unit can develop several hematoma types. These include: (1) retroplacental hematoma—between the placenta and its adjacent decidua; (2) marginal hematoma—between the chorion and decidua at the placental periphery—known clinically as subchorionic hemorrhage; (3) subamnionic hematoma—these are of fetal vessel origin and found beneath the amnion but above the chorionic plate, and (4) subchorial thrombus along the roof of the intervillous space and beneath the chorionic plate. With this last type, *massive subchorionic hematomas* are also known as a *Breus mole.*

Sonographically, hematomas evolve with time and appear hyperechoic to isoechoic in the first week after hemorrhage, hypoechoic at 1 to 2 weeks, and finally, anechoic after 2 weeks. Most subchorionic hematomas visible sonographically are fairly small and of no clinical consequence. However, extensive retroplacental, marginal, and subchorial collections have been associated with higher rates of miscarriage, stillbirth, placental abruption, and preterm delivery (Ball, 1996; Fung, 2010; Madu, 2006; Tuuli, 2011). In essence, placental abruption is a large, clinically significant retroplacental hematoma.

Fetal Blood Flow Disruption

Fetal Thrombotic Vasculopathy

Placental lesions that arise from fetal circulatory disturbances are also depicted in Figure 6-3. Deoxygenated fetal blood flows from the two umbilical arteries into arteries within the chorionic plate that divide and send branches out across the placental surface. These eventually supply individual stem villi, and their thrombosis will obstruct fetal blood flow. Distal to the obstruction, affected portions of the villus become nonfunctional. Thrombi in limited numbers are normally found in mature placentas. If many villi are affected, which can be seen with preeclampsia, the fetus may suffer growth restriction, stillbirth, or nonreassuring fetal heart rate patterns (Chisholm, 2015; Lepais, 2014; Saleemuddin, 2010).

Villous Vascular Lesions

There is a spectrum of villous capillary lesions. *Chorangiosis* describes an increased number of capillaries within terminal villi. Its definition requires ≥10 capillaries to be present in ≥10 villi in ≥10 fields viewed through a 10× microscope lens (Altshuler, 1984). Clinically, long-standing hypoperfusion or hypoxia is thought to be causative (Stanek, 2016). It is often associated with maternal diabetes mellitus (Ogino, 2000). *Chorangiomatosis* describes increased capillary number in stem villi, but terminal villi are spared. This finding has been linked with fetal-growth restriction and anomalies (Bagby, 2011). Despite these associations, the clinical significance of both vascular conditions remains unclear. *Chorioangiomas* are described subsequently.

Subamnionic Hematoma

As indicated earlier, these hematomas lie between the chorionic plate and amnion. They most often are acute events during third-stage labor when cord traction ruptures a vessel near the cord insertion.

Large chronic antepartum lesions may cause fetomaternal hemorrhage or fetal-growth restriction (Deans, 1998). They also may be confused with other placental masses such as chorioangioma. In most cases, Doppler interrogation will show absent internal blood flow within a hematoma and permit differentiation (Sepulveda, 2000).

PLACENTAL CALCIFICATION

Calcium salts can be deposited throughout the placenta but are most common on the basal plate. Calcification accrues with advancing gestation, and greater degrees are associated with smoking and increasing maternal serum calcium levels (Bedir Findik, 2015; Klesges, 1998; McKenna, 2005). These hyperechoic deposits can easily be seen sonographically, and a grading scale from 0 to 3 reflects increasing calcification with increasing numerical grade (Grannum, 1979). Following this scheme, a grade 0 placenta is homogeneous, lacks calcification, and displays a smooth, flat chorionic plate. A grade 1 placenta has scattered echogenicities and subtle chorionic plate undulations. Grade 2 shows echogenic stippling at the basal plate. Large, echogenic comma shapes originate from an indented chorionic plate, but their curve falls short of the basal plate. Last, a grade 3 placenta has echogenic indentations extending from the chorionic plate to the basal plate, which create discrete components that resemble cotyledons. Basal plate densities also increase.

As a predictor, this grading scale is not useful for neonatal outcome near term (Hill, 1983; McKenna, 2005; Montan, 1986). However, data from two small studies link grade 3 placenta prior to 32 weeks with stillbirth and some other adverse pregnancy outcomes (Chen, 2011, 2015).

PLACENTAL TUMORS

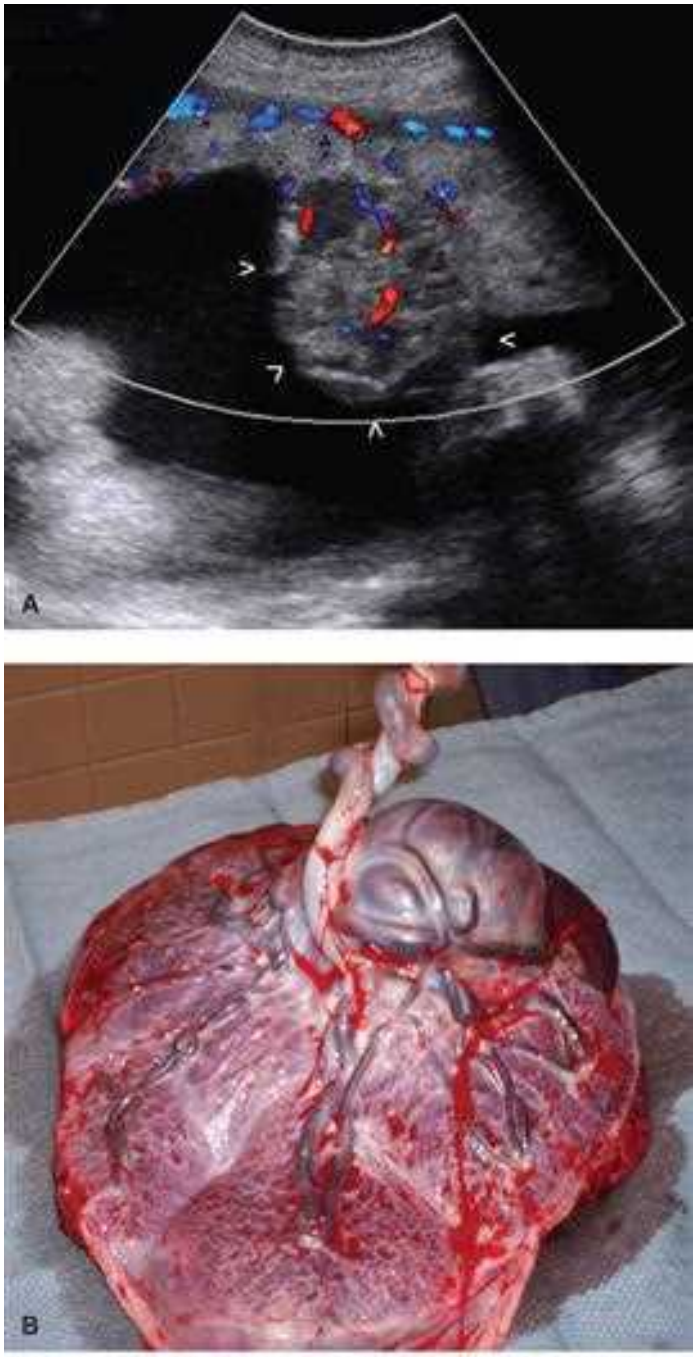
Chorioangioma

These benign tumors have components similar to blood vessels and stroma of the chorionic villus. Also called chorangiomas, these placental tumors occur with an incidence of approximately 1 percent (Guschmann, 2003). In some cases, fetal-to-maternal hemorrhage across tumor capillaries leads to elevated levels of maternal serum alpha-fetoprotein (MSAFP), prompting sonographic evaluation. Their characteristic sonographic appearance shows a well-circumscribed,

rounded, predominantly hypoechoic lesion lying near the chorionic plate and protruding into the amnionic cavity (Fig. 6-4). Documenting increased blood flow by color Doppler helps to distinguish these lesions from other placental masses such as hematoma, partial hydatidiform mole, teratoma, metastases, and leiomyoma (Prapas, 2000). Although rare, *chorangiocarcinoma* tumors clinically mirror chorangiomas (Huang, 2015).

FIGURE 6-4

Placental chorioangioma. **A.** Color Doppler imaging displays blood flow through a large chorioangioma with its border outlined by white arrows. **B.** Grossly, the chorioangioma is a round, well-circumcised mass protruding from the fetal surface.



Small chorioangiomas are usually asymptomatic. Large tumors, typically those measuring >4 cm, can create significant arteriovenous shunting within the placenta to cause high-output heart failure, hydrops, and fetal death (Al Wattar, 2014). Compression of fetal erythrocytes within tumor vessels can lead to hemolysis and microangiopathic anemia (Bauer, 1978). Hydramnios, preterm delivery, and fetal-growth restriction are other sequelae. Rare cases include tumor vessel rupture, hemorrhage, and fetal death (Batukan, 2001). At the other extreme, rare tumor infarction can lead to symptom reversal (Zalel, 2002).

Gray-scale and color Doppler interrogation of the placenta and amnionic fluid volume are used to identify these tumors. Diagnostic tools that can affirm associated fetomaternal hemorrhage include MSAFP level and Kleihauer-Betke stain. With fetal concern, echocardiography assesses cardiac function, whereas middle cerebral artery interrogation is used to identify fetal anemia.

Several fetal therapies interfere with the vascular supply to the tumor and reverse fetal heart failure. At specialized perinatal centers, endoscopic laser ablation of feeder vessels to the tumor is most frequently used and is associated with favorable fetal outcomes (Hosseinzadeh, 2015). Of other therapy, fetal transfusion can treat serious anemia, amnioreduction can temporize hydramnios, and digoxin therapy can assist fetal heart failure.

Metastatic Tumors

Maternal malignant tumors rarely metastasize to the placenta. Of those that do, melanomas, leukemias and lymphomas, and breast cancer are the most common (Al-Adnani, 2007). Tumor cells usually are confined within the intervillous space. As a result, metastasis to the fetus is uncommon but is most often seen with melanoma (Alexander, 2003).

Similarly, cases in which fetal malignancy metastasizes to the placenta are rare (Reif, 2014). These are predominantly fetal neuroectodermal tumors, and only one case in the literature describes transplantation of tumor to the maternal uterus (Nath, 1995).

AMNIOCHORION

Chorioamnionitis

Normal genital-tract flora can colonize and infect the membranes, umbilical cord, and eventually the fetus. Bacteria most commonly ascend after prolonged membrane rupture and during labor to cause infection. Organisms initially infect the chorion and adjacent decidua in the area overlying the internal os. Subsequently, progression leads to full-thickness involvement of the membranes—chorioamnionitis. Organisms often then spread along the chorioamnionic surface to colonize and replicate in amniotic fluid. Inflammation of the chorionic plate and of the umbilical cord—*funisitis*—may follow (Kim, 2015; Redline, 2012).

Most commonly, there is microscopic or occult chorioamnionitis, which is caused by a wide variety of microorganisms. This is frequently cited as a possible explanation for many otherwise unexplained cases of ruptured membranes, preterm labor, or both as discussed in Chapter 42 (Cervical Dysfunction). In some cases, gross infection is characterized by membrane clouding and is sometimes accompanied by a foul odor that depends on bacterial species.

Other Membrane Abnormalities

Amnion nodosum is a condition characterized by numerous small, light-tan nodules on the amnion overlying the chorionic plate. These may be scraped off the fetal surface and contain deposits of fetal squames and fibrin that reflect prolonged and severe oligohydramnios (Adeniran, 2007).

Two notable bandlike structures can be formed by the fetal membranes. Of these, *amnionic band sequence* is an anatomical disruption sequence in which amnion bands tether, constrict, or amputate fetal parts. Amnionic bands commonly cause limb-reduction defects, facial clefts, or encephalocele (Barzilay, 2015; Guzmán-Huerta, 2013). Umbilical cord compromise is another sequela (Barros, 2014; Heifetz, 1984b). Severe defects of the spine or ventral wall that accompany amnionic bands suggest a *limb-body wall complex*, described in Chapter 10 (Gastrointestinal Tract).

Clinically, sonography often first identifies the sequelae of this sequence rather than the bands themselves. As with any fetal anomaly, targeted sonography is indicated. Identification of a limb-reduction defect, an encephalocele in an atypical location, or an extremity with edema or positional deformity should prompt careful evaluation for amnionic bands.

Management depends on the degree of anatomic deformity. Fetoscopic laser interruption of the band may be suitable in highly selected antepartum cases (Javadian, 2013; Mathis, 2015).

In contrast, an *amnionic sheet* is formed by normal amniochorion draped over a preexisting uterine synechia. Generally, these sheets pose little fetal risk, although slightly higher rates of preterm membrane rupture and placental abruption have been described (Korbin, 1998; Nelson, 2010; Tuuli, 2012).

UMBILICAL CORD

Length

Most umbilical cords at delivery are 40 to 70 cm long, and very few measure <30 cm or >100 cm. Cord length is influenced positively by both amnionic fluid volume and fetal mobility (Miller, 1982). In retrospective studies, short cords have been linked with congenital malformations and intrapartum distress (Baergen, 2001; Krakowiak, 2004; Yamamoto, 2016). Excessively long cords are linked with cord entanglement or prolapse and with fetal anomalies (Olaya-C, 2015; Rayburn, 1981).

Because antenatal determination of cord length is technically limited, cord diameter has been evaluated as a predictive marker for fetal outcomes. Some have linked lean cords with poor fetal growth and large-diameter cords with macrosomia (Proctor, 2013). However, the clinical utility of this parameter is still unclear (Barbieri, 2008; Cromi, 2007; Raio, 1999b, 2003).

Coiling

Cord coiling characteristics have been reported but are not currently part of standard sonographic evaluation. Usually the umbilical vessels spiral through the cord in a sinistral, that is, left-twisting direction (Fletcher, 1993; Lacro, 1987). The number of complete coils per centimeter of cord length is termed the *umbilical*

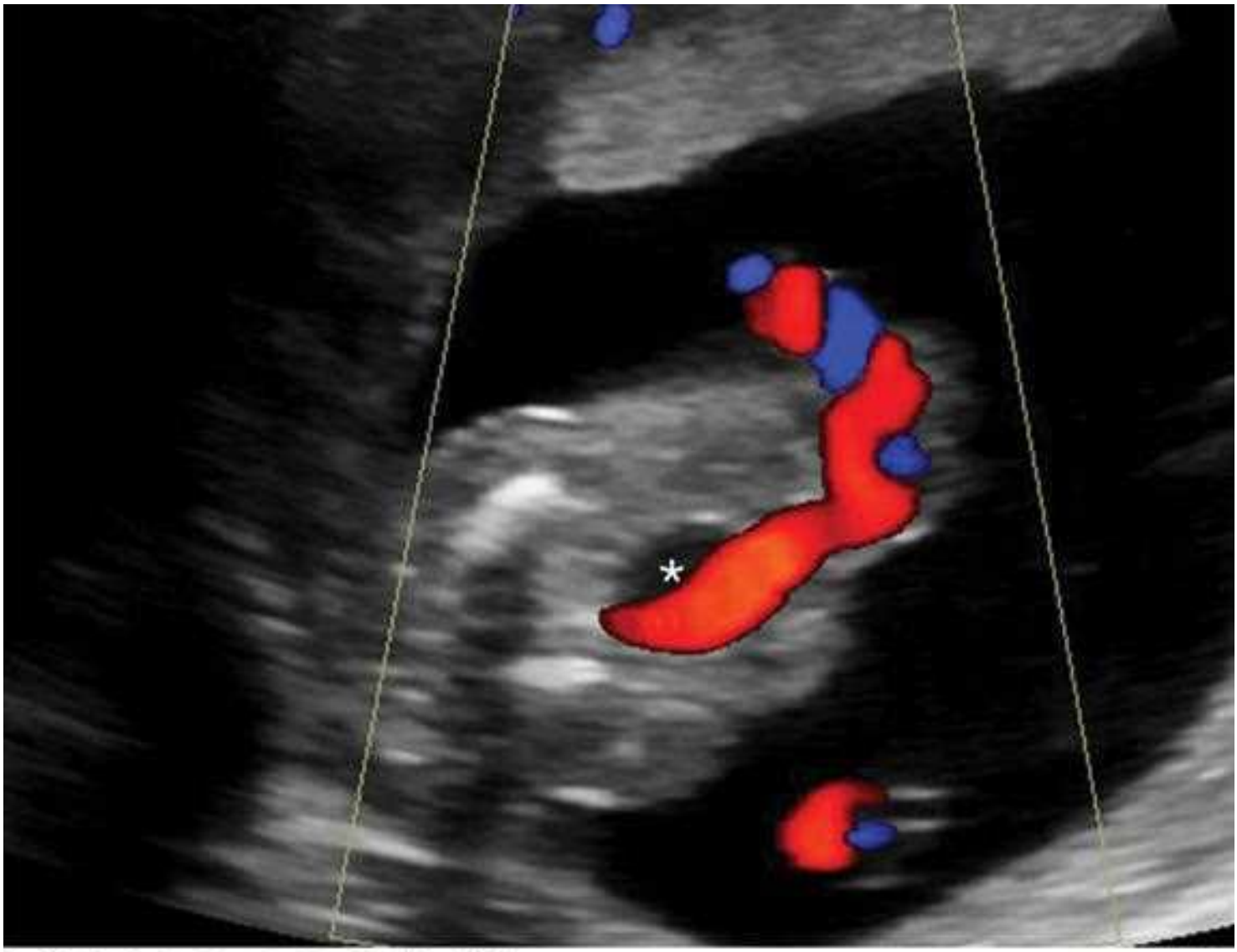
coiling index—UCI (Strong, 1994). A normal, antepartum, sonographically derived UCI is 0.4, and this contrasts with a normal, postpartum, physically measured value of 0.2 (Sebire, 2007). UCIs <10th percentile are considered *hypocoiled,* and those >90th percentile are *hypercoiled.* Clinically, the significance of coiling extremes is controversial. Some studies evaluating large, unselected cohorts find no associations between UCI values and poor neonatal outcome (Jessop, 2014; Pathak, 2010). In others, extremes are linked with various adverse outcomes but most consistently with intrapartum fetal heart rate abnormalities, preterm labor, or fetal-growth restriction (Chitra, 2012; de Laat, 2006; Predanic, 2005; Rana, 1995).

Vessel Number

Counting cord vessel number is a standard component of anatomical evaluation during fetal sonographic examination and immediately after delivery (Fig. 6-5). Embryos initially have two umbilical veins. In the first trimester, the right vein typically atrophies to leave one large vein to accompany the two, thick-walled umbilical arteries. Four-vessel cords are rare and often associated with congenital anomalies (Puvabanditsin, 2011). If it is an isolated finding, however, prognosis can be good (Avnet, 2011).

FIGURE 6-5

Two umbilical arteries are typically documented sonographically in the second trimester. They encircle the fetal bladder (*asterisk*) as extensions of the superior vesical arteries. In this color Doppler sonographic image, a single umbilical artery, shown in red, runs along the bladder wall before joining the umbilical vein (blue) in the cord. Below this, the two vessels of the cord, seen as a larger red and smaller blue circle, are also seen floating in a cross section of a cord segment.



The most common aberration is that of a single umbilical artery (SUA), with a cited incidence of 0.63 percent in liveborn neonates, 1.92 percent with perinatal deaths, and 3 percent in twins (Heifetz, 1984a). Fetuses with major malformations frequently have a single artery. Thus, its identification often prompts consideration for targeted sonography and possibly fetal echocardiography. The most frequent anomalies are cardiovascular and genitourinary (Hua, 2010; Murphy-Kaulbeck, 2010). In an anomalous fetus, a single artery greatly increases the aneuploidy risk, and amniocentesis is recommended (Dagklis, 2010; Lubusky, 2007).

If target sonography finds otherwise normal anatomy, an isolated single artery in an otherwise low-risk pregnancy does not significantly increase the fetal aneuploidy risk. However, as in isolated finding, it has been associated with fetal-growth restriction and perinatal death in some but not all studies (Chetty-John, 2010; Gutvirtz, 2016; Hua, 2010; Murphy-Kaulbeck, 2010; Voskamp, 2013). Thus, while clinical monitoring of growth is reasonable, the value of sonographic surveillance is unclear.

A rare anomaly is that of a fused umbilical artery with a shared lumen. It arises from failure of the two arteries to split during embryological development. The common lumen may extend through the entire cord, but, if partial, it is typically found near the placental insertion site (Yamada, 2005). In one report, these were associated with a higher incidence of marginal or velamentous cord insertion, but not congenital fetal anomalies (Fujikura, 2003).

Found in most placentas, the *Hyrtl anastomosis* is a connection between the two umbilical arteries and lies near the cord insertion into the placenta. This anastomosis acts as a pressure-equalizing system between the arteries (Gordon, 2007). As a result, redistribution of pressure gradients and blood flow improves placental perfusion, especially during uterine contractions or during compression of one umbilical artery. Fetuses with a single umbilical artery lack this safety valve (Raio, 1999a, 2001).

Remnants and Cysts

Several structures are housed in the umbilical cord during fetal development, and their remnants may be seen when the mature cord is viewed transversely. Indeed, Jauniaux and colleagues (1989) sectioned 1000 cords, and in one fourth of the specimens, they found remnants of vitelline duct, allantoic duct, and embryonic vessels. These were not associated with congenital malformations or perinatal complications.

Cysts occasionally are found along the course of the cord. They are designated according to their origin. *True cysts* are epithelium-lined remnants of the allantoic or vitelline ducts and tend to be located closer to the fetal insertion site. In contrast, the more common *pseudocysts* form from local degeneration of Wharton jelly and occur anywhere along the cord. Both have a similar sonographic appearance. Single umbilical cord cysts identified in the first trimester tend to resolve completely, however, multiple cysts may portend miscarriage or aneuploidy (Ghezzi, 2003; Hannaford, 2013). Cysts persisting beyond this time are associated with a risk for structural defects and chromosomal anomalies (Bonilla, 2010; Zangen, 2010).

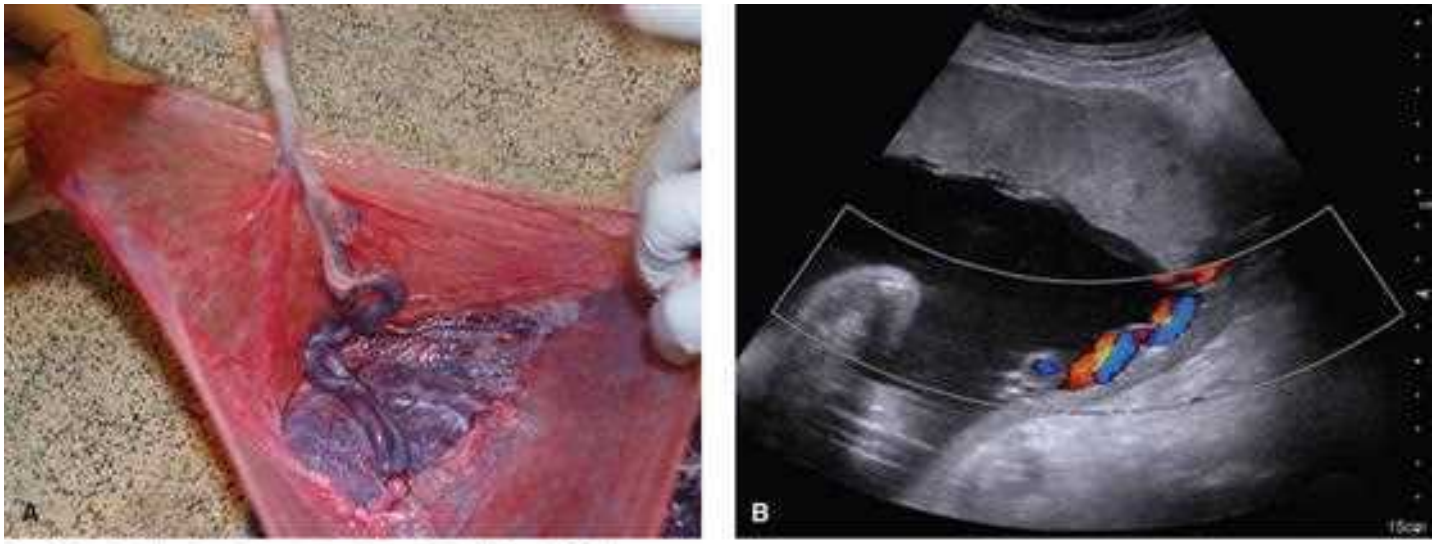
Insertion

The cord normally inserts centrally into the placental disc, but eccentric, marginal, or velamentous insertions are variants. Of these, eccentric insertions in general pose no identifiable fetal risk. Marginal insertion is a common variant—sometimes referred to as a *battledore placenta*—in which the cord anchors at the placental margin. In one population-based study, the rate was 6 percent in singleton gestations and 11 percent in twins (Ebbing, 2013). This common insertion variant rarely causes problems, but it and velamentous insertion occasionally result in the cord being pulled off during delivery of the placenta (Ebbing, 2015; Luo, 2013). In monochorionic twins, this insertion may be associated with weight discordance (Kent, 2011).

With velamentous insertion, the umbilical vessels characteristically travel within the membranes before reaching the placental margin (Fig. 6-6) The incidence of velamentous insertion approximates 1 percent but is 6 percent with twins (Ebbing, 2013). It is more commonly seen with placenta previa (Papinniemi, 2007; Räisänen, 2012). Antenatal diagnosis is possible sonographically, and with velamentous insertion, cord vessels are seen traveling along the uterine wall before entering the placental disc. Clinically, vessels are vulnerable to compression, which may lead to fetal hypoperfusion and acidemia. Higher associated rates of low Apgar scores, stillbirth, preterm delivery, and small for gestational age have been noted (Ebbing, 2017; Esakoff, 2015; Heinonen, 1996; Vahanian, 2015). Accordingly, monitoring of fetal growth is reasonable either clinically or sonographically (Vintzileos, 2015).

FIGURE 6-6

Velamentous cord insertion. **A.** The umbilical cord inserts into the membranes. From here, the cord vessels branch and are supported only by membrane until they reach the placental disc. **B.** When viewed sonographically and using color Doppler, the cord vessels appear to lie against the myometrium as they travel to insert marginally into the placental disc, which lies at the top of this image.



Last, with the very uncommon furcate insertion, umbilical vessels lose their protective Wharton jelly shortly before they insert. As a result, they are covered only by an amnion sheath and prone to compression, twisting, and thrombosis.

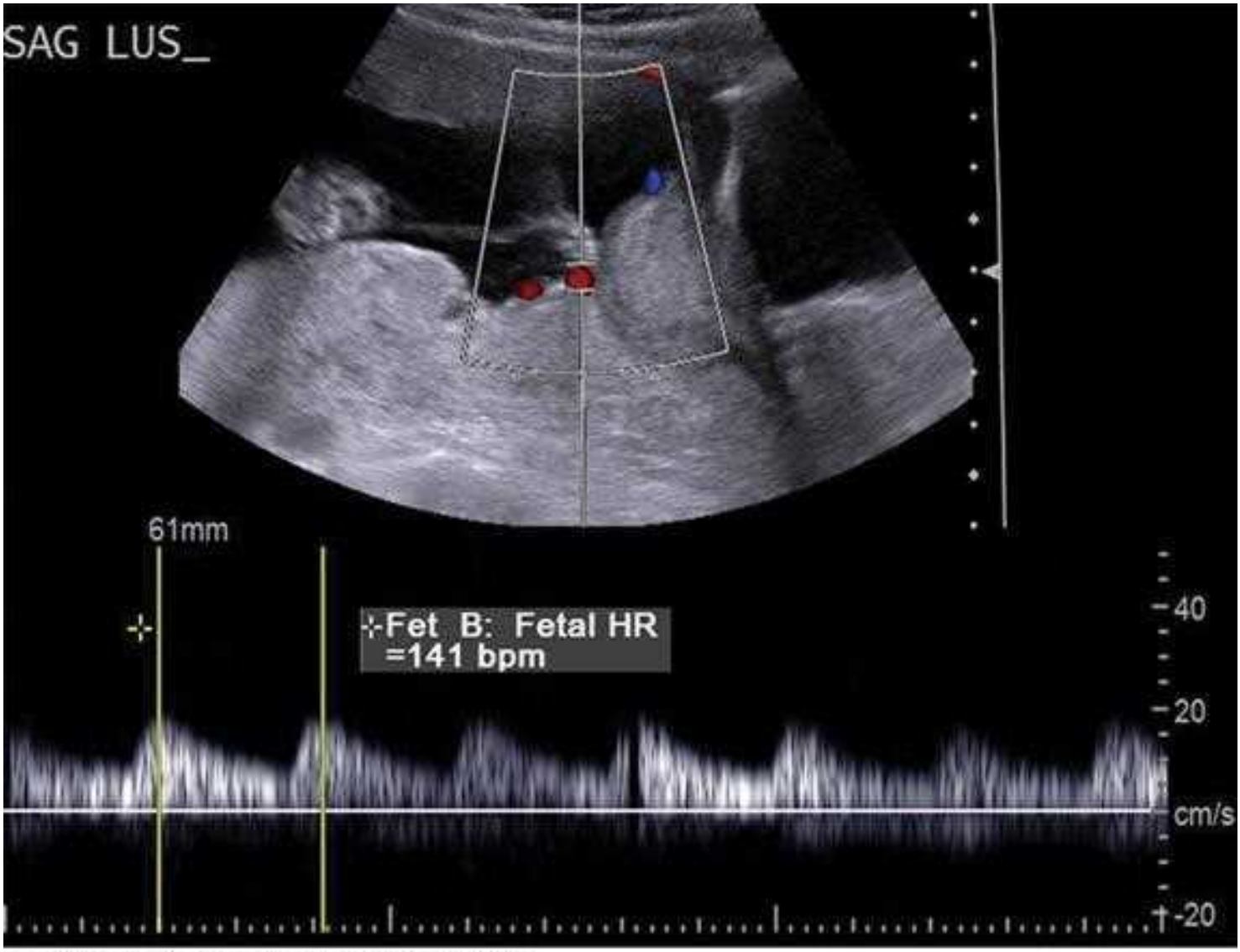
Vasa Previa

With this condition, vessels travel within the membranes and overlie the cervical os. There, they can be torn with cervical dilatation or membrane rupture, and laceration can lead to rapid fetal exsanguination. Over the cervix, vessels can also be compressed by a presenting fetal part. Fortunately, vasa previa is uncommon and has an incidence of 2 to 6 per 10,000 pregnancies (Ruiter, 2016; Sullivan, 2017). Vasa previa is classified as type 1, in which vessels are part of a velamentous cord insertion, and type 2, in which involved vessels span between portions of a bilobate or a succenturiate placenta (Catanzarite, 2001). Two other risks are conception with in vitro fertilization and second-trimester placenta previa, with or without later migration (Baulies, 2007; Schachter, 2003).

Compared with intrapartum diagnosis, antepartum diagnosis greatly improves the perinatal survival rate, which ranges from 97 to 100 percent (Oyelese, 2004; Rebarber, 2014; Swank, 2016). Thus, vasa previa is ideally identified early, although this is not always possible. Clinically, an examiner is occasionally able to palpate or directly see a tubular fetal vessel in the membranes overlying the presenting part. Effective screening for vasa previa begins during scheduled midtrimester sonographic examination. In suspicious cases, transvaginal sonography is added and shows cord vessels inserting into the membranes—rather than directly into the placenta—and vessels running above the cervical internal os (Fig. 6-7). Routine color Doppler interrogation of the placental cord insertion site, particularly in cases of placenta previa or low-lying placenta, may aid its detection. With this, the vessel waveform reflects the fetal heart rate. In one systematic review, the median prenatal detection rate was 93 percent (Ruiter, 2015).

FIGURE 6-7

Vasa previa. Using color Doppler, an umbilical vessel (*red circle*) is seen overlying the internal os. At the bottom, the Doppler waveform seen with this vasa previa has the typical appearance of an umbilical artery, with a pulse rate of 141 beats per minute.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Once vasa previa is identified, subsequent imaging is reasonable because 6 to 17 percent of cases ultimately resolve (Rebarber, 2015; Swank, 2016). Bed rest apparently has no added advantage. Antenatal corticosteroids can be provided as indicated or given prophylactically at 28 to 32 weeks' gestation to cover possible urgent preterm delivery. Antenatal hospitalization may be considered at 30 to 34 weeks to permit surveillance and expedited delivery for labor, bleeding, or rupture of membranes. Data supporting this is limited, and admission may best serve women with risk factors that portend early delivery (Society for Maternal-Fetal Medicine, 2015). A few cases of antepartum fetoscopic surgery with vessel laser ablation are described (Hosseinzadeh, 2015; Johnston, 2014). However, current practice is early scheduled cesarean delivery. Robinson and Grobman (2011) performed a decision analysis and recommend elective cesarean delivery at 34 to 35 weeks' gestation to balance the risks of perinatal exsanguination versus preterm birth morbidity. The Society for Maternal-Fetal Medicine (2015) considers planned cesarean delivery at 34 to 37 weeks' gestation reasonable.

At delivery, the fetus is expeditiously delivered after the hysterotomy incision in case a vessel is lacerated during uterine entry. Delayed cord clamping is not encouraged.

In all pregnancies, otherwise unexplained vaginal bleeding either antepartum or intrapartum should prompt consideration of vasa previa and a lacerated fetal vessel. In many cases, bleeding is rapidly fatal, and infant salvage is not possible. With less hemorrhage, however, it may be possible to distinguish fetal versus maternal bleeding. Various tests may be used, and each relies on the increased resistance of fetal hemoglobin to denaturing by alkaline or acid reagents (Odunsi, 1996; Oyelese, 1999).

Knots, Strictures, and Loops

Various mechanical abnormalities in the cord can impede blood flow and sometimes cause fetal harm. Of these, *true knots* are found in approximately 1 percent of births. These form from fetal movement, and associated risks include hydramnios and diabetes (Hershkovitz, 2001; Räisänen, 2013). Knots are especially common and dangerous in monoamnionic twins, which are discussed in Chapter 45 (Unique Fetal Complications). When true knots are associated with singleton fetuses, the stillbirth risk is increased four- to tenfold (Airas, 2002; Sørnes, 2000).

Knots can be found incidentally during antepartum sonography, and a “hanging noose” sign is suggestive (Ramon y Cajal, 2006). Three-dimensional and color Doppler aid diagnostic accuracy (Hasbun, 2007). With these knots, optimal fetal surveillance is unclear but may include umbilical artery Doppler velocimetry, nonstress testing, or subjective fetal movement monitoring (Rodriguez, 2012; Scioscia, 2011). Allowing vaginal delivery is suitable, but abnormal intrapartum fetal heart rate tracings are more often encountered. That said, cesarean delivery rates are not increased, and cord blood acid-base values are usually normal (Airas, 2002; Maher, 1996).

In contrast, *false knots* form from focal redundancy and folding of an umbilical cord vessel. These lack clinical significance.

Cord strictures are focal narrowings of the diameter that usually develop near the fetal cord insertion site (Peng, 2006). Characteristic pathological features include an absence of Wharton jelly and stenosis or obliteration of cord vessels at the narrow segment (Sun, 1995). In most instances, the fetus is stillborn (French, 2005). Even less common is a cord stricture caused by an amnionic band.

Cord loops are frequently encountered and are caused by coiling around various fetal parts during movement. A cord around the neck—a *nuchal cord*—is common, and vaginal delivery is suitable. One loop is reported in 20 to 34 percent of deliveries; two loops in 2.5 to 5 percent; and three loops in 0.2 to 0.5 percent (Kan, 1957; Sørnes, 1995; Spellacy, 1966). During labor, up to 20 percent of fetuses with a nuchal cord have moderate to severe variable heart rate decelerations, and these are associated with a lower umbilical artery pH (Hankins, 1987). Cords wrapped around the body can have similar effects (Kobayashi, 2015). Despite their frequency, nuchal cords are not associated with greater rates of adverse perinatal outcome (Henry, 2013; Sheiner, 2006).

Last, a *funic presentation* describes when the umbilical cord is the presenting part in labor. These are uncommon and most often are associated with fetal malpresentation (Kinugasa, 2007). A funic presentation in some cases is identified with placental sonography and color flow Doppler (Ezra, 2003). Overt or occult cord prolapse can complicate labor. Thus, once identified at term, cesarean delivery is typically recommended.

Vascular

Cord hematomas are rare and generally follow rupture of an umbilical vessel, usually the vein, and bleeding into the Wharton jelly. Hematomas have been associated with abnormal cord length, umbilical vessel aneurysm, trauma, entanglement, umbilical vessel venipuncture, and funisitis (Gualandri, 2008). Most are identified postpartum, but hematomas are recognized sonographically as hypoechoic masses that lack blood flow (Chou, 2003). Sequelae include stillbirth or intrapartum abnormal fetal heart rate pattern (Abraham, 2015; Barbati, 2009; Sepulveda, 2005; Towers, 2009).

Umbilical cord vessel thromboses are rare in utero events and seldom diagnosed antepartum. Approximately 70 percent are venous, 20 percent are venous and arterial, and 10 percent are arterial thromboses (Heifetz, 1988). These all have high associated rates of stillbirth, fetal-growth restriction, and intrapartum fetal distress (Minakami, 2001; Sato, 2006; Shilling, 2014). If these are identified antepartum as hypoechoic masses without blood flow, data from case reports support consideration of prompt delivery if of viable age (Kanenishi, 2013).

An *umbilical vein varix* can complicate either the intraamnionic or fetal intraabdominal portion of the umbilical vein. Sonographically and complemented by color Doppler, rare intraamnionic varices show cystic dilatation of the umbilical vein that is contiguous with a normal-caliber portion. Of complications, an intraamnionic varix may compress an adjacent umbilical artery or can rupture or thrombose. In cases without these, White and colleagues (1994) recommend fetal surveillance and delivery once fetal maturity is confirmed. However, data are limited and derived from case reports.

The rare *umbilical artery aneurysm* is caused by congenital thinning of the vessel wall with diminished support from Wharton jelly. Indeed, most form at or near the cord placental insertion site, where this support is absent. These are associated with single umbilical artery, trisomy 18, amnionic fluid volume extremes, fetal-growth restriction, and stillbirth (Hill, 2010; Vyas, 2016). At least theoretically, these aneurysms could cause fetal compromise and death by compression of the umbilical vein. These aneurysms may appear sonographically as a cyst with a hyperechoic rim. Within the aneurysm, color flow and spectral Doppler interrogation demonstrate either low-velocity or turbulent nonpulsatile flow (Olog, 2011; Sepulveda, 2003; Shen, 2007b). Although not codified, management may include fetal karyotyping, antenatal fetal surveillance, and early delivery to prevent stillbirth (Doehrman, 2014).

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CHAPTER 7: Embryogenesis and Fetal Development

Our knowledge concerning the physiology of the foetus has been markedly enriched during recent years; nevertheless, when compared with the adult, it offers many points concerning which we are but slightly informed or profoundly ignorant.

—J. Whitridge Williams (1903)

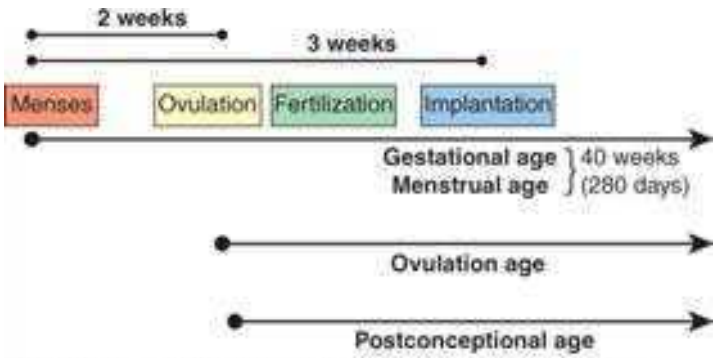
INTRODUCTION

Since these words were written by Williams in 1903, great strides in the understanding of fetal organogenesis and physiology have been gained. Contemporary obstetrics incorporates physiology and pathophysiology of the fetus, its development, and its environment. An important result is that fetal status has been elevated to that of a patient who, in large measure, can be given the same meticulous care that obstetricians provide for gravidas. In our 25th edition, the entirety of Section 5 is dedicated to the fetal patient, as are individual chapters in other sections. Indeed, virtually every aspect of obstetrics can affect the developing fetus.

GESTATIONAL AGE

Several terms define pregnancy duration and thus fetal age (Fig. 7-1). *Gestational age* or *menstrual age* is the time elapsed since the first day of the last menstrual period (LMP), a time that actually precedes conception. This starting time, which is usually approximately 2 weeks before ovulation and fertilization and nearly 3 weeks before blastocyst implantation, has traditionally been used because most women know their approximate last period. Embryologists describe embryofetal development in *ovulation age,* or the time in days or weeks from ovulation. Another term is *postconceptional age,* which is nearly identical to ovulation age.

FIGURE 7-1
Terminology used to describe pregnancy duration.



Until recently, clinicians customarily calculated menstrual age with term pregnancy averaging approximately 280 days, or 40 weeks between the first day of the LMP and birth. This corresponds to 9 and 1/3 calendar months. However, menstrual cycle length variability among women renders many of these calculations inaccurate. This realization, combined with the frequent use of first-trimester sonography, has led to more accurate gestational age determination (Duryea, 2015). Much of this change hinges on the accuracy of early sonographic measurement. As a result, the American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine (Reddy, 2014) together recommend the following:

1. First-trimester sonography is the most accurate method to establish or reaffirm gestational age.
2. In conceptions achieved with assisted-reproductive technology, this gestational age is used.
3. If available, the gestational ages calculated from the LMP and from first-trimester sonography are compared, and the estimated date of confinement (EDC) recorded and discussed with the patient.
4. The best obstetrical estimate of gestational age at delivery is recorded on the birth certificate.

The embryofetal crown-rump length in the first trimester is accurate ±5 to 7 days. Thus, if sonographic assessment of gestational age differs by more than 5 days prior to 9 weeks' gestation, or by more than 7 days later in the first trimester, the estimated delivery date is changed.

Naegele Rule

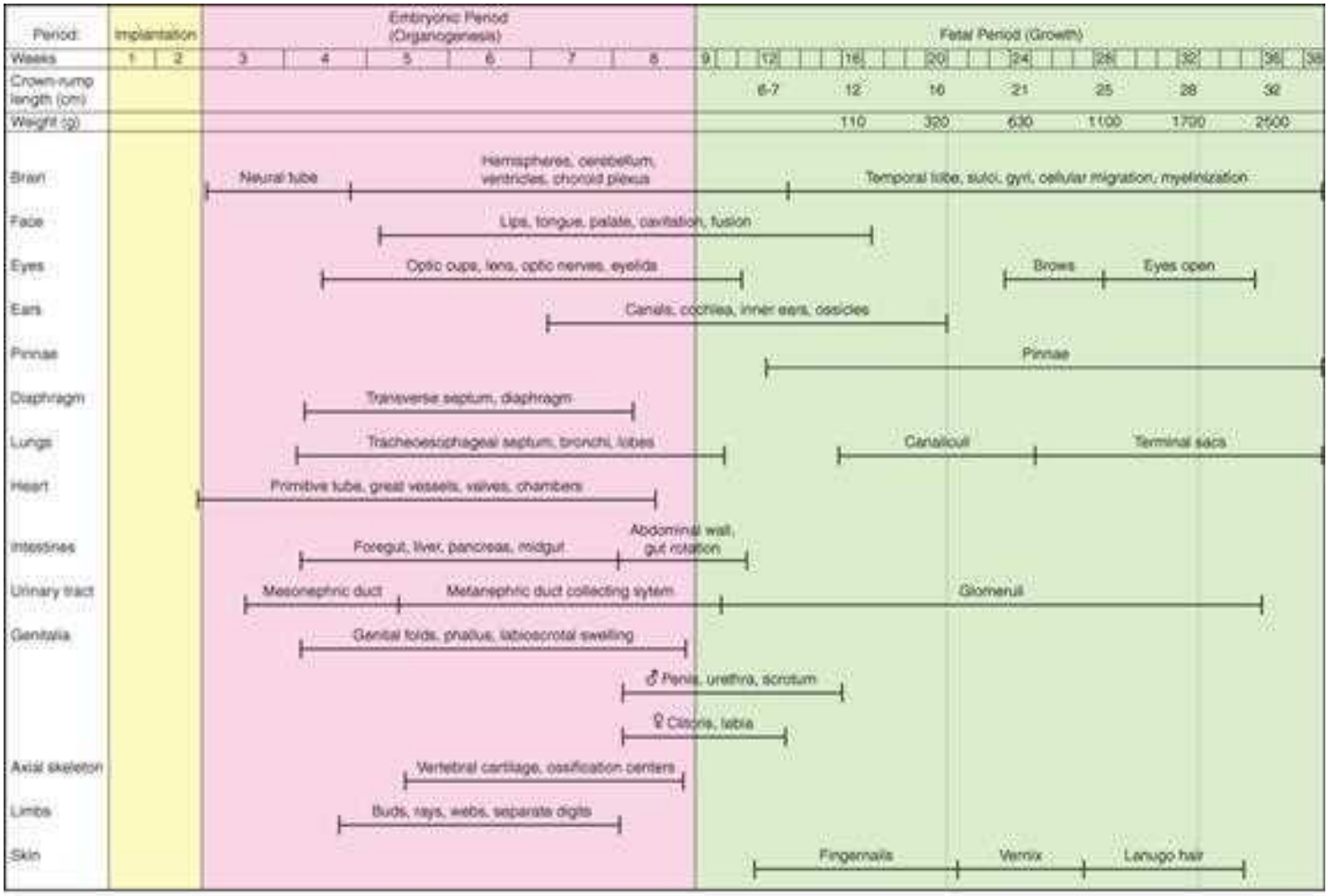
An EDC based on LMP can be quickly estimated as follows: add 7 days to the first day of the LMP and subtract 3 months. For example, if the first day of the LMP was October 5, the due date is 10–05 minus 3 (months) plus 7 (days) = 7–12, or July 12 of the following year. This calculation has been termed the *Naegele rule*. The period of gestation can also be divided into three units of approximately 14 weeks each. These three *trimesters* are important obstetrical milestones.

In addition to estimating the EDC with either Naegele rule or pregnancy "wheels," calculator tools in the electronic medical record and smartphone applications can provide a calculated EDC and gestational age. For example, the American College of Obstetricians and Gynecologists (2016) has developed a calculator application that incorporates sonographic criteria and the LMP or embryo transfer date. This is discussed further in Chapter 10 (Gestational Age Assessment).

EMBRYONIC DEVELOPMENT

The complexity of embryofetal development is almost beyond comprehension. Figure 7-2 shows a developmental sequence of various organ systems. New information regarding organ development continues to accrue. For example, imaging techniques help unravel the contributions of gene regulation and tissue interaction to eventual three-dimensional organ morphology (Anderson, 2016; Mohun, 2011). Others have described the sequence of gene activation that underlies cardiac development.

FIGURE 7-2
Embryofetal development according to gestational age determined by the first day of the last menses. Times are approximate.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

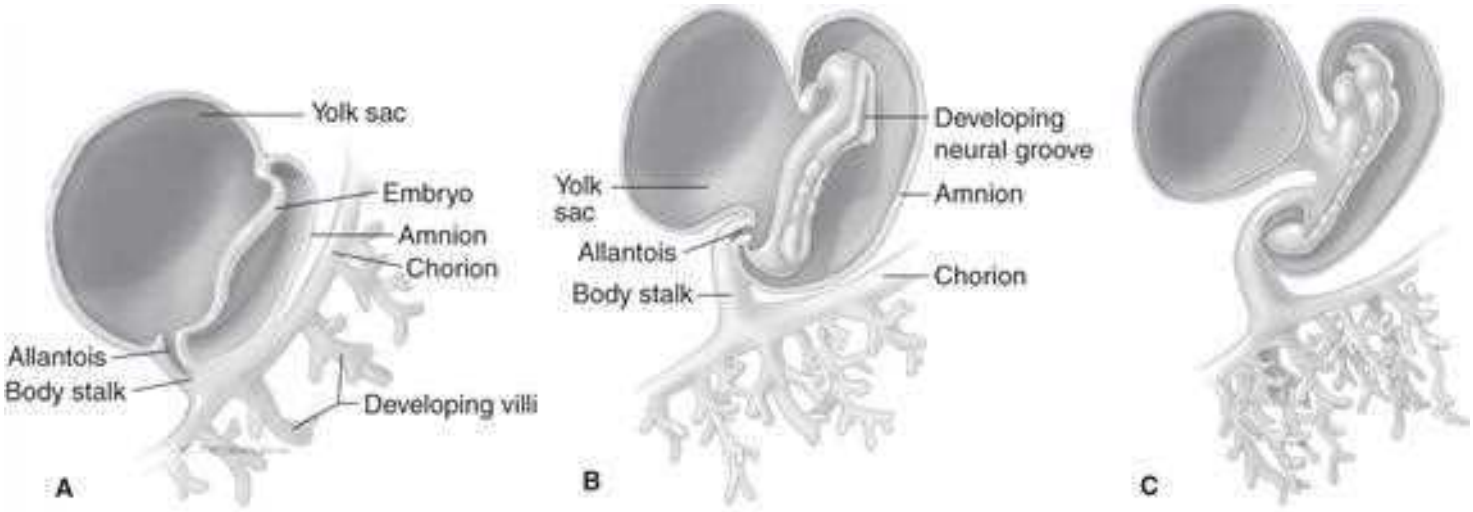
Zygote and Blastocyst Development

During the first 2 weeks after ovulation and then fertilization, the zygote—or preembryo—develops to the blastocyst stage. The blastocyst implants 6 or 7 days following fertilization. The 58-cell blastocyst differentiates into five embryo-producing cells—*the inner cell mass*—and the remaining 53 cells form placental trophoblast. Details of implantation and early development of the blastocyst and placenta are described in Chapter 5 (Implantation and Early Trophoblast Formation).

Embryonic Period

The conceptus is termed an embryo at the beginning of the third week after ovulation and fertilization. Primitive chorionic villi form, and this coincides with the expected day of menses. The embryonic period, during which time organogenesis takes place, lasts 6 weeks. It begins the third week from the LMP through the eighth week. The embryonic disc is well defined, and most pregnancy tests that measure human chorionic gonadotropin (hCG) become positive by this time. As shown in Figure 7-3, the body stalk is now differentiated. There are villous cores in which angioblastic chorionic mesoderm can be distinguished and a true intervillous space that contains maternal blood.

FIGURE 7-3
Early human embryos. Ovulation ages: **A.** 19 days (presomite). **B.** 21 days (7 somites). **C.** 22 days (17 somites). (After drawings and models in the Carnegie Institute.)



During the third week, fetal blood vessels in the chorionic villi appear. In the fourth week, a cardiovascular system has formed (Fig. 7-4). Thereby, a true circulation is established both within the embryo and between the embryo and the chorionic villi. Partitioning of the primitive heart begins. Also in the fourth week, the neural plate forms, and it subsequently folds to form the neural tube. By the end of the fifth menstrual week, the chorionic sac measures approximately 1 cm in diameter. The embryo is 3 mm long and can be measured sonographically. Arm and leg buds have developed, and the amnion is beginning to ensheathe the body stalk, which thereafter becomes the umbilical cord. At the end of the sixth week, the embryo measures approximately 9 mm long, and the neural tube has closed (Fig. 7-5). Cardiac motion is almost always discernable sonographically (Fig. 7-6). The cranial end of the neural tube closes by 38 days from the LMP, and the caudal end closes by 40 days. Thus, the neural tube has closed by the end of the sixth week. And by the end of the eighth week, the crown-rump length approximates 22 mm. Fingers and toes are present, and the arms bend at the elbows. The upper lip is complete, and the external ears form definitive elevations on either side of the head. Three-dimensional images and videos of human embryos from the MultiDimensional Human Embryo project are found at: http://embryo.soad.umich.edu/index.html.

FIGURE 7-4
Three- to four-week-old embryos. **A, B.** Dorsal views of embryos during 22 to 23 days of development showing 8 and 12 somites, respectively. **C–E.** Lateral views of embryos during 24 to 28 days, showing 16, 27, and 33 somites, respectively. (Redrawn from Moore KL: The Developing Human: Clinically Oriented Embryology, 4th ed. Philadelphia, Saunders, 1988.)

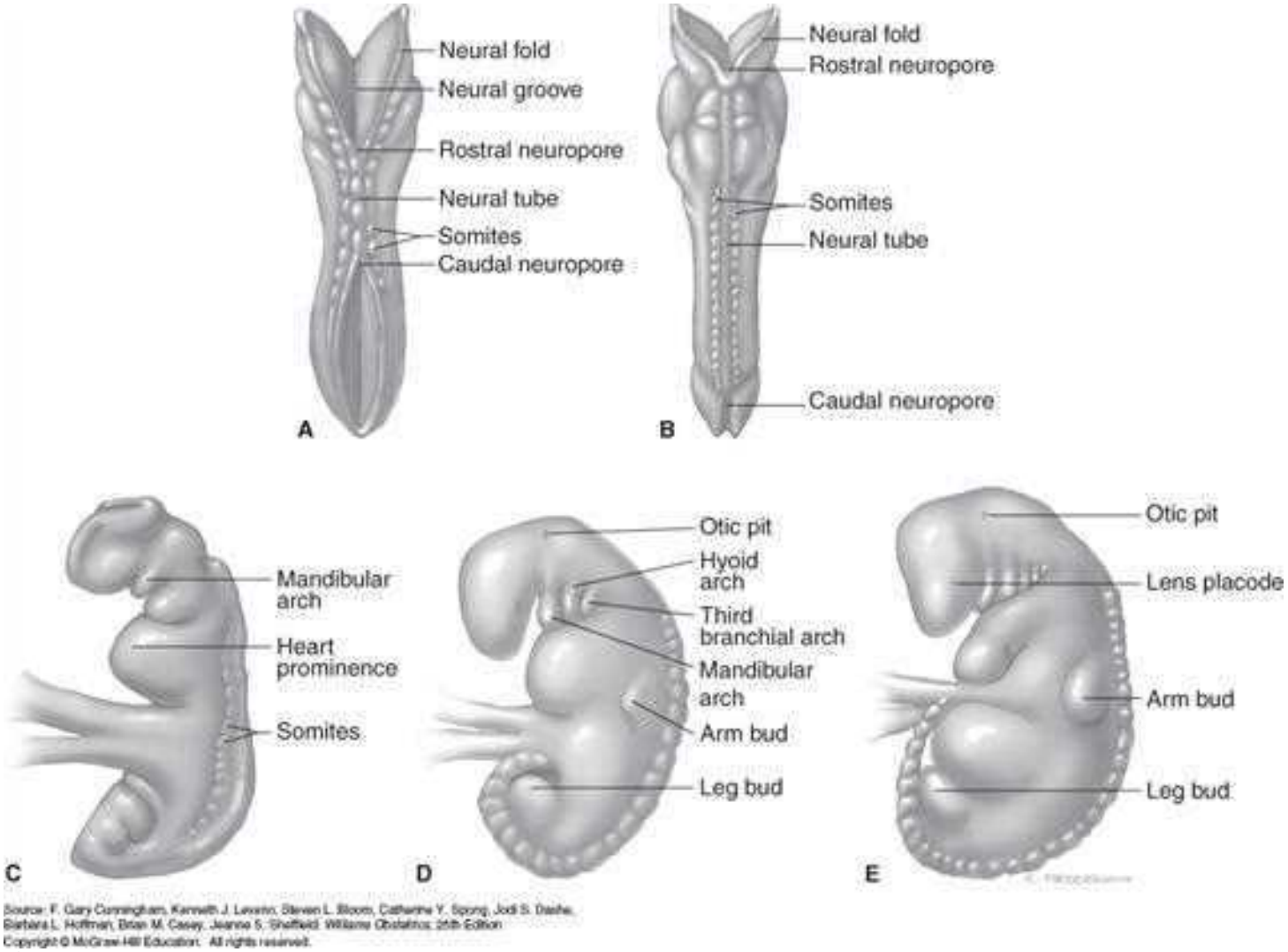


FIGURE 7-5

Embyro photographs. **A.** Dorsal view of an embryo at 24 to 26 days and corresponding to Figure 7-4C. **B.** Lateral view of an embryo at 28 days and corresponding to Figure 7-4D. **C.** Lateral view of embryofetus at 56 days, which marks the end of the embryonic period and the beginning of the fetal period. The liver is within the white, halo circle. (From Werth B, Tsiaras A: From Conception to Birth: A Life Unfolds. New York, Doubleday, 2002.)

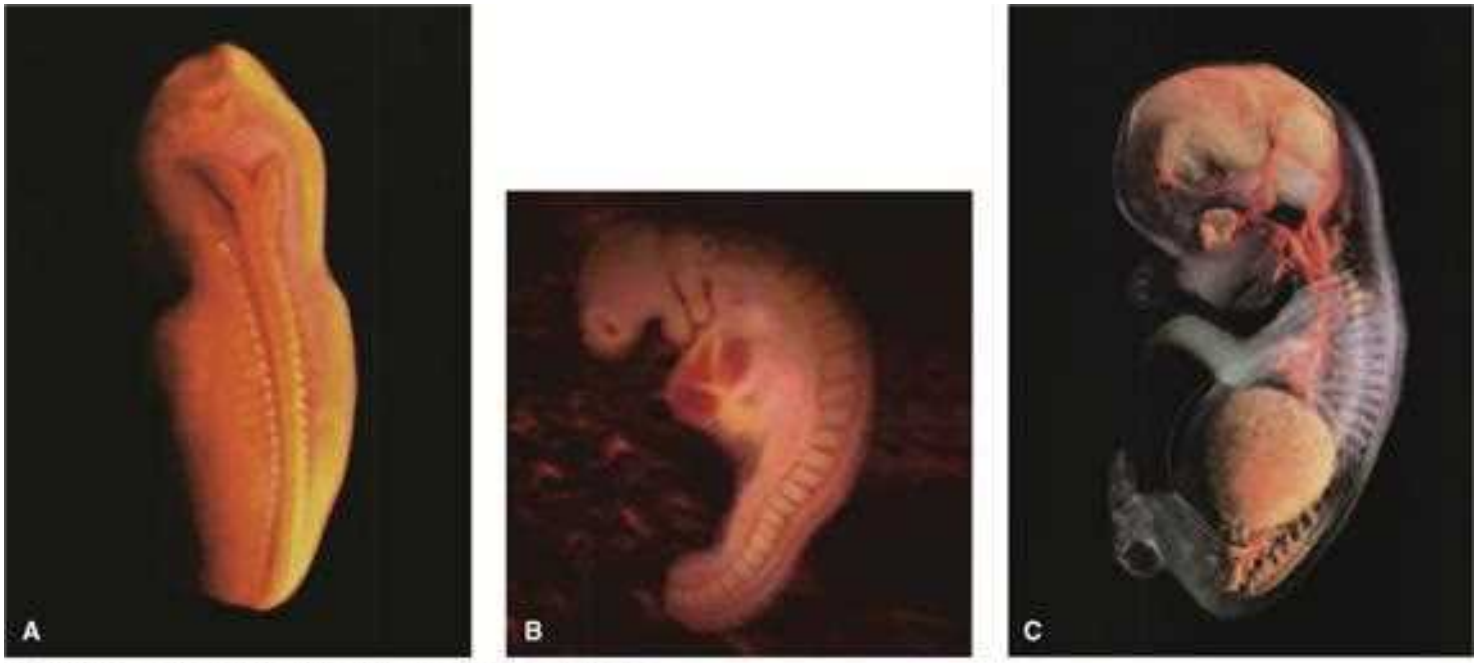
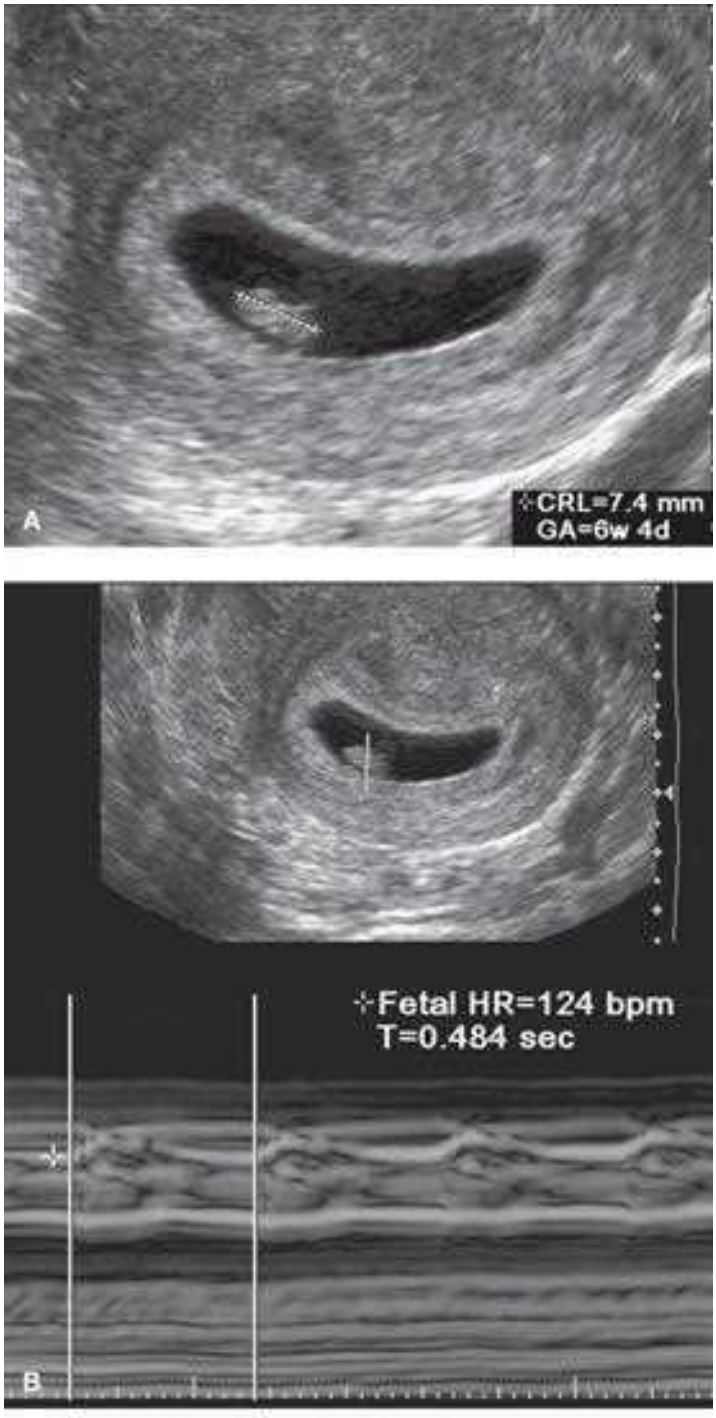


FIGURE 7-6

A. This image of a 6-week, 4-day embryo depicts measurement of the crown-rump length, which is 7.4 mm at this gestational age. **B.** Despite the early gestational age, M-mode imaging readily demonstrates embryonic cardiac activity. The heart rate in this image is 124 beats per minute.



FETAL DEVELOPMENT AND PHYSIOLOGY

Fetal Period Epochs

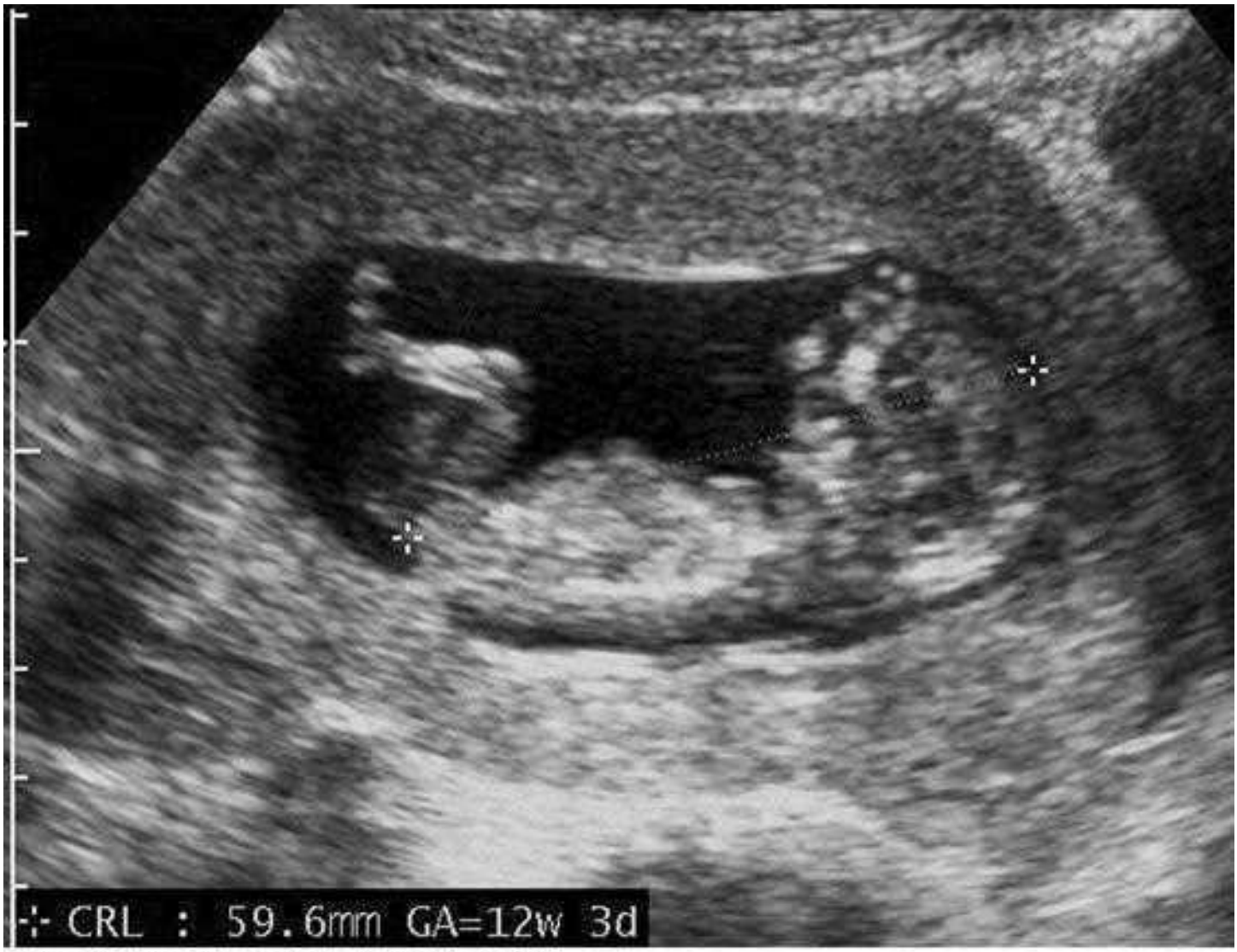
Transition from the embryonic period to the fetal period occurs at 7 weeks after fertilization, corresponding to 9 weeks after onset of the last menses. At this time, the fetus approximates 24 mm in length, most organ systems have developed, and the fetus enters a period of growth and maturation. These phases are outlined in Figure 7-2.

12 Gestational Weeks

The uterus usually is just palpable above the symphysis pubis. Fetal growth is rapid, and the fetal crown-rump length is 5 to 6 cm (Fig. 7-7). Centers of ossification have appeared in most fetal bones, and the fingers and toes have become differentiated. Skin and nails develop, and scattered rudiments of hair appear. The external genitalia are beginning to show definitive signs of male or female gender. The fetus begins to make spontaneous movements.

FIGURE 7-7

This image of a 12-week, 3-day embryo depicts measurement of the crown-rump length. The fetal profile, cranium, and a hand and foot are also visible in this image.



16 Gestational Weeks

Fetal growth slows at this time. The crown-rump length is 12 cm, and the fetal weight approximates 150 g (Hadlock, 1991). Practically speaking, the sonographic crown-rump length is not measured beyond 13 weeks, which corresponds to approximately 8.4 cm. Instead, biparietal diameter, head circumference, abdominal circumference, and femur length are measured. Fetal weight in the second and third trimesters is estimated from a combination of these measurements (Chap. 10, Gestational Age Assessment).

Eye movements begin at 16 to 18 weeks, coinciding with midbrain maturation. By 18 weeks in the female fetus, the uterus is formed and vaginal canalization begins. By 20 weeks in the male, testicles start to descend.

20 Gestational Weeks

This is the midpoint of pregnancy as estimated from the LMP. The fetus now weighs somewhat more than 300 g, and weight increases substantially in a linear manner. From this point onward, the fetus moves approximately every minute and is active 10 to 30 percent of the day (DiPietro, 2005). Brown fat forms, and the fetal skin becomes less transparent. Downy lanugo covers its entire body, and some scalp hair can be seen. Cochlear function develops between 22 and 25 weeks, and its maturation continues for 6 months after delivery.

24 Gestational Weeks

The fetus now weighs almost 700 g (Duryea, 2014). The skin is characteristically wrinkled, and fat deposition begins. The head is still comparatively large, and eyebrows and eyelashes are usually recognizable. By 24 weeks, the secretory type II pneumocytes have initiated surfactant secretion (Chap. 32, Care in the Delivery Room). The canalicular period of lung development, during which the bronchi and bronchioles enlarge and alveolar ducts develop, is nearly completed. Despite this, a fetus born at this time will attempt to breathe, but many will die because the terminal sacs, required for gas exchange, have not yet formed. The overall survival rate at 24 weeks is barely above 50 percent, and only approximately 30 percent survive without severe morbidity (Rysavy, 2015). By 26 weeks, the eyes open. Nociceptors are present over all the body, and the neural pain system is developed (Kadic, 2012). The fetal liver and spleen are important sites for hemopoiesis.

28 Gestational Weeks

The crown-rump length approximates 25 cm, and the fetus weighs about 1100 g. The thin skin is red and covered with **vernix caseosa**. The pupillary membrane has just disappeared from the eyes. Isolated eye blinking peaks at 28 weeks. The bone marrow becomes the major site of hemopoiesis. The otherwise normal neonate born at this age has a 90-percent chance of survival without physical or neurological impairment.

32 and 36 Gestational Weeks

At 32 weeks, the fetus has attained a crown-rump length approximating 28 cm and a weight of about 1800 g. The skin surface is still red and wrinkled. In contrast, by 36 weeks, the fetal crown-rump length averages about 32 cm, and the weight approximates 2800 g (Duryea, 2014). Because of subcutaneous fat deposition, the body has become more rotund, and the previous wrinkled facies is now fuller. Normal fetuses have nearly 100-percent survival rate.

40 Gestational Weeks

This is considered term, and the fetus is now fully developed. The average crown-rump length measures about 36 cm, and the average weight approximates 3500 g.

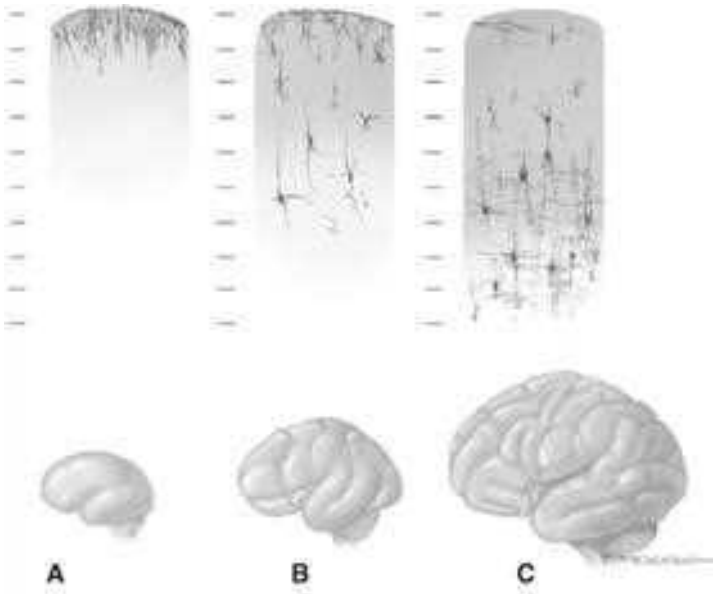
Central Nervous System Development

Brain Development

The cranial end of the neural tube closes by 38 days from the LMP, and the caudal end closes by 40 days. Hence, folic acid supplementation to prevent neural-tube defects must be in place before this point to be efficacious (Chap. 9, Pragmatic Nutritional Surveillance). The walls of the neural tube form the brain and spinal cord. The lumen becomes the ventricular system of the brain and the central canal of the spinal cord. During the sixth week, the cranial end of the neural tube forms three primary vesicles. In the seventh week, five secondary vesicles develop: the telencephalon—future cerebral hemispheres; diencephalon—thalami; mesencephalon—midbrain; metencephalon—pons and cerebellum; and myelencephalon—medulla. Meanwhile, flexures develop and fold the brain into its typical configuration. The end of the embryonic period signifies completion of primary and secondary neuralization.

At 3 to 4 months' gestation, *neuronal proliferation* peaks. As expected, disorders in this cerebral development phase profoundly worsen function (Volpe, 2008). *Neuronal migration* occurs almost simultaneously and peaks at 3 to 5 months. This process is characterized by movement of millions of neuronal cells from their ventricular and subventricular zones to areas of the brain in which they reside for life (Fig. 7-8). Upregulation of gene expression for neuronal migration has been described (Iruretagoyena, 2014). Noninvasive methods to study fetal neurodevelopment have also been reported (Goetzl, 2016).

FIGURE 7-8
Neuronal proliferation and migration are complete at 20 to 24 weeks. During the second half of gestation, organizational events proceed with gyral formation and proliferation, differentiation, and migration of cellular elements. Approximate gestational ages are shown. **A.** 20 weeks. **B.** 35 weeks. **C.** 40 weeks.



As gestation progresses, the fetal brain appearance steadily changes. Thus, it is possible to identify fetal age from its external appearance (Volpe, 2008). Neuronal proliferation and migration proceed along with gyral growth and maturation (see Fig. 7-8). Sequential maturation studies by Manganaro (2007) and Dubois (2014) and their colleagues have characterized the developing fetal brain image using magnetic resonance (MR) imaging. Other recent investigations that also used MR imaging have quantified development of subcortical brain structures from 12 to 22 weeks (Meng, 2012).

Myelination of the ventral roots of the cerebrospinal nerves and brainstem begins at approximately 6 months, but most myelination progresses after birth. This lack of myelin and incomplete skull ossification permit fetal brain structure to be seen sonographically throughout gestation.

Spinal Cord

Whereas the superior two thirds of the neural tube give rise to the brain, the inferior third forms the spinal cord. In the embryo, the spinal cord extends along the entire vertebral column length, but after that it lags behind vertebral growth. Ossification of the entire sacrum is visible sonographically by approximately 21 weeks (Chap. 10, Normal and Abnormal Fetal Anatomy). By 24 weeks, the spinal cord extends to S_1, at birth to L_3, and in the adult to L_1. Spinal cord myelination begins at midgestation and continues through the first year of life. Synaptic function is sufficiently developed by the eighth week to demonstrate flexion of the neck and trunk (Temiras, 1968). During the third trimester, integration of nervous and muscular function proceeds rapidly.

Cardiovascular System

The embryology of the heart is complex. At its earliest stages of formation, the fetal heart undergoes molecular programming, and more than a hundred genes and molecular factors are integral to its morphogenesis. To summarize, the straight cardiac tube is formed by the 23rd day during an intricate morphogenetic sequence, during which each *segment* arises at a unique time. The tube then undergoes *looping,* and the chambers then fuse and form septa (Manner, 2009). The valves develop, and the aortic arch forms by vasculogenesis. For a complete description, refer to Chapter 9 in *Hurst's The Heart* (Keller, 2013).

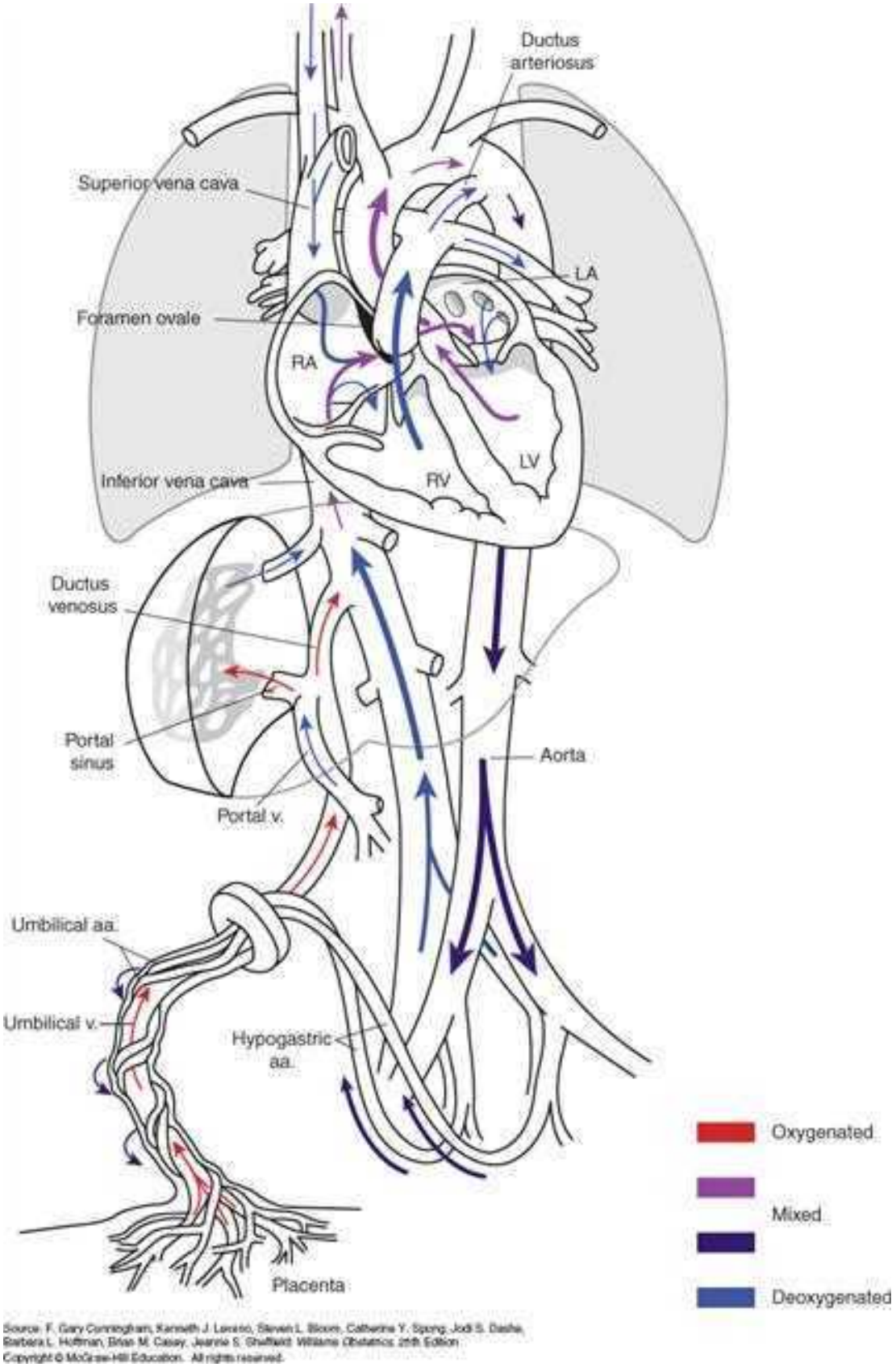
Fetal Circulation

This unique circulation is substantially different from that of the adult and functions until birth, when it changes dramatically. For example, because fetal blood does not need to enter the pulmonary vasculature to be oxygenated, most of the right ventricular output bypasses the lungs. In addition, the fetal heart chambers work in parallel, not in series, which effectively supplies the brain and heart with more highly oxygenated blood than the rest of the body.

Oxygen and nutrient materials required for fetal growth and maturation are delivered from the placenta by the single umbilical vein (Fig. 7-9). The vein then divides into the ductus venosus and the portal sinus. The ductus venosus is the major branch of the umbilical vein and traverses the liver to enter the inferior vena cava directly. Because it does not supply oxygen to the intervening tissues, it carries well-oxygenated blood directly to the heart. In contrast, the portal sinus carries blood to the hepatic veins primarily on the left side of the liver, and oxygen is extracted. The relatively deoxygenated blood from the liver then flows back into the inferior vena cava, which also receives more deoxygenated blood returning from the lower body. Blood flowing to the fetal heart from the inferior vena cava, therefore, consists of an admixture of arterial-like blood that passes directly through the ductus venosus and less well-oxygenated blood that returns from most of the veins below the level of the diaphragm. The oxygen content of blood delivered to the heart from the inferior vena cava is thus lower than that leaving the placenta.

FIGURE 7-9

The intricate nature of the fetal circulation is evident. The degree of blood oxygenation in various vessels differs appreciably from that in the postnatal state. aa = arteries; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; v = vein.



As discussed, the ventricles of the fetal heart work in parallel, not in series. Well-oxygenated blood enters the left ventricle, which supplies the heart and brain, and less oxygenated blood enters the right ventricle, which supplies the rest of the body. These two separate circulations are maintained by the right atrial structure, which effectively directs entering blood to either the left atrium or the right ventricle, depending on its oxygen content. This separation of blood according to its oxygen content is aided by the pattern of blood flow in the inferior vena cava. The well-oxygenated blood tends to course along the medial aspect of the inferior vena cava and the less oxygenated blood flows along the lateral vessel wall. This aids their shunting into opposite sides of the

heart. Once this blood enters the right atrium, the configuration of the upper interatrial septum—the *crista dividens*—preferentially shunts the well-oxygenated blood from the medial side of the inferior vena cava and the ductus venosus through the foramen ovale into the left heart and then to the heart and brain (Dawes, 1962). After these tissues have extracted needed oxygen, the resulting less oxygenated blood returns to the right atrium through the superior vena cava.

The less oxygenated blood coursing along the lateral wall of the inferior vena cava enters the right atrium and is deflected through the tricuspid valve to the right ventricle. The superior vena cava courses inferiorly and anteriorly as it enters the right atrium, ensuring that less well-oxygenated blood returning from the brain and upper body also will be shunted directly to the right ventricle. Similarly, the ostium of the coronary sinus lies just superior to the tricuspid valve so that less oxygenated blood from the heart also returns to the right ventricle. As a result of this blood flow pattern, blood in the right ventricle is 15 to 20 percent less saturated than blood in the left ventricle.

Almost 90 percent of blood exiting the right ventricle is shunted through the ductus arteriosus to the descending aorta. High pulmonary vascular resistance and comparatively lower resistance in the ductus arteriosus and the umbilical–placental vasculature ensure that only about 8 percent of right ventricular output goes to the lungs (Fineman, 2014). Thus, one third of the blood passing through the ductus arteriosus is delivered to the body. The remaining right ventricular output returns to the placenta through the two hypogastric arteries. These two arteries course from the level of the bladder along the abdominal wall to the umbilical ring and into the cord as the umbilical arteries. In the placenta, this blood picks up oxygen and other nutrients and is recirculated through the umbilical vein.

Circulatory Changes at Birth

After birth, the umbilical vessels, ductus arteriosus, foramen ovale, and ductus venosus normally constrict or collapse. With the functional closure of the ductus arteriosus and the expansion of the lungs, blood leaving the right ventricle preferentially enters the pulmonary vasculature to become oxygenated before it returns to the left heart (Hillman, 2012). Virtually instantaneously, the ventricles, which had worked in parallel in fetal life, now effectively work in series. The more distal portions of the hypogastric arteries undergo atrophy and obliteration within 3 to 4 days after birth. These become the umbilical ligaments, whereas the intraabdominal remnants of the umbilical vein form the ligamentum teres. The ductus venosus constricts by 10 to 96 hours after birth and is anatomically closed by 2 to 3 weeks. This ultimately forms the ligamentum venosum (Fineman, 2014).

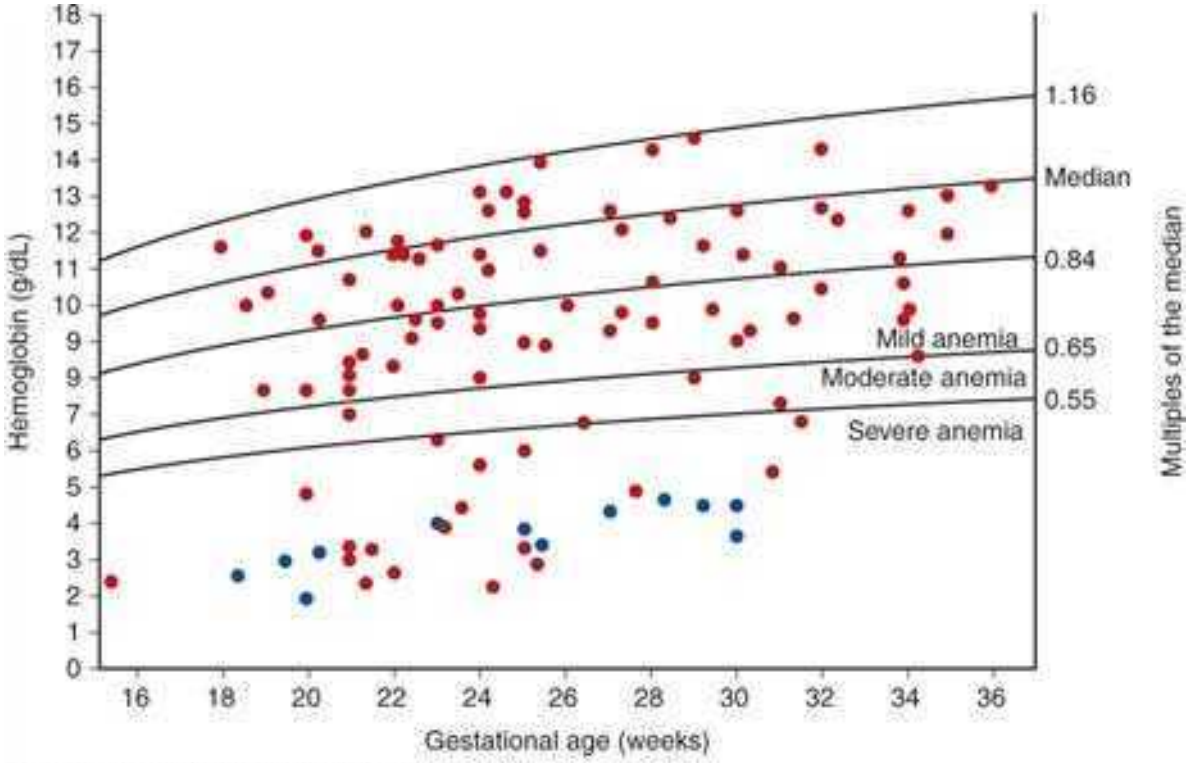
Fetoplacental Blood Volume

Although precise measurements of human fetoplacental blood volume are lacking, Usher and associates (1963) reported values in term normal newborns to average 78 mL/kg when immediate cord clamping was conducted. Gruenwald (1967) found the fetal blood volume contained in the placenta after prompt cord clamping to average 45 mL/kg of fetal weight. Thus, fetoplacental blood volume at term is approximately 125 mL/kg of fetal weight. This is important when assessing the magnitude of fetomaternal hemorrhage as discussed in Chapter 15 (Fetal Thrombocytopenia).

Hemopoiesis

In the early embryo, hemopoiesis is demonstrable first in the yolk sac, followed by the liver, and finally spleen and bone marrow. Both myeloid and erythroid cells are continually produced by progenitors that are from hematopoietic stem cells (Golub, 2013; Heinig, 2015). The first erythrocytes released into the fetal circulation are nucleated and macrocytic. The mean cell volume is at least 180 fL in the embryo and decreases to 105 to 115 fL at term. The erythrocytes of aneuploid fetuses generally do not undergo this maturation and maintain high mean cell volumes—130 fL on average (Sipes, 1991). As fetal development progresses, more and more of the circulating erythrocytes are smaller and nonnucleated. With fetal growth, both the blood volume in the common fetoplacental circulation and hemoglobin concentration increase. As shown in Figure 7-10, fetal hemoglobin concentrations rise across pregnancy. The Society for Maternal-Fetal Medicine (2015) recommends a cutoff hematocrit value of 30 percent to define anemia.

FIGURE 7-10
Relationship between fetal hemoglobin across gestational age. Blue dots indicate fetuses with hydrops. (Reproduced with permission from Mari G, Deter RL, Carpenter RL, et al: Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses (Level II-I), N Engl J Med 2000 Jan 6;342(1):9–14.)



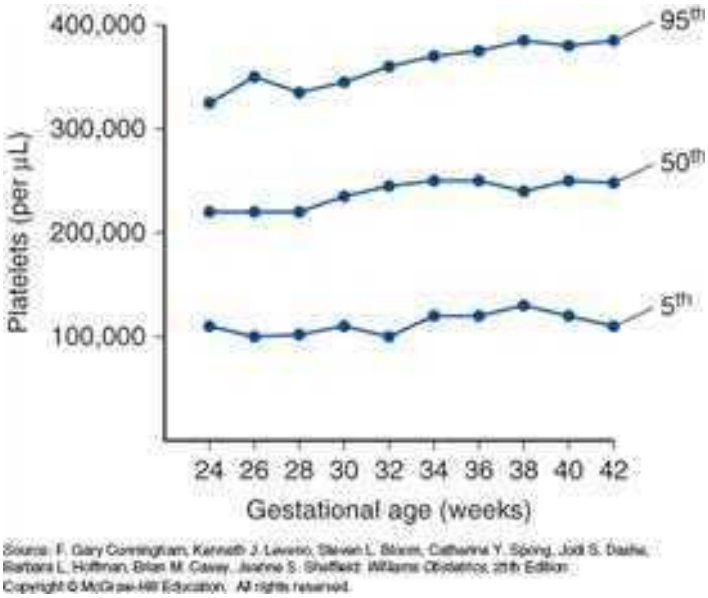
Because of their large size, fetal erythrocytes have a short life span, which progressively lengthens to approximately 90 days at term (Pearson, 1966). As a consequence, red blood cell production rises. Reticulocytes are initially present at high levels, but decrease to 4 to 5 percent of the total at term. Fetal erythrocytes differ structurally and metabolically from those in the adult (Baron, 2012). They are more deformable, which serves to offset their higher viscosity. They also contain several enzymes with appreciably different activities.

Erythropoiesis is controlled primarily by fetal erythropoietin because maternal erythropoietin does not cross the placenta. Fetal hormone production is influenced by testosterone, estrogen, prostaglandins, thyroid hormone, and lipoproteins (Stockman, 1992). Serum erythropoietin levels rise with fetal maturity. Although the exact production site is disputed, the fetal liver appears to be an important source until renal production begins. There is a close correlation between the erythropoietin concentration in amnionic fluid and that in umbilical venous blood obtained by cordocentesis. After birth, erythropoietin normally may not be detectable for up to 3 months.

In contrast, platelet production reaches stable levels by midpregnancy, although there is some variation across gestation (Fig. 7-11). The fetal and neonatal platelet count is subject to various agents as discussed in Chapter 15 (Fetal Thrombocytopenia).

FIGURE 7-11

Platelet counts by gestational age obtained the first day of life. Mean values and 5th and 95th percentiles are shown. (Data from Christensen RD, Henry E, Antonio DV: Thrombocytosis and thrombocytopenia in the NICU: incidence, mechanisms and treatments, J Matern Fetal Neonatal Med 2012 Oct;25 Suppl 4:15–17)



Fetal Hemoglobin

This tetrameric protein is composed of two copies of two different peptide chains, which determine the type of hemoglobin produced. Normal adult hemoglobin A is made of α and β chains. During embryonic and fetal life, various α and β chain precursors are produced. This results in the serial production of several different embryonic hemoglobins. Genes for β-type chains are on chromosome 11, and those for α-type chains on chromosome 16. Each of these genes is turned on and then off during fetal life, until α and β genes, which direct the production of adult hemoglobin A, are permanently activated.

The timing of production of each of these early hemoglobins corresponds to the site of hemoglobin production. Fetal blood is first produced in the yolk sac, where hemoglobins Gower 1, Gower 2, and Portland are made. Erythropoiesis then moves to the liver, where fetal hemoglobin F is produced. When hemopoiesis finally moves to the bone marrow, adult-type hemoglobin A appears in fetal red blood cells and is present in progressively greater amounts as the fetus matures (Pataryas, 1972).

The final adult version of the α chain is produced exclusively by 6 weeks. After this, there are no functional alternative versions. If an α-gene mutation or deletion occurs, no alternate α-type chain can be substituted to form functional hemoglobin. In contrast, at least two versions of the β chain—δ and γ—remain in production throughout fetal life and beyond. In the case of a β-gene mutation or deletion, these two other versions of the β chain often continue to be produced, resulting in hemoglobin A_2 or hemoglobin F, which substitute for the abnormal or missing hemoglobin.

Genes are turned off by methylation of their control region, which is discussed in Chapter 13 (DNA Triplet Repeat Expansion—Anticipation). In some situations, methylation does not occur. For example, in newborns of diabetic women, hemoglobin F may persist due to hypomethylation of the γ gene (Perrine, 1988). With sickle cell anemia, the γ gene remains unmethylated, and large quantities of fetal hemoglobin continue to be produced. As discussed in Chapter 56 (Polycythemias), elevated hemoglobin F levels are associated with fewer sickle-cell disease symptoms, and pharmacological modification of these levels by hemoglobin F-inducing drugs is one approach to treatment.

As discussed in Placental Transfer, there is a functional difference between hemoglobins A and F. At any given oxygen tension and at identical pH, fetal erythrocytes that contain mostly hemoglobin F bind more oxygen than do those that contain nearly all hemoglobin A (Fig. 47-2). This is because hemoglobin A binds 2,3-diphosphoglycerate (2,3-DPG) more avidly than does hemoglobin F, thus lowering the affinity of hemoglobin A for oxygen. During pregnancy, maternal 2,3-DPG levels are greater, and because fetal erythrocytes have lower concentrations of 2,3-DPG, the latter has increased oxygen affinity.

The amount of hemoglobin F in fetal erythrocytes begins to decrease in the last weeks of pregnancy. At term, approximately three fourths of total hemoglobin levels are hemoglobin F. During the first 6 to 12 months of life, the hemoglobin F proportion continues to decline and eventually reaches the low levels found in adult erythrocytes.

Coagulation Factors

With the exception of fibrinogen, there are no embryonic forms of the various hemostatic proteins. The fetus starts producing normal, adult-type procoagulant, fibrinolytic, and anticoagulant proteins by 12 weeks. Because they do not cross the placenta, their concentrations at birth are markedly below the levels that develop within a few weeks of life (Corrigan, 1992). In normal neonates, the levels of factors II, VII, IX, X, XI, and of protein S, protein C, antithrombin, and plasminogen all approximate 50 percent of adult levels. In contrast, levels of factors V, VIII, XIII, and fibrinogen are closer to adult values (Saracco, 2009). Without prophylactic treatment, the levels of vitamin K-dependent coagulation factors usually decrease even further during the first few days after birth. This decline is amplified in breastfed infants and may lead to newborn hemorrhage (Chap. 33, Polycythemia and Hyperviscosity).

Fetal fibrinogen, which appears as early as 5 weeks, has the same amino acid composition as adult fibrinogen, however, it has different properties (Klagsbrun, 1988). It forms a less compressible clot, and the fibrin monomer has a lower degree of aggregation (Heimark, 1988). Although plasma fibrinogen levels at birth are less than those in nonpregnant adults, the protein is functionally more active than adult fibrinogen (Ignjatovic, 2011).

Levels of functional fetal factor XIII—fibrin stabilizing factor—are significantly reduced compared with those in adults (Henriksson, 1974). Nielsen (1969) described low levels of plasminogen and elevated fibrinolytic activity in cord plasma compared with that of maternal plasma. Platelet counts in cord blood are in the normal range for nonpregnant adults (see Fig. 7-11).

Despite this relative reduction in procoagulants, the fetus appears to be protected from hemorrhage, and fetal bleeding is rare. Even after invasive fetal procedures such as cordocentesis, excessive bleeding is uncommon. Ney and coworkers (1989) have shown that amnionic fluid thromboplastins and a factor(s) in Wharton jelly combine to aid coagulation at the umbilical cord puncture site.

Various *thrombophilias* may cause thromboses and pregnancy complications in adults (Chap. 52, Acquired Thrombophilias). If the fetus inherits one of these mutations, thrombosis and infarction can develop in the placenta or fetal organs. This is usually seen with homozygous inheritance. One example is homozygous protein C mutation, which causes *purpura fulminans*.

Plasma Proteins

Liver enzymes and other plasma proteins are produced by the fetus, and these levels do not correlate with maternal levels (Weiner, 1992). Concentrations of plasma proteins, which include albumin, lactic dehydrogenase, aspartate aminotransferase, γ-glutamyl transpeptidase, and alanine transferase, all rise. Conversely, prealbumin levels decline with gestational age (Fryer, 1993). At birth, mean total plasma protein and albumin concentrations in fetal blood are similar to maternal levels. This is important because albumin binds unconjugated bilirubin to prevent *kernicterus* in the newborn (Chap. 33, Polycythemia and Hyperviscosity).

Respiratory System

Lung maturation and biochemical indices of functional fetal lung maturity are important predictors of early neonatal outcome. Morphological or functional immaturity at birth leads to the development of the *respiratory distress syndrome* (Chap. 34, Respiratory Distress Syndrome). A sufficient amount of surface-active materials—collectively referred to as *surfactant*—in the amnionic fluid is evidence of fetal lung maturity. As Liggins (1994) emphasized, however, the structural and morphological maturation of fetal lung also is extraordinarily important to proper lung function.

Anatomical Maturation

The limits of viability appear to be determined by the usual process of pulmonary growth. Like the branching of a tree, lung development proceeds along an established timetable that apparently cannot be hastened by antenatal or neonatal therapy. Within this framework, four essential lung development stages are described by Moore (2000). First, the ***pseudoglandular stage*** entails growth of the intrasegmental bronchial tree between the 5th and 17th weeks. During this period, the lung looks microscopically like a gland. Second, during the ***canalicular stage***, from 16 to 25 weeks, the bronchial cartilage plates extend peripherally. Each terminal bronchiole gives rise to several respiratory bronchioles, and each of these in turn divides into multiple saccular ducts. Third, the ***terminal sac stage*** begins after 25 weeks. During this stage, alveoli give rise to primitive pulmonary alveoli, that is, the terminal sacs. Simultaneously, an extracellular matrix develops from proximal to distal lung segments until term. Finally, the alveolar stage begins during the late fetal period and continues well into childhood. An extensive capillary network is built, the lymph system forms, and type II pneumocytes begin to produce surfactant. At birth, only approximately 15 percent of the adult number of alveoli is present. Thus, the lung continues to grow, adding more alveoli for up to 8 years.

Various insults can upset this process, and their timing determines the sequelae. One example is fetal renal agenesis, in which amnionic fluid is absent at the beginning of lung growth, and major defects occur in all four developmental stages. In another instance, the fetus with membrane rupture and subsequent oligohydramnios before 20 weeks usually exhibits nearly normal bronchial branching and cartilage development but has immature alveoli. In contrast, membrane rupture after 24 weeks may have minimal long-term effect on pulmonary structure. In another example, various growth factors are expressed abnormally in the fetus with a diaphragmatic hernia (Candilira, 2015). Finally, vitamin D is thought to be important for several aspects of lung development (Hart, 2015; Lykkedegn, 2015).

Pulmonary Surfactant

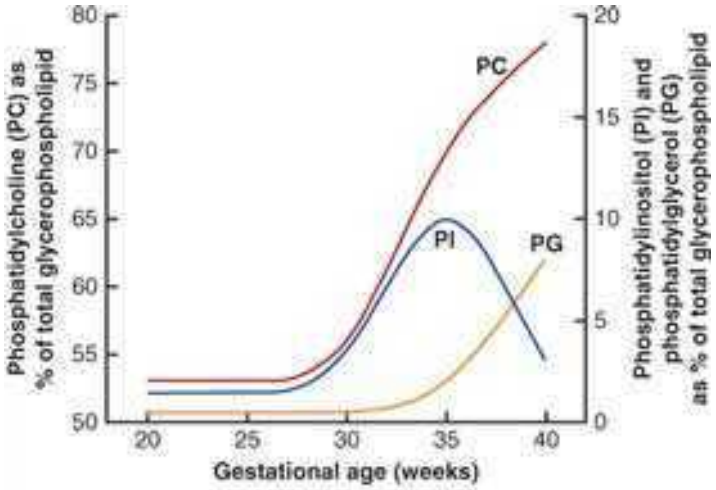
After the first breath, the terminal sacs must remain expanded despite the pressure imparted by the tissue-to-air interface, and surfactant keeps them from collapsing. Surfactant is formed in type II pneumonocytes that line the alveoli. These cells are characterized by multivesicular bodies that produce the lamellar bodies in which surfactant is assembled. During late fetal life, at a time when the alveolus is characterized by a water-to-tissue interface, the intact lamellar bodies are secreted from the lung and swept into the amnionic fluid during respiratory-like movements that are termed fetal breathing. At birth, with the first breath, an air-to-tissue interface is established in the lung alveolus. Surfactant uncoils from the lamellar bodies and spreads to line the alveolus to prevent alveolar collapse during expiration. Thus, the fetal lungs' capacity to produce surfactant establishes lung maturity.

Surfactant Composition

Gluck (1972) and Hallman (1976) and their coworkers approximated that 90 percent of surfactant's dry weight is lipid, specifically glycerophospholipids. Proteins account for the other 10 percent. Nearly 80 percent of the glycerophospholipids are phosphatidylcholines (lecithins). The principal active

component that constitutes half of surfactant is a specific lecithin, which is dipalmitoylphosphatidylcholine (DPPC or PC). Phosphatidylglycerol (PG) accounts for another 8 to 15 percent. Its precise role is unclear because newborns without PG usually do well. The other major constituent is phosphatidylinositol (PI). The relative contributions of each component are shown in Figure 7-12.

FIGURE 7-12
Relationship between the levels of lecithin— dipalmitoyl phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylglycerol (PG) in amnionic fluid.



Surfactant Synthesis

Biosynthesis takes place in the type II pneumocytes. The apoproteins are produced in the endoplasmic reticulum, and the glycerophospholipids are synthesized by cooperative interactions of several cellular organelles. Phospholipid is the primary surface tension-lowering component of surfactant, whereas the apoproteins aid the forming and reforming of a surface film.

The major apoprotein is surfactant A (SP-A), which is a glycoprotein with a molecular weight of 28,000 to 35,000 Da (Whitsett, 1992). It is synthesized in the type II cells, and its content in amnionic fluid increases with gestational age and fetal lung maturity. *SP-A* gene expression is demonstrable by 29 weeks (Mendelson, 2005). Specifically, *SP-A1* and *SP-A2* are two separate genes on chromosome 10, but their regulation is distinctive and different (McCormick, 1994).

Several smaller apoproteins such as SP-B and SP-C are likely important in optimizing the action of surfactant. For example, deletions in *SP-B* gene are incompatible with survival despite production of large amounts of surfactant (Hallman, 2013).

Corticosteroids and Fetal Lung Maturation

Since Liggins (1969) observed accelerated lung maturation in lamb fetuses given glucocorticosteroids prior to preterm delivery, many suggested that fetal cortisol stimulates lung maturation and surfactant synthesis. It is unlikely that corticosteroids are the only stimulus for augmented surfactant formation. However, when these are administered at certain critical times, they may improve preterm fetal lung maturation. As fetal lung therapy, antenatal betamethasone and dexamethasone use and neonatal replacement surfactant therapy are discussed in Chapter 34 (Clinical Course).

Breathing

Fetal respiratory muscles develop early, and chest wall movements are detected sonographically as early as 11 weeks (Koos, 2014). From the beginning of the fourth month, the fetus engages in respiratory movement sufficiently intense to move amnionic fluid in and out of the respiratory tract. Some extrauterine events have effects on fetal breathing, for example, maternal exercise stimulates it (Sussman, 2016).

Digestive System

After its embryogenic formation from the yolk sac as the primordial gut, the digestive system forms the intestines and various appendages. The foregut gives rise to the pharynx, lower respiratory system, esophagus, stomach, proximal duodenum, liver, pancreas, and biliary tree. The midgut gives rise to the distal duodenum, jejunum, ileum, cecum, appendix, and the right colon. The hindgut develops into the left colon, rectum, and the superior portion of the anal canal. Numerous malformations develop in these structures from improper rotation, fixation, and partitioning.

Swallowing begins at 10 to 12 weeks, coincident with the ability of the small intestine to undergo peristalsis and actively transport glucose (Koldovsky, 1965). As a correlate, neonates born preterm may have swallowing difficulties because of immature gut motility (Singendonk, 2014). Much of the water in swallowed fluid is absorbed, and unabsorbed matter is propelled to the lower colon. Gitlin (1974) demonstrated that late in pregnancy, approximately 800 mg of soluble protein is ingested daily by the fetus. The stimulus for swallowing is unclear, but the fetal neural analogue of thirst, gastric emptying, and change in the amnionic fluid composition are potential factors (Boyle, 1992). The fetal taste buds may play a role because saccharin injected into amnionic fluid increases swallowing, whereas injection of a noxious chemical inhibits it (Liley, 1972).

Fetal swallowing appears to have little effect on amnionic fluid volume early in pregnancy because the volume swallowed is small compared with the total. However, term fetuses swallow between 200 and 760 mL per day—an amount comparable to that of the term neonate (Pritchard, 1966). Thus at term, amnionic fluid volume regulation can be substantially altered by fetal swallowing. For example, as discussed in Chapter 11 (Hydramnios), if swallowing is inhibited, hydramnios is common.

Hydrochloric acid and some digestive enzymes are present in the stomach and small intestine in minimal amounts in the early fetus. Intrinsic factor is detectable by 11 weeks, and pepsinogen by 16 weeks. The preterm neonate, depending on its gestational age, may have transient deficiencies of these enzymes (Lebenthal, 1983).

Stomach emptying appears to be stimulated primarily by volume. Movement of amnionic fluid through the gastrointestinal system may enhance growth and development of the alimentary canal. That said, other regulatory factors likely are involved. For example, anencephalic fetuses, in which swallowing is limited, often have normal amnionic fluid volume and normal-appearing gastrointestinal tract.

Meconium

Fetal bowel contents consist of various products of secretion, such as glycerophospholipids from the lung, desquamated fetal cells, lanugo, scalp hair, and vernix. It also contains undigested debris from swallowed amnionic fluid. The dark greenish-black color forms from bile pigments, especially biliverdin. Meconium can pass from normal bowel peristalsis in the mature fetus or from vagal stimulation. It can also pass when hypoxia stimulates arginine vasopressin (AVP) release from the fetal pituitary gland. AVP stimulates colonic smooth muscle to contract, resulting in intraamnionic defecation (deVane, 1982; Rosenfeld, 1985). Meconium is toxic to the respiratory system, and its inhalation can result in *meconium aspiration syndrome* (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy).

Liver

The hepatic diverticulum is an outgrowth of the endodermal lining of the foregut. Epithelial liver cords and primordial cells differentiate into hepatic parenchyma. Serum liver enzyme levels increase with gestational age. Still, the fetal liver has a gestational-age-related diminished capacity for converting free unconjugated bilirubin to conjugated bilirubin (Morioka, 2015). Because of hepatic immaturity, the preterm newborn is at particular risk for hyperbilirubinemia (Chap. 33, Polycythemia and Hyperviscosity). And because the life span of normal fetal macrocytic erythrocytes is shorter than that of the adult, relatively more unconjugated bilirubin is produced. As just noted, the fetal liver conjugates only a small fraction, and this is excreted into the intestine and ultimately oxidized to biliverdin. Most of the unconjugated bilirubin is excreted into the amnionic fluid after 12 weeks and transferred across the placenta (Bashore, 1969).

Importantly, placental bilirubin transfer is bidirectional. Thus, a woman with severe hemolysis from any cause has excess unconjugated bilirubin that readily passes to the fetus and then into the amnionic fluid. Conversely, conjugated bilirubin is not exchanged to any significant degree between mother and fetus.

Most fetal cholesterol derives from hepatic synthesis, which satisfies the large demand for low-density lipoprotein (LDL) cholesterol by the fetal adrenal glands. Hepatic glycogen is present in low concentration during the second trimester, but near term, levels rise rapidly and markedly to reach concentrations that are two- to threefold higher than those in the adult liver. After birth, glycogen content falls precipitously.

Pancreas

This organ arises from dorsal and ventral pancreatic buds from the endoderm of the foregut. Gene regulation of its development was recently reviewed (Jennings, 2015). Insulin-containing granules can be identified by 9 to 10 weeks, and insulin is detectable in fetal plasma at 12 weeks (Adam, 1969). The pancreas responds to hyperglycemia by secreting insulin (Obenshain, 1970). Glucagon has been identified in the fetal pancreas at 8 weeks. Although hypoglycemia does not cause an increase in fetal glucagon levels, similar stimuli do so by 12 hours after birth (Chez, 1975). At the same time, however, fetal pancreatic α cells do respond to L-dopa infusions (Epstein, 1977). Therefore, unresponsiveness to hypoglycemia is likely the consequence of failed glucagon release rather than inadequate production. This is consistent with developmental expression of pancreatic genes in the fetus (Mally, 1994).

Most pancreatic enzymes are present by 16 weeks. Trypsin, chymotrypsin, phospholipase A, and lipase are found in the 14-week fetus, and their concentrations increase with gestational age (Werlin, 1992). Amylase has been identified in amnionic fluid at 14 weeks (Davis, 1986). The exocrine function of the fetal pancreas is limited. Physiologically important secretion occurs only after stimulation by a secretagogue such as acetylcholine, which is released locally after vagal stimulation (Werlin, 1992). Cholecystokinin normally is released only after protein ingestion and thus ordinarily would not be found in the fetus.

Urinary System

Renal development involves interaction between pluripotential stem cells, undifferentiated mesenchymal cells, and epithelial components (Fanos, 2015). Two primitive urinary systems—the pronephros and the mesonephros—precede development of the metanephros, which forms the final kidney (Chap. 3, Genitourinary Tract Development). The pronephros involutes by 2 weeks, and the mesonephros produces urine at 5 weeks and degenerates by 11 to 12 weeks. Failure of these two structures either to form or to regress may result in anomalous urinary system development. Between 9 and 12 weeks, the

ureteric bud and the nephrogenic blastema interact to produce the metanephros. The kidney and ureter develop from intermediate mesoderm. The bladder and urethra develop from the urogenital sinus. The bladder also develops in part from the allantois.

By week 14, the loop of Henle is functional and reabsorption occurs (Smith, 1992). New nephrons continue to be formed until 36 weeks. In preterm neonates, their formation continues after birth. Although the fetal kidneys produce urine, their ability to concentrate and modify the pH is limited even in the mature fetus. Fetal urine is hypotonic with respect to fetal plasma and has low electrolyte concentrations.

Renal vascular resistance is high, and the filtration fraction is low compared with adult values (Smith, 1992). Fetal renal blood flow and thus urine production are controlled or influenced by the renin-angiotensin system, the sympathetic nervous system, prostaglandins, kallikrein, and atrial natriuretic peptide. The glomerular filtration rate increases with gestational age from less than 0.1 mL/min at 12 weeks to 0.3 mL/min at 20 weeks. In later gestation, the rate remains constant when corrected for fetal weight (Smith, 1992). Hemorrhage or hypoxia generally results in a decrease in renal blood flow, glomerular filtration rate, and urine output.

Urine usually is found in the bladder even in small fetuses. The fetal kidneys start producing urine at 12 weeks. By 18 weeks, they are producing 7 to 14 mL/day, and at term, this increases to 650 mL/day (Wladimiroff, 1974). Maternally administered furosemide increases fetal urine formation, whereas uteroplacental insufficiency, fetal growth restriction, and other fetal disorders can lower it. Obstruction of the urethra, bladder, ureters, or renal pelves can damage renal parenchyma and distort fetal anatomy (Müller Brochut, 2014). Kidneys are not essential for survival in utero but influence control of amnionic fluid composition and volume. Thus, abnormalities that cause chronic fetal anuria are usually accompanied by oligohydramnios and pulmonary hypoplasia. Pathological correlates and prenatal therapy of urinary tract obstruction are discussed in Chapter 16 (Urinary Shunts).

Endocrine Gland Development

Pituitary Gland

The fetal endocrine system is functional for some time before the central nervous system reaches maturity (Mulchahey, 1987). The anterior pituitary gland develops from oral ectoderm—*Rathke pouch*, whereas the posterior pituitary gland derives from neuroectoderm. As with other organ systems, embryonic development involves a complex and highly spatiotemporally regulated network of signaling molecules and transcription factors (Bancalari, 2012; de Moraes, 2012).

Anterior and Intermediate Lobes

The adenohypophysis, or anterior pituitary, differentiates into five cell types that secrete six protein hormones. Of these types, lactotropes produce prolactin (PRL), somatotropes produce growth hormone (GH), corticotropes produce adrenocorticotropic hormone (ACTH), thyrotropes produce thyroid-stimulating hormone (TSH), and gonadotropes produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

ACTH is first detected in the fetal pituitary gland at 7 weeks, and GH and LH have been identified by 13 weeks. By the end of the 17th week, the fetal pituitary gland synthesizes and stores all pituitary hormones. Moreover, the fetal pituitary is responsive to tropic hormones and is capable of secreting these early in gestation (Grumbach, 1974). The fetal pituitary secretes β-endorphin, and cord blood levels of β-endorphin and β-lipotrophin rise with fetal P_{CO_2} (Browning, 1983).

The intermediate lobe in the fetal pituitary gland is well developed. The cells of this structure begin to disappear before term and are absent from the adult pituitary. The principal secretory products of the intermediate lobe cells are α-melanocyte–stimulating hormone (α-MSH) and β-endorphin.

Neurohypophysis

The posterior pituitary gland or neurohypophysis is well developed by 10 to 12 weeks, and oxytocin and arginine vasopressin are demonstrable. Both hormones probably function in the fetus to conserve water by actions directed largely at the lung and placenta rather than kidney. Vasopressin levels in umbilical cord plasma are increased strikingly compared with maternal levels (Chard, 1971).

Thyroid Gland

This gland arises from the endoderm of the second pharyngeal pouch. The thyroid migrates to its final position and the obliterated thyroglossal duct connects to the foramen cecum of the tongue. The pituitary–thyroid system is functional by the end of the first trimester. The thyroid gland is able to synthesize hormones by 10 to 12 weeks, and thyrotropin, thyroxine, and thyroid-binding globulin (TBG) have been detected in fetal serum as early as 11 weeks (Bernal, 2007). The placenta actively concentrates iodide on the fetal side, and by 12 weeks and throughout pregnancy, the fetal thyroid concentrates iodide more avidly than does the maternal thyroid. Thus, maternal administration of either radioiodide or appreciable amounts of ordinary iodide is hazardous after this time (Chap. 58, Fetal and Neonatal Effects). Normal fetal levels of free thyroxine (T_4), free triiodothyronine (T_3), and thyroxin-binding globulin increase steadily throughout gestation (Ballabio, 1989). Compared with adult levels, by 36 weeks, fetal serum concentrations of TSH are higher, total and free T_3 concentrations are lower, and T_4 is similar. This suggests that the fetal pituitary may not become sensitive to feedback until late pregnancy (Thorpe-Beeston, 1991).

Fetal thyroid hormone plays a role in the normal development of virtually all fetal tissues, especially the brain (Forhead, 2014; Rovet, 2014). Its influence is illustrated by congenital hyperthyroidism, which develops when maternal thyroid-stimulating antibody crosses the placenta to stimulate the fetal gland to secrete thyroxine (Donnelley, 2015). These fetuses develop large goiters as shown in Figure 58-3. They also display tachycardia, hepatosplenomegaly,

hematological abnormalities, craniosynostosis, and growth restriction. As children, they have perceptual motor difficulties, hyperactivity, and reduced growth (Wenstrom, 1990). Fetal thyroid disease and its treatment are discussed in Chapter 16 (Surgical Therapy). Neonatal effects of fetal thyroid deficiency are discussed in Chapter 58 (Iodine Deficiency).

The placenta prevents substantial passage of maternal thyroid hormones to the fetus by rapidly deiodinating maternal T_4 and T_3 to form reverse T_3, a relatively inactive thyroid hormone (Vulsma, 1989). Several antithyroid antibodies cross the placenta when present in high concentrations (Pelag, 2002). Those include the long-acting thyroid stimulators (LATS), LATS-protector (LATS-P), and thyroid-stimulating immunoglobulin (TSI). It was previously believed that normal fetal growth and development, which occurred despite fetal hypothyroidism, provided evidence that T_4 was not essential for fetal growth. It is now known, however, that growth proceeds normally because small quantities of maternal T_4 prevent antenatal cretinism in fetuses with thyroid agenesis (Forhead, 2014; Vulsma, 1989). The fetus with congenital hypothyroidism typically does not develop stigmata of cretinism until after birth (Abduljabbar, 2012). Because administration of thyroid hormone will prevent this, by state law, all newborns are tested for high serum levels of TSH (Chap. 32, Routine Newborn Care).

Immediately after birth, thyroid function and metabolism undergo major change. Cooling to room temperature evokes sudden and marked increase in TSH secretion. This in turn causes a progressive increase in serum T_4 levels that are maximal 24 to 36 hours after birth. There are nearly simultaneous elevations of serum T_3 levels.

Adrenal Glands

These glands develop from two separate tissues. The medulla derives from neural crest ectoderm, whereas the fetal and adult cortex arise from intermediate mesoderm. The gland grows rapidly through cell proliferation and angiogenesis, cellular migration, hypertrophy, and apoptosis (Ishimoto, 2011). Fetal glands are much larger in relation to total body size than in adults. The bulk is made up of the inner or fetal zone of the adrenal cortex and involutes rapidly after birth. This zone is scant to absent in rare instances in which the fetal pituitary gland is congenitally absent. The function of the fetal adrenal glands is discussed in detail in Chapter 5 (Fetal Adrenal Gland–placental Interactions).

Immunological System

Infections in utero have provided an opportunity to examine mechanisms of the fetal immune response. Evidence of immunological competence has been reported as early as 13 weeks (Kohler, 1973; Stabile, 1988). In cord blood at or near term, the average level for most components is approximately half that of the adult values (Adinolfi, 1977).

B cells differentiate from pluripotent hemopoietic stem cells that migrate to the liver (Melchers, 2015; Muzzio, 2013). Despite this, in the absence of a direct antigenic stimulus such as infection, fetal plasma immunoglobulins consist almost totally of transferred maternal immunoglobulin G (IgG). Thus, antibodies in the newborn are most often reflective of maternal immunological experiences (American College of Obstetricians and Gynecologists, 2017). The interaction between maternal and fetal T cells is described in detail in Chapter 5 (Amnion).

Immunoglobulin G

Maternal IgG transport to the fetus begins at approximately 16 weeks and increases thereafter. The bulk of IgG is acquired during the last 4 weeks of pregnancy (Gitlin, 1971). Accordingly, preterm neonates are poorly endowed with protective maternal antibodies. Newborns begin to slowly produce IgG, and adult values are not attained until age 3 years. In certain situations, the transfer of IgG antibodies from mother to fetus can be harmful rather than protective to the fetus. The classic example is hemolytic disease of the fetus and newborn resulting from Rh-antigen alloimmunization (Chap. 15, Red Cell Alloimmunization).

Immunoglobulins M and A

In the adult, production of immunoglobulin M (IgM) in response to an antigenic stimulus is superseded in a week or so predominantly by IgG production. In contrast, very little IgM is produced by normal fetuses. With infection, the IgM response is dominant in the fetus and remains so for weeks to months in the newborn. And, because IgM is not transported from the mother, any IgM in the fetus or newborn is that which it produced. Thus, specific IgM levels in umbilical cord blood may be useful in fetal infection diagnosis. According to the American College of Obstetricians and Gynecologists (2017), elevated levels of IgM are usually found in newborns with congenital infection such as rubella, cytomegalovirus infection, or toxoplasmosis. In infants, adult levels of IgM are normally attained by age 9 months.

Immunoglobulin A (IgA) ingested in colostrum provides mucosal protection against enteric infections. This may explain the small amount of fetal secretory IgA found in amnionic fluid (Quan, 1999).

Lymphocytes and Monocytes

The immune system develops early, and B lymphocytes appear in fetal liver by 9 weeks and in blood and spleen by 12 weeks. T lymphocytes begin to leave the thymus at approximately 14 weeks. Despite this, the newborn responds poorly to immunization, and especially poorly to bacterial capsular

polysaccharides. This immature response may stem from a deficient response of newborn B cells to polyclonal activators or from a lack of T cells that proliferate in response to specific stimuli (Hayward, 1983). In the newborn, monocytes are able to process and present antigen when tested with maternal antigen-specific T cells. DNA methylation patterns are developmentally regulated during monocyte-macrophage differentiation and contribute to the antiinflammatory phenotype in macrophages (Kim, 2012).

Musculoskeletal System

The origin of most muscles and bones is mesodermal. The skeleton arises from condensed mesenchyme—embryonic connective tissue—which eventually forms hyaline cartilage models of the bones. By the end of the embryonic period, ossification centers have developed, and bones harden by endochondral ossification. The limb buds appear by the fourth week. Most skeletal muscle derives from myogenic precursor cells in the somites.

ENERGY AND NUTRITION

Because of the small amount of yolk in the human ovum, growth of the embryofetus is dependent on maternal nutrients during the first 2 months. During the first few days after implantation, blastocyst nutrition comes from the interstitial fluid of the endometrium and the surrounding maternal tissue.

Maternal adaptations to store and transfer nutrients to the fetus are discussed in Chapter 4 and summarized here. Three major maternal storage depots are the liver, muscle, and adipose tissue. These maternal depots and the storage hormone insulin are intimately involved in the metabolism of the nutrients absorbed from the gut. Maternal insulin secretion is sustained by increased serum levels of glucose and amino acids. The net effect is maternal storage of glucose as glycogen primarily in liver and muscle, retention of some amino acids as protein, and storage of the excess as fat. Storage of maternal fat peaks in the second trimester and then declines as fetal energy demands rise in the third trimester (Pipe, 1979). Interestingly, the placenta appears to act as a nutrient sensor, altering transport based on the maternal supply and environmental stimuli (Fowden, 2006; Jansson, 2006b).

During times of fasting, glucose is released from glycogen, but maternal glycogen stores cannot provide an adequate amount of glucose to meet requirements for maternal energy and fetal growth. Augmentation is provided by cleavage of triacylglycerols, stored in adipose tissue, which result in free fatty acids and activation of lipolysis.

Glucose and Fetal Growth

Although dependent on the mother for nutrition, the fetus also actively participates in providing its own nutrition. At midpregnancy, fetal glucose concentration is independent of maternal levels and may exceed them (Bozzetti, 1988). Glucose is the major nutrient for fetal growth and energy. Logically, mechanisms exist during pregnancy to minimize maternal glucose use so that the limited maternal supply is available to the fetus. Human placental lactogen (hPL), a hormone normally abundant in the mother but not the fetus, has an insulin antagonist effect. It blocks the peripheral uptake and use of glucose, while promoting mobilization and use of free fatty acids by maternal tissues (Chap. 5, Human Placental Lactogen). This hormone is also diabetogenic as discussed in Chapter 57 (Gestational Diabetes).

Glucose Transport

The transfer of d-glucose across cell membranes is accomplished by a carrier-mediated, stereospecific, nonconcentrating process of facilitated diffusion. There are 14 glucose transport proteins (GLUTs) encoded by the *SLC2A* gene family and characterized by tissue-specific distribution (Leonce, 2006). GLUT-1 and GLUT-3 primarily facilitate glucose uptake by the placenta and are located in the plasma membrane of the syncytiotrophoblast microvilli (Acosta, 2015). DNA methylation regulates expression of placental *GLUT* genes, with epigenetic modification across gestation (Novakovic, 2013). It increases as pregnancy advances and is induced by almost all growth factors (Frolova, 2011). GLUT-3 expression is upregulated with fetal growth restriction (Janzen, 2013).

Lactate is a product of glucose metabolism and transported across the placenta also by facilitated diffusion. By way of cotransport with hydrogen ions, lactate is probably transported as lactic acid.

Fetal Macrosomia

The precise biomolecular events in the pathophysiology of fetal macrosomia are not defined. Nonetheless, fetal hyperinsulinemia is clearly one driving force (Luo, 2012). As discussed in Chapter 44 (Normal Birthweight), insulin-like growth factor, fibroblast growth factor, and corticotropin-releasing hormone (CRH) and are important regulators of placental development and function (Gao, 2012; Giudice, 1995). Maternal obesity begets fetal macrosomia (Chap. 44, Definition). In addition, it is hypothesized that maternal obesity affects fetal cardiomyocyte growth that may result in fetal cardiomyopathy or even congenital heart disease (Roberts, 2015).

Leptin

This polypeptide hormone was originally identified as a product of adipocytes and a regulator of energy homeostasis by curbing appetite. It also contributes to angiogenesis, hemopoiesis, osteogenesis, pulmonary maturation, and neuroendocrine, immune, and reproductive functions (Briffa, 2015; Maymó, 2009). Leptin is produced by the mother, fetus, and placenta. It is expressed in syncytiotrophoblast and fetal vascular endothelial cells. Of placental production, 5

percent enters the fetal circulation, whereas 95 percent is transferred to the mother (Hauguel-de Mouzon, 2006). Leptin concentrations peak in amnionic fluid at midpregnancy (Scott-Finley, 2015).

Fetal leptin levels begin rising at approximately 34 weeks and are correlated with fetal weight. This hormone is involved in the development and maturation of the heart, brain, kidneys, and pancreas, and its levels are decreased with fetal growth restriction (Briffa, 2015). Abnormal levels have been associated with fetal growth disorders, gestational diabetes, and preeclampsia (Fasshauer, 2014). Postpartum, leptin levels decline in both the newborn and mother. Perinatal leptin is associated with the development of metabolic syndromes later in life (Briffa, 2015; Granado, 2012).

Free Fatty Acids and Triglycerides

The newborn has a large proportion of fat, which averages 15 percent of body weight (Kimura, 1991). Thus, late in pregnancy, a substantial part of the substrate transferred to the human fetus is stored as fat. Although maternal obesity raises placental fatty acid uptake and fetal fat deposition, it does not appear to affect fetal organ growth (Dubé, 2012). Neutral fat in the form of triglycerides does not cross the placenta, but glycerol does. Despite this, evidence supports that abnormal maternal concentrations of triglycerides—both low and high levels—are associated with major congenital anomalies (Nederlof, 2015).

There is preferential placental-fetal transfer of long-chain polyunsaturated fatty acids (Gil-Sanchez, 2012). Lipoprotein lipase is present on the maternal but not on the fetal side of the placenta. This arrangement favors hydrolysis of triacylglycerols in the maternal intervillous space yet preserves these neutral lipids in fetal blood. Fatty acids transferred to the fetus can be converted to triglycerides in the fetal liver.

The placental uptake and use of LDL is an alternative mechanism for fetal assimilation of essential fatty acids and amino acids (Chap. 5, Placental Estrogen Production). LDL binds to specific receptors in the coated-pit regions of the syncytiotrophoblast microvilli. The large LDL particle, measuring about 250,000 Da, is taken up by a process of receptor-mediated endocytosis. The apoprotein and cholesterol esters of LDL are hydrolyzed by lysosomal enzymes in the syncytium to yield: (1) cholesterol for progesterone synthesis; (2) free amino acids, including essential amino acids; and (3) essential fatty acids, primarily linoleic acid.

Amino Acids

The placenta concentrates many amino acids in the syncytiotrophoblast, which are then transferred to the fetal side by diffusion. Based on data from cordocentesis blood samples, the amino acid concentration in umbilical cord plasma is greater than in maternal venous or arterial plasma (Morriss, 1994). Transport system activity is influenced by gestational age and environmental factors. These include heat stress, hypoxia, under- and overnutrition, and hormones such as glucocorticoids, growth hormone, and leptin (Briffa, 2015; Fowden, 2006). Trophoblastic mammalian target of rapamycin complex 1 (mTORC1) regulates placental amino acid transporters and modulates transfer across the placenta (Jansson, 2012). In vivo studies suggest an upregulation of transport for certain amino acids and a greater delivery rate of these to the fetuses of women with gestational diabetes associated with fetal overgrowth (Jansson, 2006a).

Proteins

Placental transfer of larger proteins is limited, but there are exceptions. IgG crosses the placenta in large amounts via endocytosis and trophoblast Fc receptors. IgG transfer depends on maternal levels of total IgG, gestational age, placental integrity, IgG subclass, and antigenic potential (Palmeira, 2012). Conversely, the larger immunoglobulins—IgA and IgM—of maternal origin are effectively excluded from the fetus.

Ions and Trace Metals

Calcium and phosphorus are actively transported from mother to fetus. Calcium is transferred for fetal skeletal mineralization (Olausson, 2012). A calcium-binding protein is produced in placenta. Parathyroid hormone-related protein (PTH-rP), as the name implies, acts as a surrogate PTH in many systems (Chap. 5, Placental Progesterone Production). PTH is not found in fetal plasma, but PTH-rP is present, suggesting that PTH-rP is the fetal parathormone. The expression of PTH-rP in cytotrophoblasts is modulated by the extracellular concentration of Ca^{2+} (Hellman, 1992). It seems possible, therefore, that PTH-rP synthesized in decidua, placenta, and other fetal tissues is important in fetal Ca^{2+} transfer and homeostasis.

Iodide transport is clearly attributable to a carrier-mediated, energy-requiring active process. And indeed, the placenta concentrates iodide. The concentrations of zinc in the fetal plasma also are greater than those in maternal plasma. Conversely, copper levels in fetal plasma are less than those in maternal plasma. This fact is of particular interest because important copper-requiring enzymes are necessary for fetal development.

Placental Sequestration of Heavy Metals

The heavy metal–binding protein metallothionein-1 is expressed in human syncytiotrophoblast. This protein binds and sequesters a host of heavy metals, including zinc, copper, lead, and cadmium. Despite this, fetal exposure is variable (Caserta, 2013). For example, lead enters the fetal environment at a level 90 percent of maternal concentrations. In contrast, placental transfer of cadmium is limited (Kopp, 2012). The most common source of environmental cadmium is cigarette smoke.

Metallothionein also binds and sequesters copper (Cu^{2+}) in placental tissue. This accounts for the low levels of Cu^{2+} in cord blood (Iyengar, 2001). It is possible that cadmium provokes metallothionein synthesis in the amnion. This may cause Cu^{2+} sequestration, a pseudo–copper deficiency, and in turn, diminished tensile strength of the amnion.

Vitamins

The concentration of vitamin A (retinol) is greater in fetal than in maternal plasma and is bound to retinol-binding protein and to prealbumin. Retinol-binding protein is transferred from the maternal compartment across the syncytiotrophoblast. The transport of vitamin C—ascorbic acid—from mother to fetus is accomplished by an energy-dependent, carrier-mediated process. Levels of principal vitamin D metabolites, including 1,25-dihydroxycholecalciferol, are greater in maternal plasma than in fetal plasma. The 1β-hydroxylation of 25-hydroxyvitamin D_3 is known to take place in placenta and in decidua.

PLACENTAL ROLE IN EMBRYOFETAL DEVELOPMENT

The placenta is the organ of transfer between mother and fetus. Within this maternal-fetal interface, oxygen and nutrients transfer from the mother to the fetus, whereas CO_2 and metabolic wastes are directed from fetus to mother. Fetal blood, which is contained in the fetal capillaries of the chorionic villi, has no direct contact with maternal blood, which remains in the intervillous space. Instead, bidirectional transfer depends on processes that allow or aid the transport through the syncytiotrophoblast that lines chorionic villi.

Over the past few years, it has become apparent that breaks in the chorionic villi permit escape of fetal cells and other blood-borne material into the maternal circulation. This leakage is the mechanism by which some D-negative women become sensitized by the erythrocytes of their D-positive fetus (Chap. 15, Red Cell Alloimmunization). In fact, after 10 weeks, 10 to 15 percent of cell-free DNA (cfDNA) in maternal plasma is placental in origin, that is, trophoblastic DNA (Norton, 2012). The escape of fetal cells can also lead to fetal microchimerism from entrance of allogeneic fetal cells, including trophoblast, into maternal blood and other organs (Rijnik, 2015). Volumes are estimated to range from 1 to 6 cells/mL at midpregnancy. Some fetal cells become “immortal” in that they persist in the maternal circulation and organs following pregnancy. As discussed in Chapter 59 (Systemic Lupus Erythematosus), the clinical corollary is that some maternal autoimmune diseases may be provoked by such microchimerism.

The Intervillous Space

Maternal blood within the intervillous space is the primary source of maternal–fetal transfer. Blood from the maternal spiral arteries directly bathes the trophoblast layer that surrounds the villi. Substances transferred from mother to fetus first enter the intervillous space and are then transported to the syncytiotrophoblast. As such, the chorionic villi and intervillous space function together as the fetal lung, gastrointestinal tract, and kidney.

Circulation within the intervillous space is described in Chapter 5 (Breaks in the Placental “Barrier”). Intervillous and uteroplacental blood flow increases throughout the first trimester of normal pregnancies (Mercé, 2009). At term, the residual volume of the intervillous space approximates 140 mL. Moreover, uteroplacental blood flow near term is estimated to be 700 to 900 mL/min, and most of this blood apparently goes to the intervillous space (Pates, 2010).

Active labor contractions reduce blood flow into the intervillous space to a degree that depends on contraction intensity. Blood pressure within the intervillous space is significantly less than uterine arterial pressure, but somewhat greater than venous pressure. The latter, in turn, varies depending on several factors, including maternal position (Nelson, 2015). When supine, for example, pressure in the lower part of the inferior vena cava is elevated, and consequently, pressure in the uterine and ovarian veins, and in turn in the intervillous space, is increased.

Placental Transfer

Substances that pass from maternal to fetal blood must first traverse the syncytiotrophoblast, the attenuated cytotrophoblast layer, the villous stroma, and finally, the fetal capillary wall. Although this histological barrier separates maternal and fetal circulations, it is not a simple physical barrier. First, throughout pregnancy, syncytiotrophoblast actively or passively permits, facilitates, and adjusts the amount and rate of substance transfer to the fetus. The maternal-facing syncytiotrophoblast surface is characterized by a complex microvillous structure. The fetal-facing basal cell membrane is the site of transfer to the intravillous space. Finally, the villous capillaries are an additional site for transport from the intravillous space into fetal blood, or vice versa. In determining the effectiveness of the human placenta as an organ of transfer, several variables are important and shown in Table 7-1. Zhao and coworkers (2014) have provided a review of the pharmacology of these interactions.

TABLE 7-1

Variables of Maternal-Fetal Substance Transfer

Maternal plasma concentration and carrier-protein binding of the substance
Maternal blood flow rate through the intervillous space
Trophoblast surface area size available for exchange
Physical trophoblast properties to permit simple diffusion
Trophoblast biochemical machinery for active transport
Substance metabolism by the placenta during transfer
Fetal intervillous capillary surface area size for exchange
Fetal blood concentration of the substance
Specific binding or carrier proteins in the fetal or maternal circulation
Villous capillary blood flow rate

Mechanisms of Transfer

Most substances with a molecular mass <500 Da pass readily through placental tissue by simple diffusion. These include oxygen, CO_2, water, most electrolytes, and anesthetic gases (Carter, 2009). Some low-molecular-weight compounds undergo transfer facilitated by syncytiotrophoblast. These are usually those that have low concentrations in maternal plasma but are essential for normal fetal development.

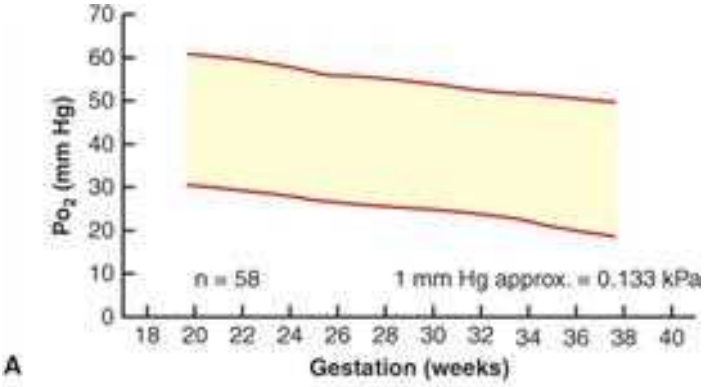
Insulin, steroid hormones, and thyroid hormones cross the placenta, but very slowly. The hormones synthesized in situ in the syncytiotrophoblast enter both the maternal and fetal circulations, but not equally (Chap. 5, Placental Hormones). Examples are hCG and hPL concentrations, which are much lower in fetal plasma than in maternal plasma. High-molecular-weight substances usually do not traverse the placenta, but there are important exceptions. One is immunoglobulin G—molecular weight 160,000 Da—which is transferred by way of a specific trophoblast receptor–mediated mechanism (Stach, 2014).

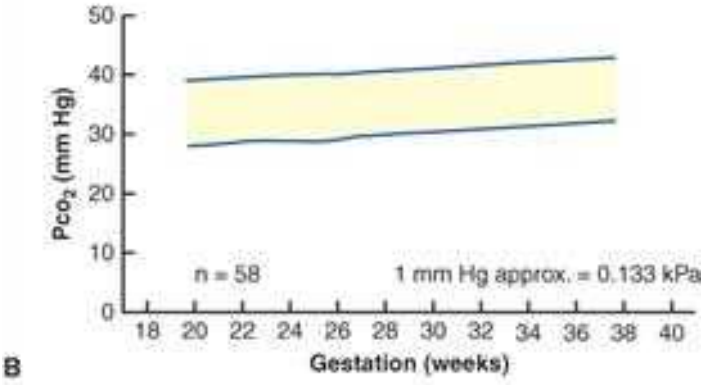
Transfer of Oxygen and Carbon Dioxide

Placental oxygen transfer is blood flow limited. Using estimated uteroplacental blood flow, Longo (1991) calculated oxygen delivery to be approximately 8 mL O_2/min/kg of fetal weight. Normal values for oxygen and CO_2 are presented in Figure 7-13. Because of the continuous passage of oxygen from maternal blood in the intervillous space to the fetus, its oxygen saturation resembles that in maternal capillaries. The average oxygen saturation of intervillous blood is estimated to be 65 to 75 percent, with a partial pressure (Po_2) of 30 to 35 mm Hg. The oxygen saturation of umbilical vein blood is similar but has a somewhat lower oxygen partial pressure. Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin. This is illustrated by the oxyhemoglobin disassociation curve, which is described in Chapter 47 (Positive End-Expiratory Pressure).

FIGURE 7-13

Umbilical venous cordocentesis samples obtained in fetuses being evaluated for possible intrauterine infections or hemolysis, but who were found to be healthy. **A.** Oxygen pressure (Po_2). **B.** Carbon dioxide pressure (Pco_2). Shaded areas represent 5th to 95th percentiles. (Modified from Ramsey, MM: Normal Values in Pregnancy. Ramsay MM, James DK, Steer PJ, et al (eds). London, Elsevier, 1996, p 106.)





The placenta is highly permeable to CO_2, which traverses the chorionic villus by diffusion more rapidly than oxygen. Near term, the partial pressure of carbon dioxide (Pco_2) in the umbilical arteries averages 50 mm Hg, which is approximately 5 mm Hg higher than in the maternal intervillous blood. Fetal blood has less affinity for CO_2 than does maternal blood, thereby favoring CO_2 transfer from fetus to mother. Also, mild maternal hyperventilation results in a fall in Pco_2 levels, favoring a transfer of CO_2 from the fetal compartment to maternal blood.

Selective Transfer and Facilitated Diffusion

Although simple diffusion is an important method of placental transfer, the trophoblast and chorionic villus unit demonstrate enormous selectivity in transfer. This results in different metabolite concentrations on the two sides of the villus. Importantly, the levels of many substances that are not synthesized by the fetus are several times higher in fetal than in maternal blood. Ascorbic acid is one example. This relatively low-molecular-weight substance might be expected to traverse the placenta by simple diffusion. The concentration of ascorbic acid, however, is two to four times higher in fetal plasma than in maternal plasma (Morriss, 1994). Another example is the unidirectional transfer of iron. Typically, maternal plasma iron concentration is much lower than that in her fetus. Even with severe maternal iron-deficiency anemia, the fetal hemoglobin mass is normal.

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CHAPTER 8: Preconceptional Care

Pregnancy may be associated with certain diseases that existed before the inception of pregnancy. As a rule, all diseases which subject the organism to a considerable strain are much more serious when occurring in a pregnant woman.

—J. Whitridge Williams (1903)

INTRODUCTION

The Centers for Disease Control and Prevention (CDC) (2015) defines preconceptional care as "a set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management." To achieve this goal, the CDC has developed an action plan for preconceptional health care in the United States (Johnson, 2006). The American College of Obstetricians and Gynecologists (2017e) and the Society for Maternal-Fetal Medicine (2014) also reaffirm the importance of preconceptional care, and the following objectives have been established for advancing it:

1. Improve knowledge, attitudes, and behaviors of men and women related to preconceptional health
2. Assure that all childbearing-aged women receive preconceptional care services—including evidence-based risk screening, health promotion, and interventions—that will enable them to enter pregnancy in optimal health
3. Reduce risks indicated by a previous adverse pregnancy outcome through interconceptional interventions to prevent or minimize recurrent adverse outcomes
4. Reduce the disparities in adverse pregnancy outcomes

To illustrate potentially modifiable conditions, data that describe the health status of women who delivered liveborn neonates in the United States in 2004 are reviewed. Table 8-1 demonstrates the high prevalence of many conditions that may be amenable to intervention during the preconceptional and interpregnancy periods. To be successful, however, strategies that mitigate these potential pregnancy risks must be provided before conception. By the time most women realize they are pregnant—usually 1 to 2 weeks after the first missed period—the embryo has already begun to form. Thus, many preventive steps—for example, folic acid to avoid neural-tube defects—will be ineffective if initiated at this time. Importantly, up to half of all pregnancies in the United States in 2008 were unplanned according to the Guttmacher Institute (2015), and often these are at greatest risk.

TABLE 8-1

Prevalence of Prepregnancy Maternal Behaviors, Experiences, Health Conditions, and Previous Poor Birth Outcomes[a]

Factor	Prevalence (%)
Tobacco use	23
Alcohol use	50
Multivitamin use	35
Contraceptive nonuse[b]	53
Dental visit	78
Health counseling	30
Physical abuse	4
Stress	19
Underweight	13
Overweight	13
Obesity	22
Diabetes	2
Asthma	7
Hypertension	2
Heart problem	1
Anemia	10
Prior low-birthweight neonate	12
Prior preterm neonate	12

[a]In the United States in 2004.

[b]Among women who were not trying to become pregnant.

Data from D'Angelo D, Williams L, Morrow B, et al: Preconception and interconception health status of women who recently gave birth to a live-born infant—Pregnancy Risk Assessment Monitoring System (PRAMS), United States, 26 reporting areas, 2004. MMWR 56(10):1, 2007.

Few randomized trials evaluate preconceptional counseling efficacy, in part because withholding such counseling would be unethical. Also, pregnancy outcomes are dependent on the interaction of various maternal, fetal, and environmental factors. Thus, ascribing a salutary outcome to a specific intervention is difficult (Moos, 2004; Temel, 2014). However, prospective observational and case-control studies have demonstrated the successes of preconceptional counseling (American College of Obstetrics and Gynecologists, 2016b). Moos and coworkers (1996) assessed the effectiveness of a preconceptional counseling program administered during routine health care provision to reduce unintended pregnancies. The 456 counseled women had a 50-percent greater likelihood of subsequent pregnancies that they considered "intended" compared with 309 uncounseled women. Moreover, compared with another group of women who had no health care before pregnancy, the counseled group had a 65-percent higher rate of intended pregnancy. Interesting ethical aspects of *paternal* lifestyle modification were reviewed by van der Zee and associates (2013).

COUNSELING SESSION

Gynecologists, internists, family practitioners, and pediatricians have the best opportunity to provide preventive counseling during periodic health maintenance examinations. The occasion of a negative pregnancy test is also an excellent time for education. Jack and colleagues (1995) administered a comprehensive preconceptional risk survey to 136 such women, and almost 95 percent reported at least one problem that could affect a future pregnancy. These included medical or reproductive problems—52 percent; family history of genetic disease—50 percent; increased risk of human immunodeficiency virus infection—30 percent; increased risk of hepatitis B and illegal substance abuse—25 percent; alcohol use—17 percent; and nutritional risks—54 percent. Counselors should be knowledgeable regarding relevant medical diseases, prior surgery, reproductive disorders, or genetic conditions and must be able to interpret data and recommendations provided by other specialists (Simpson, 2014). If the practitioner is uncomfortable providing guidance, the woman or couple should be referred to an appropriate counselor.

Women presenting specifically for preconceptional evaluation should be advised that information collection may be time consuming, depending on the number and complexity of factors that require assessment. The intake evaluation includes a thorough review of the medical, obstetrical, social, and family histories. Useful information is more likely to be obtained by asking specific questions regarding each of these histories and each family member than by asking general, open-ended questions. Some important information can be obtained by questionnaires that address these topics. Answers are reviewed with the couple to ensure appropriate follow-up, including obtaining relevant medical records.

MEDICAL HISTORY

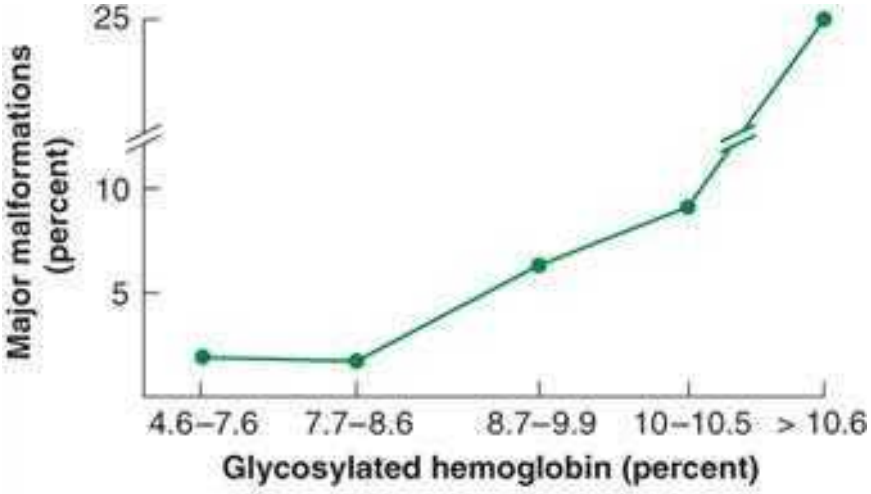
With specific medical conditions, general points include how pregnancy will affect maternal health and how a high-risk condition might affect the fetus. Afterward, advice for improving outcome is provided. Some chronic conditions that may affect pregnancy outcomes include treated or active cancer, prior peripartum cardiomyopathy, and systemic lupus erythematosus (Amant, 2015; Buyon, 2015; McNamara, 2015). Importantly, psychological health should be considered (Lassi, 2014). Detailed preconceptional information regarding a few exemplary conditions is found in the next sections and in the other topic-specific chapters of this text.

Diabetes Mellitus

Because maternal and fetal pathology associated with hyperglycemia is well known, diabetes is the prototype of a condition for which preconceptional counseling is beneficial. Diabetes-associated risks to both mother and fetus are discussed in detail in Chapter 57 (Impact on Pregnancy). Many of these complications can be avoided if glucose control is optimized before conception. Another important aspect of counseling pertains to the frequent use of teratogenic angiotensin-converting enzyme inhibitors in this population (Podymow, 2015).

The American College of Obstetricians and Gynecologists (2016a) has concluded that preconceptional counseling for women with pregestational diabetes is both beneficial and cost-effective and should be encouraged. The American Diabetes Association has promulgated consensus recommendations for preconceptional care for diabetic women (Kitzmiller, 2008). These guidelines advise obtaining a thorough inventory of disease duration and related complications and completing a clinical and laboratory examination for end-organ damage. Perhaps most essential, they encourage a preconceptional goal of the lowest hemoglobin A_{1c} level possible without undue hypoglycemic risk to the mother. In addition to assessing diabetic control during the preceding 6 weeks, hemoglobin A_{1c} measurement can also be used to estimate risks for major anomalies as shown in Figure 8-1. Although these data are from women with severe overt diabetes, the incidence of fetal anomalies in women who have gestational diabetes with fasting hyperglycemia is increased fourfold compared with that in normal women (Sheffield, 2002).

FIGURE 8-1
Relationship between first-trimester glycosylated hemoglobin values and risk for major congenital malformations in 320 women with insulin-dependent diabetes. (Data from Kitzmiller JL, Gavin LA, Gin GD, et al: Preconception care of diabetics. JAMA 265:731, 1991.)



Such counseling in diabetic women has been shown to be effective. Leguizamón and associates (2007) identified 12 studies that included more than 3200 pregnancies in women with insulin-dependent diabetes. Of the 1618 women without preconceptional counseling, 8.3 percent had a fetus with a major congenital anomaly, and this compared with a rate of 2.7 percent in the 1599 women who did have counseling. Tripathi and coworkers (2010) compared outcomes in 588 women with pregestational diabetes in whom approximately half had preconceptional counseling. Those women who received counseling had improved glycemic control before pregnancy and in the first trimester. This group also had higher folate intake rates preconceptionally, and they experienced lower rates of adverse outcomes—defined as a perinatal death or major congenital anomaly. These cited benefits are accompanied by reduced health-care costs in diabetic women. From their review, Reece and Homko (2007) found that each $1 expended for a preconceptional care program saved between $1.86 and $5.19 in averted medical costs. Despite such benefits, the proportion of diabetic women receiving preconceptional care is suboptimal. In their study of approximately 300 diabetic women in a managed-care plan, Kim and colleagues (2005) found that only approximately one half had preconceptional counseling. Counseling rates are undoubtedly much lower among uninsured and indigent women.

Epilepsy

Compared with unaffected women, those with a seizure disorder carry an undisputed augmented risk of having neonates with structural anomalies (Chap. 12, Antiepileptic Medications). Some early reports indicated that epilepsy conferred an elevated a priori risk for congenital malformations that was independent of anticonvulsant treatment effects. Although more recent publications have largely failed to confirm this increased risk in untreated women, it is difficult to refute entirely because

women who are controlled without medication generally have less severe disease (Cassina, 2013; Vajda, 2015). Fried and associates (2004) conducted a metaanalysis of studies comparing epileptic women, both treated and untreated, with controls. In this study, greater malformation rates could only be demonstrated in the offspring of women who had been exposed to anticonvulsant therapy. Veiby and coworkers (2009) used the Medical Birth Registry of Norway and identified an increased malformation risk only in women who were exposed to valproic acid (5.6 percent) or polytherapy (6.1 percent). Untreated women had anomaly rates that were similar to those of nonepileptic controls. Risks for miscarriage and stillbirths in exposed epileptic women do not appear elevated (Aghajanian, 2015; Bech, 2014).

Ideally, seizure control is optimized preconceptionally. For example, Vajda and colleagues (2008) analyzed data from the Australian Register of Antiepileptic Drugs in Pregnancy. They found the seizure risk during pregnancy was 50- to 70-percent lower in women without a seizure in the year preceding pregnancy compared with a group experiencing seizures in this preceding year. No further advantages accrued if the seizure-free period exceeded a year.

Treatment goals attempt to achieve seizure control with monotherapy and with medications considered less teratogenic (Aguglia, 2009; Tomson, 2009). As discussed in detail in Chapter 60 (Preconceptional Counseling) and shown in Table 8-2, some one-drug regimens are more teratogenic than others. Valproic acid, in particular, is avoided if possible, as this medication has consistently been associated with a greater risk for major congenital malformations than other antiepileptic drugs (Jentink, 2010; Vajda, 2015). Trimethadione is contraindicated (Aghajanian, 2015). The American Academy of Neurology recommends consideration of antiseizure medication discontinuation before pregnancy in suitable candidates (Jeha, 2005). These include women who satisfy the following criteria: (1) have been seizure-free for 2 to 5 years, (2) display a single seizure type, (3) have a normal neurological examination and normal intelligence, and (4) show electroencephalogram results that have normalized with treatment.

TABLE 8-2

First-Trimester Antiepileptic Monotherapy and the Associated Major Malformation Risk

Antiepileptic (n)	Malformations (%)	Relative Risk (95% CI)[a]
Unexposed controls (442)	1.1	Reference
Lamotrigine (1562)	2.0	1.8 (0.7–4.6)
Carbamazepine (1033)	3.0	2.7 (1.0–7.0)
Phenytoin (416)	2.9	2.6 (0.9–7.4)
Levetiracetam (450)	2.4	2.2 (0.8–6.4)
Topiramate (359)	4.2	3.8 (1.4–10.6)
Valproate (323)	9.3	9.0 (3.4–23.3)
Phenobarbital (199)	5.5	5.1 (1.8–14.9)
Oxcarbazepine (182)	2.2	2.0 (0.5–7.4)
Gabapentin (145)	0.7	0.6 (0.07–5.2)
Clonazepam (64)	3.1	2.8 (0.5–14.8)

[a]Risk compared with that of the unexposed reference population of nonepileptic women.

Data from Hernández-Díaz S, Smith CR, Shen A, et al: Comparative safety of antiepileptic drugs during pregnancy. Neurology 78:1692, 2012.

Epileptic women should be advised to daily take a 4-mg folic acid supplement. Even so, it is not entirely clear that folate supplementation reduces the fetal malformation risk in pregnant women taking anticonvulsant therapy. In one case-control study, Kjær and associates (2008) reported that the congenital abnormality risk was reduced by maternal folate supplementation in fetuses exposed to carbamazepine, phenobarbital, phenytoin, and primidone. Conversely, from the United Kingdom Epilepsy and Pregnancy Register, Morrow and coworkers (2009) compared fetal outcomes of women who received preconceptional folic acid with those who did not receive it until later in pregnancy or not at all. In this study, a paradoxical *increase* in the number of major congenital malformations was observed in the group who received preconceptional folate. These investigators concluded that folate metabolism may be only a part of the mechanism by which malformations are induced in women taking these medications.

Immunizations

Preconceptional counseling includes assessment of immunity against common pathogens. Also, depending on health status, travel plans, and time of year, other immunizations may be indicated as discussed in Chapter 9 (Table 9-7). Vaccines that contain toxoids such as tetanus are suitable before or during gestation. Also, those containing killed bacteria or viruses—such as influenza, pneumococcus, hepatitis B, meningococcus, and rabies vaccines—are not associated with adverse fetal outcomes and are not contraindicated preconceptionally or during pregnancy. Conversely, live-virus vaccines are not recommended

during pregnancy. Examples are vaccines against varicella-zoster, measles, mumps, rubella, polio, chickenpox, and yellow fever. Moreover, 1 month or longer should ideally pass between vaccination and conception attempts. That said, inadvertent administration of measles, mumps, rubella (MMR) or varicella vaccines during pregnancy should not generally be considered indications for pregnancy termination. Most reports indicate that the fetal risk is only theoretical. Immunization to smallpox, anthrax, and other bioterrorism diseases should be discussed if clinically appropriate (Chap. 64, Mycotic Infections).

With some infections, vaccines are unavailable. One recent example is the Zika virus (Brasil, 2016). For this virus, the CDC has issued travel advisories for pregnant women (Petersen, 2016; Schuler-Faccini, 2016).

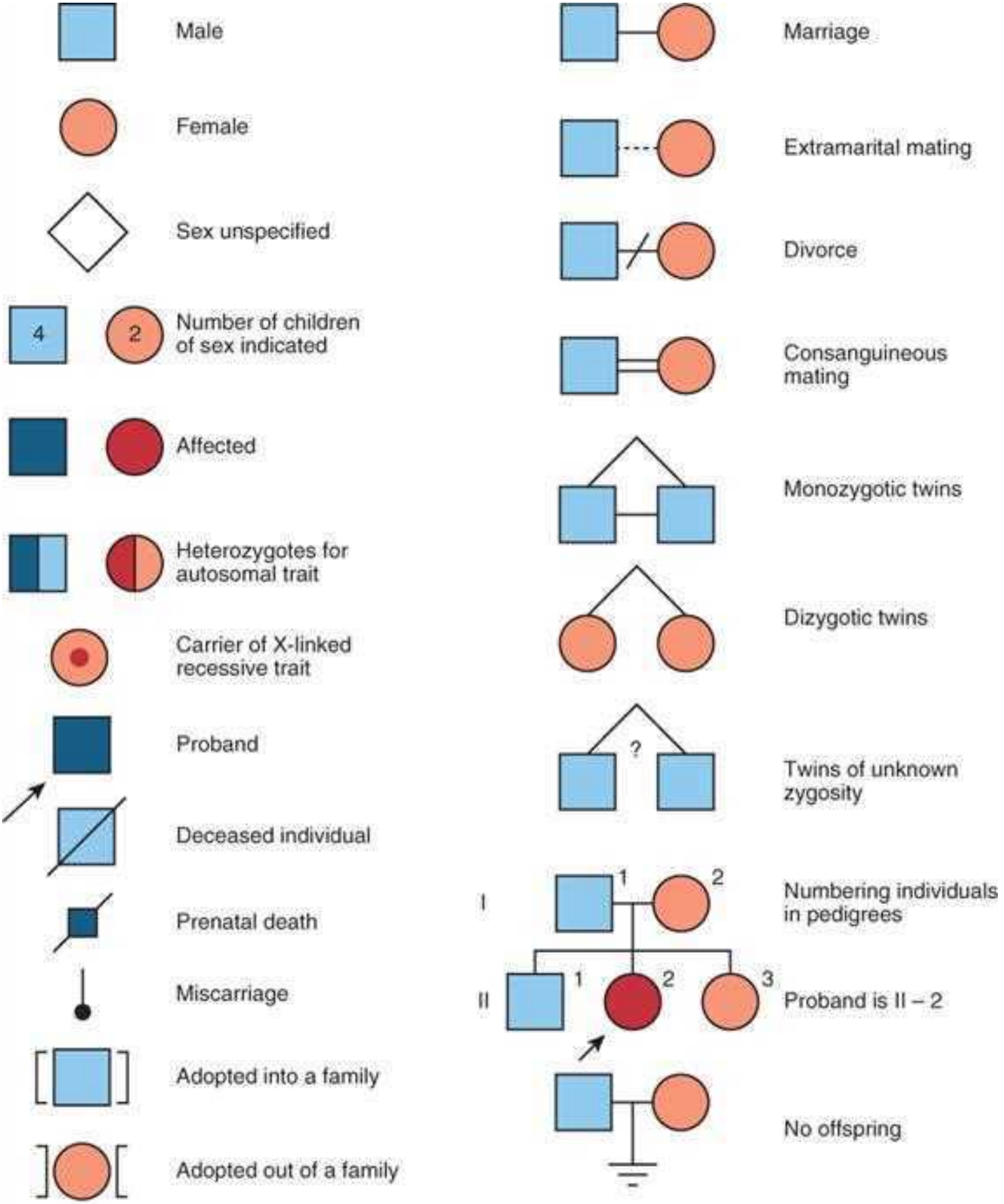
GENETIC DISEASES

The CDC (2016) estimates that 3 percent of neonates born each year in the United States will have at least one birth defect. Importantly, such defects are the leading cause of infant mortality and account for 20 percent of deaths. The benefits of preconceptional counseling usually are measured by comparing the incidence of new cases before and after initiation of a counseling program. Congenital conditions that clearly benefit from patient education include neural-tube defects, phenylketonuria, thalassemias, and other genetic diseases more common in individuals of Eastern European Jewish descent.

Family History

Pedigree construction using the symbols shown in Figure 8-2 is the most thorough method for obtaining a family history as a part of genetic screening. The health and reproductive status of each “blood relative” should be individually reviewed for medical illnesses, mental retardation, birth defects, infertility, and pregnancy loss. Certain racial, ethnic, or religious backgrounds may indicate elevated risk for specific recessive disorders.

FIGURE 8-2
Symbols used for pedigree construction. (Modified with permission from Thompson MW, McInnes RR, Huntington FW (eds): Genetics in Medicine, 5th ed. Philadelphia, Saunders, 1991.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catharine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Although most women can provide some information regarding their history, their understanding may be limited. For example, several studies have shown that pregnant women often fail to report a birth defect in the family or they report it incorrectly.

Thus, any disclosed defect or genetic disease should be confirmed by reviewing pertinent medical records or by contacting affected relatives for additional information.

Neural-Tube Defects

The incidence of neural-tube defects (NTDs) is 0.9 per 1000 live births, and they are second only to cardiac anomalies as the most frequent structural fetal malformation (Chap. 13, Genetic Tests). Some NTDs, as well as congenital heart defects, are associated with specific mutations. One example is the 677C → T substitution in the gene that encodes methylene tetrahydrofolate reductase. For this and similar gene defects, the trial conducted by the Medical Research Council Vitamin Study Research Group (1991) showed that preconceptional folic acid therapy significantly reduced the risk for a recurrent NTD by 72 percent. More importantly, because more than 90 percent of neonates with NTDs are born to women at low risk, Czeizel and Dudas (1992) showed that supplementation reduced the a priori risk of a first NTD occurrence. It is currently recommended, therefore, that all women who may become pregnant take daily 400 to 800 µg of folic acid orally before conception and through the first trimester (U.S Preventive Services Task Force, 2009). Folate fortification of cereal grains has been mandatory in the United States since 1998, and this practice has also resulted in decreased neural-tube defect rates (Williams, 2015). Despite the demonstrated benefits of folate supplementation, only half of women have taken folic acid supplementation periconceptionally (de Jong-van den Berg, 2005; Goldberg, 2006). The strongest predictor of use appears to be consultation with a health-care provider before conception.

Phenylketonuria

More than 600 mutations have been identified in the phenylalanine hydroxylase gene. The inherited defect in phenylalanine metabolism exemplifies diseases in which the fetus may not be at risk to inherit the disorder but may be damaged by maternal disease. Specifically, mothers with phenylketonuria (PKU) who eat an unrestricted diet have abnormally high blood phenylalanine levels. This amino acid readily crosses the placenta and can damage developing fetal organs, especially neural and cardiac tissues (Table 8-3).

TABLE 8-3

Frequency of Complications in the Offspring of Women with Untreated Phenylketonuria

Complication	Frequency (%)
Spontaneous abortion	24
Developmental delays	92
Microcephaly	73
Congenital heart disease	12
Fetal-growth restriction	40

Data from American Academy of Pediatrics: Maternal phenylketonuria, Pediatrics 2008 Aug;122(2):445–449.

With appropriate preconceptional counseling and adherence to a phenylalanine-restricted diet before pregnancy, the incidence of fetal malformations is dramatically reduced (Camp, 2014; Vockley, 2014). Therefore, the phenylalanine concentration is ideally normalized 3 months before conception and then maintained throughout pregnancy (American College of Obstetricians and Gynecologists, 2017b). The target phenylalanine blood concentration is 120 to 360 µmol/L (Camp, 2014).

Thalassemias

These disorders of globin-chain synthesis are the most common single-gene disorders worldwide (Forget, 2013; Vichinsky, 2013). As many as 200 million people carry a gene for one of these hemoglobinopathies, and hundreds of mutations are known to cause thalassemia syndromes (Chap. 56, Thalassemia Syndromes). In endemic areas such as Mediterranean and Southeast Asian countries, counseling and other prevention strategies have reduced the incidence of new cases by up to 80 percent (Cao, 2013).

The American College of Obstetricians and Gynecologists (2015a) recommends that individuals of high-risk ancestry be offered carrier screening to allow them informed decision making regarding reproduction and prenatal diagnosis. One method of early prenatal diagnosis is *preimplantation genetic diagnosis (PGD),* which is coupled with assisted reproductive technologies. Described in Chapter 14 (Preimplantation Genetic Testing), PGD is available for patients at risk for certain thalassemia syndromes (Kuliev, 2011).

Individuals of Eastern European Jewish Descent

Most individuals of Jewish ancestry in North America are descended from Ashkenazi Jewish communities and are at increased risk for having offspring with one of several autosomal recessive disorders. These include Tay-Sachs disease, Gaucher disease, cystic fibrosis, Canavan disease, familial dysautonomia, mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, and Bloom syndrome. The American College of Obstetricians and Gynecologists (2016c, 2017a) recommends preconceptional counseling and screening for these in this population. Carrier frequency and features of these conditions are discussed in Chapter 14 (Sickle Hemoglobinopathies).

REPRODUCTIVE HISTORY

During preconceptional screening, information is sought regarding infertility; abnormal pregnancy outcomes that may include miscarriage, ectopic pregnancy, and recurrent pregnancy loss; and obstetrical complications such as cesarean delivery, preeclampsia, placental abruption, and preterm delivery (Stubblefield, 2008). As discussed in Chapter 35 (Risk Factors), details involving a prior stillbirth are especially important. For example, Korteweg and associates (2008) identified chromosomal abnormalities in 13 percent of stillborns who underwent karyotyping. Reddy and colleagues (2012) confirmed that chromosomal microarray analysis (CMA) yielded better detection of genetic abnormalities than did standard karyotyping, primarily because nonviable tissue can be used for the analysis. CMA is described and illustrated in Chapter 13 (Chromosomal Microarray Analysis). Identification of a genetic abnormality in a stillborn can help determine the recurrence risk and aid in the preconceptional or prenatal management in subsequent pregnancies.

PARENTAL AGE

Maternal Age

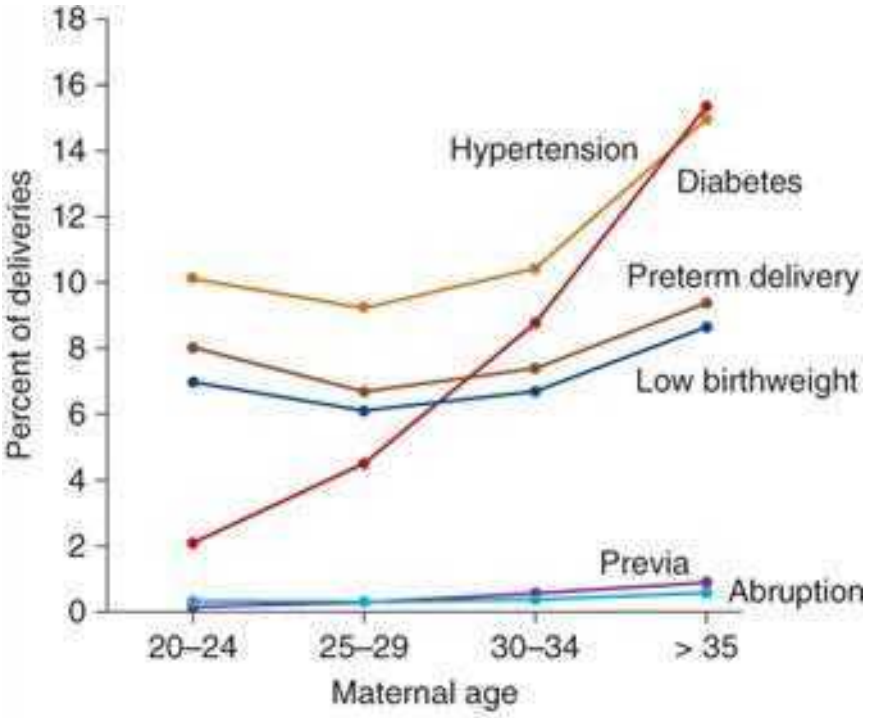
Women at both ends of the reproductive-age spectrum have unique outcomes to be considered. First, according to the CDC, in 2010, 3.4 percent of births in the United States were in women between the ages of 15 and 19 years (Martin, 2012). These adolescents are at increased risk for anemia, preterm delivery, and preeclampsia compared with women aged 20 to 35 years (Usta, 2008). The incidence of sexually transmitted diseases—common in adolescents—is even higher during pregnancy (Niccolai, 2003). Unfortunately, because most of their pregnancies are unplanned, adolescents rarely seek preconceptional counseling.

Conceptions after age 35 currently comprise approximately 15 percent of pregnancies in the United States (Martin, 2012). By contrast, these older women are more likely to request preconceptional counseling, either because of postponed pregnancy with a desire to optimize outcomes or because of plans to undergo infertility treatment. Some studies—including data from

Parkland Hospital presented in Figure 8-3— indicate that after age 35, the risks for obstetrical complications and for perinatal morbidity and mortality rise (Cunningham, 1995; Waldenström, 2015). The older woman who has a chronic illness or who is in poor physical condition usually has readily apparent risks. For the physically fit woman without medical problems, however, the risks are much lower than previously reported.

FIGURE 8-3

Incidence of selected pregnancy complications in relation to maternal age among 295,667 women delivered at Parkland Hospital.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Overall, the maternal mortality rate is higher in women aged 35 and older. Compared with women in their 20s, women aged 35 to 39 are 2.5 times more likely and women aged 40 or older are 5.3 times more likely to suffer pregnancy-related mortality (Geller, 2006). Creanga and coworkers (2015) analyzed pregnancy-related deaths in the United States for 2006 through 2010. Although women older than 35 years contributed less than 15 percent of all live births, they constituted 27 percent of maternal deaths. For the fetus, maternal age-related risks primarily stem from: (1) indicated preterm delivery for maternal complications such as hypertension and diabetes, (2) spontaneous preterm birth, (3) fetal growth disorders related to chronic maternal disease or multifetal gestation, (4) fetal aneuploidy, and (5) pregnancies resulting from assisted reproductive technology.

Assisted Reproductive Technologies

Recall that older women have subfertility problems. And although the incidence of dizygotic twinning increases with maternal age, the more important cause of multifetal gestation in older women follows the use of assisted reproductive technology (ART) and ovulation induction. Indeed, according to the CDC, 30 to 40 percent of all multifetal gestations in the United States in 2012 were conceived with the use of ART (Sunderan, 2015). Morbidity and mortality with multifetal pregnancies stem from preterm delivery. Other obstetrical morbidities, such as placenta previa, abruption, and preeclampsia, are also risks associated with these conceptions (Lukes, 2017; Qin, 2016).

Finally, experience has accrued that links ART to higher major congenital malformation rates. Davies and colleagues (2012) reported that of 308,974 births in South Australia, 8.3 percent of neonates conceived by ART had major birth defects. In this analysis, after adjustment for maternal age and other risk factors, intracytoplasmic injection continued to be associated with a significantly elevated risk for malformations, but in vitro fertilization did not.

Paternal Age

Parental history and experiences—paternal and maternal—can exert effects through epigenomic information not contained in the DNA sequence. Examples include variations in sperm and oocyte cytosine methylation and other mechanisms (Cedars, 2015; Lane, 2014). Perhaps one example is the possible link between increasing paternal age and complex neuropsychiatric conditions (Malaspina, 2015). Finally, the incidence of genetic diseases in offspring caused by new autosomal-dominant mutations in older men is increased. Still, the incidence is low (Chap. 13, Autosomal Dominant Inheritance). Accordingly, targeted sonographic examination performed solely for advanced maternal or paternal age is controversial.

SOCIAL HISTORY

Recreational Drugs and Smoking

Fetal risks associated with alcohol, marijuana, cocaine, amphetamines, and heroin are discussed in Chapter 12 (Known and Suspected Teratogens). The first step in preventing drug-related fetal risk is an honest assessment of use by the patient (American College of Obstetricians and Gynecologists, 2017c). Toward this end, questioning should be nonjudgmental. Screening for at-risk drinking can be accomplished using several validated tools. One is the well-studied TACE questions (American College of Obstetricians and Gynecologists, 2013). This is a series of four questions concerning *tolerance* to alcohol, being *annoyed* by comments about their drinking, attempts to *cut down*, and a history of drinking early in the morning—the *eye opener*.

In a Canadian study of more than 1000 postpartum patients, Tough and coworkers (2006) found that a high percentage of women reported alcohol use concurrent with conception attempts. Specifically, nearly half of those planning for pregnancy reported a mean of 2.2 drinks daily during early gestation and before they recognized their pregnancy. Of note, Bailey and associates (2008) found that rates of binge drinking and marijuana use by men were unaffected by their partner's pregnancy. The frequency and pattern of such behaviors clearly underscore the opportunity for preconceptional counseling.

Currently 20 million women in the United States smoke cigarettes (Centers for Disease Control and Prevention, 2014). Smoking in pregnancy has been consistently associated with numerous adverse perinatal outcomes, listed in Chapter 12 (Tobacco). These risks are largely mitigated by cessation before pregnancy, highlighting the importance of screening for tobacco use in the preconceptional period and during prenatal care as outlined in Chapter 9 (Normal Pregnancy Duration).

Environmental Exposures

Contact with environmental substances is inescapable. Thus, it is fortunate that only a few agents have been shown to cause adverse pregnancy outcomes (Windham, 2008). Exposures to infectious diseases have myriad deleterious effects, and these are detailed in Chapters 64 and 65. Likewise, contact with some chemicals may impart significant maternal and fetal risks. As discussed in Chapters 9 and 12 (Common Concerns and Immunosuppressant Medications), excess exposure to methyl mercury or lead is associated with neurodevelopmental disorders.

In the past, some concerns were raised over common everyday exposure to *electromagnetic fields* such as those emanated by high-voltage power lines, electric blankets, microwave ovens, and cellular phones. Fortunately, no human or animal evidence links these and adverse fetal outcomes (Robert, 1999). The effects of *electrical shock* are discussed in Chapter 47 (Thermal Injury).

Diet

Pica is the craving for and consuming of ice, laundry starch, clay, dirt, or other nonfood items. It should be discouraged due to its inherent replacement of healthful food with nutritionally empty products (Chap. 9, Caffeine). In some cases, it may represent an unusual physiological response to iron deficiency. Many *vegetarian diets* are protein deficient but can be corrected by

increasing egg and cheese consumption. *Anorexia* and *bulimia* increase maternal risks of nutritional deficiencies, electrolyte disturbances, cardiac arrhythmias, and gastrointestinal pathology (Becker, 1999). As discussed in Chapter 61 (Schizophrenia Spectrum Disorders), pregnancy-related complications with these disorders include greater risks of low birthweight, smaller head circumference, microcephaly, and small-for-gestational-age newborns (Kouba, 2005).

In contrast to these perinatal morbidities, *obesity* is linked with several maternal complications. As discussed in Chapter 48 (Maternal Morbidity), these include preeclampsia, gestational diabetes, labor abnormalities, cesarean delivery, and operative complications (American College of Obstetricians and Gynecologists, 2015b). Obesity also appears to be associated with a range of structural fetal anomalies (Stothard, 2009).

Exercise

Conditioned pregnant women usually can continue to exercise throughout gestation (American College of Obstetricians and Gynecologists, 2017d). As discussed in Chapter 9 (Common Concerns), no data suggest that exercise is harmful during pregnancy. One caveat is that as pregnancy progresses, balance problems and joint relaxation may predispose to orthopedic injury. A woman is advised not to exercise to exhaustion, and she should augment heat dissipation and fluid replacement. Further avoidances include prolonged supine position, activities requiring good balance, and extreme weather conditions.

Intimate Partner Violence

Pregnancy can exacerbate interpersonal problems and is a time of elevated risk from an abusive partner. According to the American College of Obstetricians and Gynecologists (2012), approximately 324,000 pregnant women are abused each year. As discussed in Chapter 47 (Trauma), intimate partner violence has been associated with greater risk for several pregnancy-related complications, including hypertension, vaginal bleeding, hyperemesis, preterm delivery, and low-birthweight neonates (Silverman, 2006). Because domestic violence can escalate during pregnancy, even to the point of homicide, the preconceptional period provides an ideal time for screening and if indicated, intervention (Cheng, 2010). As detailed in Chapter 9 (Alcohol), the American College of Obstetricians and Gynecologists (2012) provides recommendations and resources for screening both pregnant and nonpregnant women for domestic violence.

SCREENING TESTS

Certain laboratory tests may help assess the risk for and prevent some pregnancy complications. These include basic tests that are usually performed during prenatal care and are enumerated in Chapter 9. More specific tests may assist evaluation of women with certain chronic medical diseases. Examples of some chronic diseases that ideally would be assessed before conception are highlighted in Table 8-4. With several of these, optimizing maternal condition before conception will improve pregnancy outcomes. Cox and coworkers (1992) reviewed pregnancy outcomes in 1075 high-risk women who received such evaluation. They reported that the 240 women with hypertension, asthma, or renal, thyroid, or cardiac disease had better outcomes compared with the outcomes from their prior pregnancies.

TABLE 8-4

Selected Preconceptional Counseling Topics

Condition	Reference Chapter	Recommendations for Preconceptional Counseling
Environmental exposure	Chap. 9, Common Concerns Chap. 12, Immunosuppressant Medications	*Methyl mercury:* Avoid shark, swordfish, king mackerel, and tile fish. Ingest no more than 12 ounces or 2 servings of canned tuna and no more than 6 ounces of albacore per week. *Lead:* Blood lead testing if a risk factor is identified; treat if indicated according to recommendations.
Abnormal weight	Chap. 48, General Considerations Chap. 61, Schizophrenia Spectrum Disorders	Calculate BMI yearly from Figure 48-1 *BMI* ≥*25 kg/m*^{2}: Counsel on diet. Test for diabetes and metabolic syndrome if indicated. Consider weight loss prior to conception. *BMI* ≤*18.5 kg/m*^{2}: Assess for eating disorder.
Cardiovascular disease	Chap. 49, Peripartum Management Considerations Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs, Warfarin	Counsel on cardiac risks during pregnancy; discuss situations in which pregnancy is contraindicated. Optimize cardiac function. Discuss medication teratogenicity (warfarin, ACE inhibitor, ARB) and, if possible, switch to less dangerous agent when conception planned. Offer genetic counseling to those with congenital cardiac anomalies (Table 49-4).
Chronic hypertension	Chap. 50, Definition and Classification	Counsel on specific risks during pregnancy. Assess those with long-standing HTN for ventricular hypertrophy, retinopathy, and renal disease. Optimize blood pressure control. If medications indicated, select or switch to an agent appropriate for pregnancy.
Asthma	Chap. 51, Asthma	Counsel on asthma risks during pregnancy. Optimize pulmonary function preconceptionally. Treat women with pharmacological step therapy for chronic asthma.
Thrombophilia	Chap. 52, Inherited Thrombophilias	Question for personal or family history of thrombotic events or recurrent poor pregnancy outcomes. If a thrombophilia is found or known, counsel and offer appropriate anticoagulation regimen.

Condition	Reference Chapter	Recommendations for Preconceptional Counseling
Renal disease	Chap. 53, Pregnancy-Induced Urinary Tract Changes Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs	Counsel on specific risks during pregnancy. Optimize blood pressure control before conception. Counsel women taking ACE inhibitors and ARBs about teratogenicity and the need to switch agents before pregnancy.
Gastrointestinal disease	Chap. 54, Inflammatory Bowel Disease and Fertility Chap. 12, Antimicrobial Drugs, Immunosuppressant Medications	*Inflammatory bowel disease:* Counsel affected women on subfertility risks and risks of adverse pregnancy outcomes. Discuss teratogenicity of methotrexate and the other immunomodulators. Offer effective contraception during their use and switch agents, if possible, before conception.
Hepatobiliary disease	Chap. 55, Pregnancy and Hepatitis B	*Hepatitis B:* Vaccinate all high-risk women before conception (Table 9-7). Counsel chronic carriers on transmission prevention to partners and fetus. Treat if indicated. *Hepatitis C:* Screen high-risk women. Counsel affected women on risks of disease and transmission. If treatment indicated, discuss ramifications and appropriateness of pregnancy.
Hematological disease	Chap. 56, Anemias	*Iron-deficiency anemia:* Iron supplementation. *Sickle-cell disease:* Screen all black women. Counsel those with trait or disease. Test partner if desired. *Thalassemias:* Screen women of Southeast Asian or Mediterranean ancestry.
Diabetes	Chap. 57, Diabetic Neuropathy	Optimize glycemic control to minimize teratogenicity of hyperglycemia. Evaluate for end-organ damage such as retinopathy, nephropathy, hypertension, and others. Discontinue ACE inhibitors.
Thyroid disease	Chap. 58, Thyroid Disorders	Screen those with thyroid disease symptoms. Ensure iodine-sufficient diet. Treat overt hyper- or hypothyroidism. Counsel on risks to pregnancy outcome.
Connective tissue disease	Chap. 59, Immune-Mediated Connective Tissue Diseases Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs	*RA:* Counsel on flare risk after pregnancy. Discuss methotrexate and leflunomide teratogenicity, as well as possible effects of other immunomodulators. Switch these agents before conception. Stop NSAIDs by 27 weeks' gestation. *SLE:* Counsel on risks during pregnancy. Optimize disease before conception. Discuss mycophenolate mofetil and cyclophosphamide teratogenicity as well as possible effects of newer immunomodulators. Switch these agents before conception.

Condition	Reference Chapter	Recommendations for Preconceptional Counseling
Psychiatric disorders	Chap. 61, Treatment Considerations	*Depression:* Screen for symptoms of depression. Counsel on risks of treatment and of untreated illness and the high risk of exacerbation during pregnancy and the puerperium.
Neurological disorders	Chap. 60, Preconceptional Counseling	*Seizure disorder:* Optimize seizure control using monotherapy if possible.
Dermatological disease	Chap. 12, Selective Serotonin- and Norepinephrine-Reuptake Inhibitors	Discuss isotretinoin and etretinate teratogenicity and effective contraception during their use; switch agents before conception.
Cancer	Chap. 63, Fertility and Pregnancy after Cancer Therapy	Counsel on fertility preservation options before cancer therapy and on decreased fertility following certain agents. Discuss appropriateness of pregnancy balanced with need for ongoing cancer therapy and prognosis of the disease state.
Infectious diseases	Chap. 64, Maternal and Fetal Immunology	*Influenza:* Vaccinate all women who will be pregnant during flu season. Vaccinate high-risk women prior to flu season. *Malaria:* Counsel to avoid travel to endemic areas during conception. If unable, offer effective contraception during travel or provide chemoprophylaxis for those planning pregnancy. *Zika virus:* See travel restrictions by CDC. *Rubella:* Screen for rubella immunity. If nonimmune, vaccinate and counsel on the need for effective contraception during the subsequent month. *Tdap: tetanus, diphtheria, pertussis*: Update vaccination in all reproductive-aged women. *Varicella:* Question regarding immunity. If nonimmune, vaccinate.
STDs	Chap. 65, Syphilis	*Gonorrhea, syphilis, chlamydial infection:* Screen high-risk women and treat as indicated. *HIV:* Screen at-risk women. Counsel affected women on risks during pregnancy and on perinatal transmission. Discuss initiation of treatment before pregnancy to decrease transmission risk. Offer effective contraception to those not desiring conception. *HPV:* Provide Pap smear screening per guidelines (Chap. 63, Epithelial Neoplasia). Vaccinate candidate patients. *HSV:* Provide serological screening to asymptomatic women with affected partners. Counsel affected women on risks of perinatal transmission and on preventative measures during the third trimester and labor.

ACE = angiotensin-converting enzyme; ACOG = American College of Obstetricians and Gynecologists; ARB = angiotensin-receptor blocker; BMI = body mass index; CDC = Centers for Disease Control and Prevention; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; HTN = hypertension; NSAID = nonsteroidal antiinflammatory drug; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; STD = sexually transmitted disease.

Data from Jack BW, Atrash H, Coonrod DV, et al: The clinical content of preconception care: an overview and preparation of this supplement, Am J Obstet Gynecol. 2008 Dec;199(6 Suppl 2):S266–S279.

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CHAPTER 9: Prenatal Care

The borderline between health and disease is less distinctly marked during gestation, and therefore, it accordingly becomes necessary to keep pregnant patients under strict supervision, and to be constantly on the alert for the appearance of untoward symptoms.

—J. Whitridge Williams (1903)

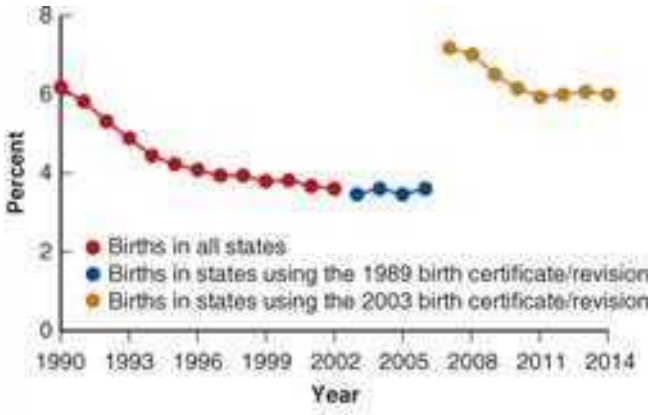
INTRODUCTION

As emphasized above by Williams, prenatal care is important. According to the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) a comprehensive antepartum program is defined as: "a coordinated approach to medical care, continuous risk assessment, and psychological support that optimally begins before conception and extends throughout the postpartum period and interconceptional period."

PRENATAL CARE IN THE UNITED STATES

Almost a century after its introduction, prenatal care has become one of the most frequently used health services in the United States. In 2001, there were approximately 50 million prenatal visits. The median was 12.3 visits per pregnancy, and many women had 17 or more visits. Still, as seen from Figure 9-1, 6 to 7 percent of women in this country have late or no prenatal care. In 2014, the percentages of non-Hispanic white, Hispanic, and African-American women who received inadequate or no prenatal care were 4.3, 7.5, and 9.7, respectively (Child Trends, 2015).

FIGURE 9-1
Percentage of births to mothers who received late or no prenatal care—United States, 1990–2014. (Data from Child Trends, 2015.)



The Centers for Disease Control and Prevention (CDC) (2000) analyzed birth certificate data and found that half of women with delayed or no prenatal care wanted to begin care earlier. Barriers to care varied by social and ethnic group, age, and payment method. The most common reason cited was late recognition of pregnancy by the patient. The second most commonly cited obstacle was lack of money or insurance. The third was inability to obtain an appointment.

Prenatal Care Effectiveness

Care designed during the early 1900s focused on lowering the extremely high maternal mortality rate. Prenatal care undoubtedly contributed to the dramatic decline in this mortality rate from 690 deaths per 100,000 births in 1920 to 50 per 100,000 by 1955 (Loudon, 1992). And, the low current maternal mortality rate of 10 to 15 per 100,000 is likely associated with the high utilization of this care (Xu, 2010). Indeed, data from 1998 to 2005 from the Pregnancy Mortality Surveillance System identified a fivefold increased risk for maternal death in women who received no prenatal care (Berg, 2010).

Other reports also attest to prenatal care efficacy. In a study of almost 29 million births, the risk for preterm birth, stillbirth, early and late neonatal death, and infant death rose linearly with decreasing prenatal care (Partridge, 2012). Similarly, Leveno and associates (2009) found that a significant decline in preterm births at Parkland Hospital correlated closely with increased use of prenatal care by medically indigent women. Moreover, National Center for Health Statistics data showed that women with prenatal care had an overall stillbirth rate of 2.7 per 1000 compared with 14.1 per 1000 for women without this care (Vintzileos, 2002).

Evaluating the format of care, Ickovics and coworkers (2016) compared individual prenatal care and group prenatal care. The latter provided traditional pregnancy surveillance in a group setting with special focus on support, education, and active health-care participation. Women enrolled in group prenatal care had significantly better pregnancy outcomes. Carter and colleagues (2016) cited similar results. Childbirth education classes are also reported to result in better

pregnancy outcomes (Afshar, 2017). Adolescent pregnancies carry special risk, and guidelines have been developed that focus on this subgroup (Fleming, 2015). Few data are available to recommend the practice of offering tangible incentives to improve prenatal care attendance (Till, 2015).

DIAGNOSIS OF PREGNANCY

Pregnancy is usually identified when a woman presents with symptoms and possibly a positive home urine pregnancy test result. Typically, these women receive confirmatory testing of urine or blood for human chorionic gonadotropin (hCG). Further, presumptive signs or diagnostic findings of pregnancy may be found during examination. Sonography is often used, particularly if miscarriage or ectopic pregnancy is a concern.

Symptoms and Signs

Amenorrhea in a healthy reproductive-aged woman who previously has experienced spontaneous, cyclical, predictable menses is highly suggestive of pregnancy. Menstrual cycles vary appreciably in length among women and even in the same woman (Chap. 5, Ovarian Cycle). Thus, amenorrhea is not a reliable pregnancy indicator until 10 days or more after expected menses have passed. Occasionally, uterine bleeding that mimics menstruation is noted after conception. During the first month of pregnancy, these episodes are likely the consequence of blastocyst implantation. Still, first-trimester bleeding should generally prompt evaluation for an abnormal pregnancy.

Of other symptoms, maternal perception of fetal movement depends on factors such as parity and habitus. In general, after a first successful pregnancy, a woman may first perceive fetal movements between 16 and 18 weeks' gestation. A primigravida may not appreciate fetal movements until approximately 2 weeks later. At about 20 weeks, depending on maternal habitus, an examiner can begin to detect fetal movements.

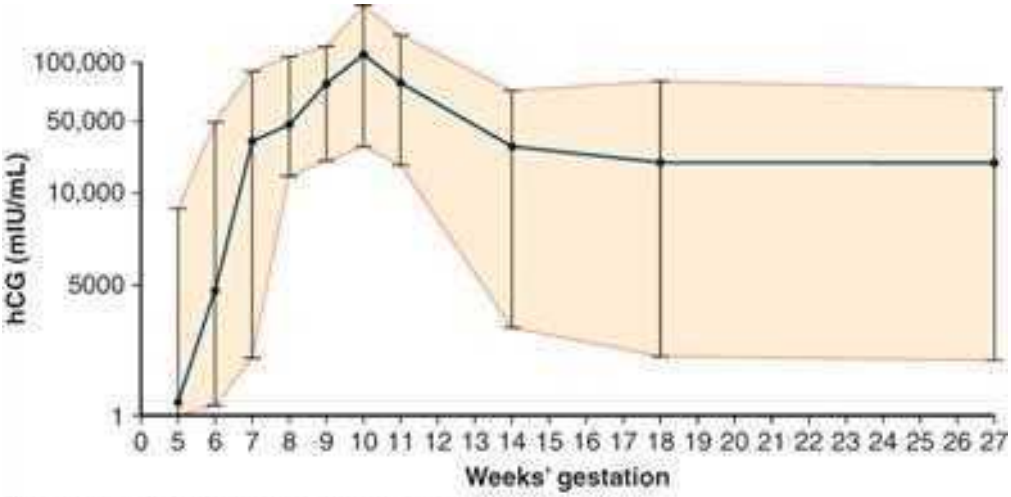
Of pregnancy signs, changes in the lower reproductive tract, uterus, and breasts develop early. These are described in detail in Chapter 4 (Reproductive Tract).

Pregnancy Tests

Detection of hCG in maternal blood and urine is the basis for endocrine assays of pregnancy. Syncytiotrophoblast produces hCG in amounts that increase exponentially during the first trimester following implantation. A main function of hCG is to prevent involution of the corpus luteum, which is the principal site of progesterone formation during the first 6 weeks of pregnancy.

With a sensitive test, the hormone can be detected in maternal serum or urine by 8 to 9 days after ovulation. The doubling time of serum hCG concentration is 1.4 to 2.0 days. As shown in Figure 9-2, serum levels range widely and increase from the day of implantation. They reach peak levels at 60 to 70 days. Thereafter, the concentration declines slowly until a plateau is reached at approximately 16 weeks' gestation.

FIGURE 9-2
Mean concentration (95% CI) of human chorionic gonadotropin (hCG) in serum of women throughout normal pregnancy.



Measurement of hCG

This hormone is a glycoprotein with high carbohydrate content. The general structure of hCG is a heterodimer composed of two dissimilar subunits, designated α and β, which are noncovalently linked. The α-subunit is identical to those of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH), but the β-subunit is structurally distinct among these. Thus, antibodies were developed with high specificity for the hCG β-subunit. This specificity allows its detection, and numerous commercial immunoassays are available for measuring serum and urine hCG levels. Although each immunoassay detects a slightly different mixture of hCG variants, its free subunits, or its metabolites, all are appropriate for pregnancy testing (Braunstein, 2014). Depending on the assay used, the sensitivity for the laboratory detection limit of hCG in serum is 1.0 mIU/mL or even lower (Wilcox, 2001).

False-positive hCG test results are rare (Braunstein, 2002). A few women have circulating serum factors that may bind erroneously with the test antibody directed to hCG in a given assay. The most common factors are heterophilic antibodies. These are produced by an individual and bind to the animal-derived test antibodies used in a given immunoassay. Thus, women who have worked closely with animals are more likely to develop these antibodies, and alternative laboratory techniques are available (American College of Obstetricians and Gynecologists, 2017a). Elevated hCG levels may also reflect molar pregnancy and its associated cancers (Chap. 20, Diagnosis). Other rare causes of positive assays without pregnancy are: (1) exogenous hCG injection used for weight loss, (2) renal failure with impaired hCG clearance, (3) physiological pituitary hCG, and (4) hCG-producing tumors that most commonly originate from gastrointestinal sites, ovary, bladder, or lung (Montagnana, 2011).

Home Pregnancy Tests

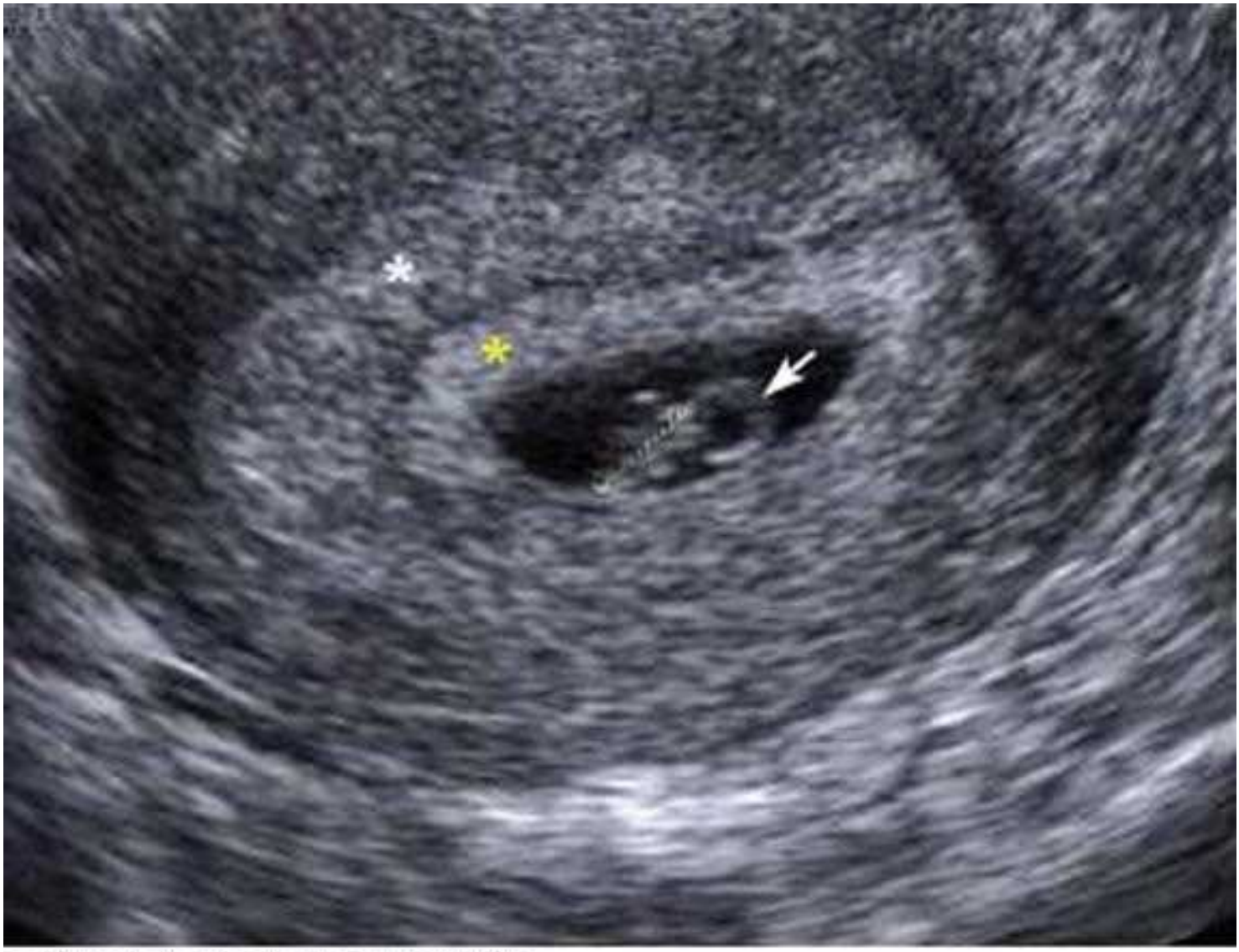
Over-the-counter pregnancy test kits have been available since the early 1970s, and millions are sold annually in the United States. More than 60 such tests are available in this country (Grenache, 2015). Unfortunately, many of these are not as accurate as advertised (Johnson, 2015). For example, Cole and associates (2011) found that a detection limit of 12.5 mIU/mL would be required to diagnose 95 percent of pregnancies at the time of missed menses, but they reported that only one brand had this degree of sensitivity. Two other brands gave false-positive or invalid results. In fact, with an hCG concentration of 100 mIU/mL, clearly positive results were displayed by only 44 percent of brands. Accordingly, only about 15 percent of pregnancies could be diagnosed at the time of the missed menses. Some manufacturers of even newer home urine assays claim >99-percent accuracy of tests done on the day of—and some up to 4 days before—the expected day of menses. Again, careful analysis suggests that these assays are often not as sensitive as advertised (Johnson, 2015).

Sonographic Recognition of Pregnancy

Transvaginal sonography has revolutionized early pregnancy imaging and is commonly used to accurately establish gestational age and confirm pregnancy location. A *gestational sac*—a small anechoic fluid collection within the endometrial cavity—is the first sonographic evidence of pregnancy. It may be seen with transvaginal sonography by 4 to 5 weeks' gestation. A fluid collection, however, can also be seen within the endometrial cavity with an ectopic pregnancy and is termed a *pseudogestational sac* or *pseudosac* (Fig. 19-4). Thus, further evaluation may be warranted if this is the only sonographic finding, particularly in a woman with pain or bleeding. A normal gestational sac implants eccentrically in the endometrium, whereas a pseudosac is seen in the midline of the endometrial cavity. Other potential indicators of early intrauterine pregnancy are an anechoic center surrounded by a single echogenic rim—the *intradecidual sign*—or two concentric echogenic rings surrounding the gestational sac—the *double decidual sign* shown in Figure 9-3. If sonography yields equivocal findings, the term *pregnancy of unknown location (PUL)* is applied. In these cases, serial serum hCG levels and transvaginal sonograms can help differentiate a normal intrauterine pregnancy from an extrauterine pregnancy or an early miscarriage (Chap. 19, Multimodality Diagnosis).

FIGURE 9-3

Transvaginal sonogram of a first-trimester intrauterine pregnancy. The double decidual sign is noted surrounding the gestational sac and is defined by the decidua parietalis (*white asterisk*) and the decidua capsularis (*yellow asterisk*). The arrow notes the yolk sac, and the crown-rump length of the embryo is marked with measuring calipers. (Used with permission from Dr. Elysia Moschos.)



If the *yolk sac*—a brightly echogenic ring with an anechoic center—is seen within the gestational sac, an intrauterine location for the pregnancy is confirmed. The yolk sac can normally be seen by the middle of the fifth week. As shown in Figure 9-3, after 6 weeks, an embryo is seen as a linear structure immediately adjacent to the yolk sac. Cardiac motion is typically noted at this point. Up to 12 weeks' gestation, the crown-rump length is predictive of gestational age within 4 days (Chap. 10, Gestational Age Assessment).

INITIAL PRENATAL EVALUATION

Prenatal care is ideally initiated early. Major goals are to: (1) define the health status of the mother and fetus, (2) estimate the gestational age, and (3) initiate a plan for continued obstetrical care. Typical components of the initial visit are summarized in Table 9-1. Subsequent care may range from relatively infrequent routine visits to prompt hospitalization because of serious maternal or fetal disease.

TABLE 9-1

Typical Components of Routine Prenatal Care

			Weeks		
	Text Referral	**First Visit**	**15–20**	**24–28**	**29–41**
History					
Complete	Chap. 9, Normal Pregnancy Duration	•			
Updated			•	•	•
Physical examination					
Complete	Chap. 9, Clinical Evaluation	•			
Blood pressure	Chap. 40, Diagnosis of Hypertensive Disorders	•	•	•	•
Maternal weight	Chap. 9, Nutritional Counseling	•	•	•	•
Pelvic/cervical examination	Chap. 9, Clinical Evaluation	•			
Fundal height	Chap. 9, Subsequent Prenatal Visits	•	•	•	•
Fetal heart rate/fetal position	Chap. 9, Nutritional Counseling	•	•	•	•
Laboratory tests					
Hematocrit or hemoglobin	Chap. 56, Anemias	•		•	
Blood type and Rh factor	Chap. 15, Red Cell Alloimmunization	•			
Antibody screen	Chap. 15, Red Cell Alloimmunization	•		**A**	
Pap smear screening	Chap. 63, Epithelial Neoplasia	•			
Glucose tolerance test	Chap. 57, Screening and Diagnosis			•	
Fetal aneuploidy screening	Chap. 14, Screening for Aneuploidy	**B**[a] and/or	**B**		
Neural-tube defect screening	Chap. 14, Maternal Serum AFP Elevation: Neural-Tube Defect Screening		**B**		
Cystic fibrosis screening	Chap. 14, Cystic Fibrosis	**B** or	**B**		
Urine protein assessment	Chap. 4, Renal Function Tests	•			
Urine culture	Chap. 53, Urinary Tract Infections	•			
Rubella serology	Chap. 64, Rubella Virus	•			
Syphilis serology	Chap. 65, Diagnosis	•			**C**
Gonococcal screening	Chap. 65, Gonorrhea	**D**			**D**
Chlamydial screening	Chap. 65, Chlamydial Infections	•			**C**
Hepatitis B serology	Chap. 55, Pregnancy and Hepatitis B	•			**D**
HIV serology	Chap. 65, Human Immunodeficiency Virus	**B**			**D**
Group B streptococcus culture	Chap. 64, Bacterial Infections				**E**

			Weeks		
	Text Referral	**First Visit**	**15–20**	**24–28**	**29–41**
Tuberculosis screening	Chap. 51, Diagnosis				

[a]First-trimester aneuploidy screening may be offered between 11 and 14 weeks.

A Performed at 28 weeks, if indicated.

B Test should be offered.

C High-risk women should be retested at the beginning of the third trimester.

D High-risk women should be screened at the first prenatal visit and again in the third trimester.

E Rectovaginal culture should be obtained between 35 and 37 weeks.

HIV = human immunodeficiency virus.

Prenatal Record

Use of a standardized record within a perinatal health-care system greatly aids antepartum and intrapartum management. Standardizing documentation allows communication and care continuity between providers and enables objective measures of care quality to be evaluated over time and across different clinical settings (Gregory, 2006). A prototype is provided by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) in their *Guidelines for Perinatal Care*, 8th edition.

Definitions

Several definitions are pertinent to establishment of an accurate prenatal record.

1. *Nulligravida*—a woman who currently is not pregnant and has never been pregnant.
2. *Gravida*—a woman who currently is pregnant or has been in the past, irrespective of the pregnancy outcome. With the establishment of the first pregnancy, she becomes a *primigravida,* and with successive pregnancies, a *multigravida*.
3. *Nullipara*—a woman who has never completed a pregnancy beyond 20 weeks' gestation. She may not have been pregnant or may have had a spontaneous or elective abortion(s) or an ectopic pregnancy.
4. *Primipara*—a woman who has been delivered only once of a fetus or fetuses born alive or dead with an estimated length of gestation of 20 or more weeks. In the past, a 500-g birthweight threshold was used to define parity. This threshold is now controversial because many states still use this weight to differentiate a stillborn fetus from an abortus (Chap. 1, Definitions). However, the survival of neonates with birthweights <500 g is no longer uncommon.
5. *Multipara*—a woman who has completed two or more pregnancies to 20 weeks' gestation or more. Parity is determined by the number of pregnancies reaching 20 weeks. It is not increased to a higher number if multiples are delivered in a given pregnancy. Moreover, stillbirth does not lower this number. In some locales, the obstetrical history is summarized by a series of digits connected by dashes. These refer to the number of term infants, preterm infants, abortuses younger than 20 weeks, and children currently alive. For example, a woman who is para 2–1–0–3 has had two term deliveries, one preterm delivery, no abortuses, and has three living children. Because these are nonconventional, it is helpful to specify the outcome of any pregnancy that did not end normally.

Normal Pregnancy Duration

The normal duration of pregnancy calculated from the first day of the last normal menstrual period is very close to 280 days or 40 weeks. In a study of 427,581 singleton pregnancies from the Swedish Birth Registry, Bergsjø and coworkers (1990) found that the mean pregnancy duration was 281 days with a standard deviation of 13 days. However, menstrual cycle length varies among women and renders many of these calculations inaccurate. This, combined with the frequent use of first-trimester sonography, has changed the method of determining an accurate gestational age (Duryea, 2015).

The American College of Obstetricians and Gynecologists (2017e), the American Institute of Ultrasound in Medicine, and the Society for Maternal-Fetal Medicine have concluded that first-trimester ultrasound is the most accurate method to establish or reaffirm gestational age. For pregnancies conceived by assisted reproductive technology, embryo age or transfer date is used to assign gestational age. If available, the gestational ages calculated from the last menstrual period and from first-trimester ultrasound are compared, and this estimated date of delivery is recorded. This is discussed in further detail in Chapter 7 (Gestational Age) and in Table 10-1 (Gestational Age Assessment).

A quick estimate of a pregnancy due date based on menstrual data can be made as follows: add 7 days to the first day of the last period and subtract 3 months. For example, if the first day of the last menses was October 5, the due date is 10–05 minus 3 (months) plus 7 (days) = 7–12, or July 12 of the following year. This calculation is the *Naegele rule* (American College of Obstetricians and Gynecologists, 2017e).

Trimesters

It has become customary to divide pregnancy into three equal epochs or trimesters of approximately 3 calendar months. Historically, the first trimester extends through completion of 14 weeks, the second through 28 weeks, and the third includes the 29th through 42nd weeks of pregnancy. Thus, there are three periods of 14 weeks each. Certain major obstetrical problems tend to cluster in each of these time periods. For example, most spontaneous abortions take place during the first trimester, whereas most women with hypertensive disorders due to pregnancy are diagnosed during the third trimester.

In modern obstetrics, the clinical use of trimesters to describe a specific pregnancy is imprecise. For example, it is inappropriate in cases of uterine hemorrhage to categorize the problem temporally as "third-trimester bleeding." Appropriate management for the mother and her fetus will vary remarkably depending on whether bleeding begins early or late in the third trimester (Chap. 41, Risks). Because precise knowledge of fetal age is imperative for ideal obstetrical management, the clinically appropriate unit is *weeks of gestation completed.* And more recently, clinicians designate gestational age using completed weeks and days, for example, $33^{4/7}$ weeks or 33 + 4, for 33 completed weeks and 4 days.

Previous and Current Health Status

As elsewhere in medicine, history taking begins with queries concerning medical or surgical disorders. Also, detailed information regarding previous pregnancies is essential as many obstetrical complications tend to recur in subsequent pregnancies. The *menstrual* and *contraceptive histories* are also important. Gestational or menstrual age is the number of weeks since the onset of the last menstrual period in women with menstrual cycles lasting 28 to 30 days. For those with irregular menses, sonography in early pregnancy will clarify gestational age. Last, some methods of birth control favor ectopic implantation following method failure (Chap. 38, Method-Specific Adverse Effects and Progestin-Only Contraceptives).

Psychosocial Screening

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) define psychosocial issues as nonbiomedical factors that affect mental and physical well-being. Women should be screened regardless of social status, education level, race, or ethnicity. Such screening should seek barriers to care, communication obstacles, nutritional status, unstable housing, desire for pregnancy, safety concerns that include intimate-partner violence, depression, stress, and use of substances such as tobacco, alcohol, and illicit drugs. This screening is performed on a regular basis, at least once per trimester, to identify important issues and reduce adverse pregnancy outcomes. Coker and colleagues (2012) compared pregnancy outcomes in women before and after implementation of a universal psychosocial screening program and found that screened women were less likely to have preterm or low-birthweight newborns, as well as other adverse outcomes. Specific screens for depression are presented in Chapter 61 (The Puerperium).

Cigarette Smoking

Data on this practice have been included on the birth certificate since 1989. The number of pregnant women who smoke continues to decline. From 2000 to 2010, the prevalences were 12 to 13 percent (Tong, 2013). Based on the Pregnancy Risk Assessment Monitoring System, these women were more likely younger, had less education, and were either Alaska Natives or American Indians (Centers for Disease Control and Prevention, 2013a).

Numerous adverse outcomes have been linked to smoking during pregnancy (U.S. Department of Health and Human Services, 2000). Potential teratogenic effects are reviewed in Chapter 12 (Tobacco). Notable among these are greater rates of miscarriage, stillbirth, low birthweight, and preterm delivery (Man, 2006; Tong, 2013). There is also a twofold risk of placenta previa, placental abruption, and premature membrane rupture compared with nonsmokers. Thus, the U.S. Preventive Services Task Force recommends that clinicians offer counseling and effective intervention options to pregnant smokers at the first and subsequent prenatal visits (Siu, 2015). Although benefits are greatest if smoking ceases early in pregnancy or preferably preconceptionally, quitting at any stage of pregnancy can improve perinatal outcomes (Fiore, 2008).

Person-to-person psychosocial interventions are significantly more successful in achieving smoking abstinence in pregnancy than is simply advising the woman to quit (Fiore, 2008). One example is a brief counseling session covering the "5As" of smoking cessation (Table 9-2). This approach can be accomplished in 15 minutes or less and is effective when initiated by health-care providers (American College of Obstetricians and Gynecologists, 2017i).

TABLE 9-2

Five A's of Smoking Cessation

ASK about smoking at the first and subsequent prenatal visits.
ADVISE with clear, strong statements that explain the risks of continued smoking to the woman, fetus, and newborn.
ASSESS the patient's willingness to attempt cessation.
ASSIST with pregnancy-specific, self-help smoking cessation materials. Offer a direct referral to the smoker's quit line (1–800-QUIT NOW) to provide ongoing counseling and support.
ARRANGE to track smoking abstinence progress at subsequent visits.

Adapted from Fiore, 2008.

Behavioral interventions and nicotine replacement products are successful in reducing smoking rates (Patnode, 2015). That said, nicotine replacement has not been sufficiently evaluated to determine its effectiveness and safety in pregnancy. Trials evaluating such therapy have yielded conflicting evidence (Coleman, 2015; Pollak, 2007; Spindel, 2016). Two recent randomized trials also produced nonconclusive results. In the Smoking and Nicotine in Pregnancy (SNAP) trial, Cooper and associates (2014) reported a temporary cessation of smoking that may have been associated with improved infant development. In the Study of Nicotine Patch in Pregnancy (SNIPP) trial, Berlin and coworkers (2014) found no differences in smoking cessation rates or birthweights.

Because of limited available evidence to support pharmacotherapy for smoking cessation in pregnancy, the American College of Obstetricians and Gynecologists (2017i) has recommended that if nicotine replacement therapy is used, it should be done with close supervision and after careful consideration of the risks of smoking versus nicotine replacement.

Alcohol

Ethyl alcohol or ethanol is a potent teratogen that causes a fetal syndrome characterized by growth restriction, facial abnormalities, and central nervous system dysfunction. As discussed in Chapter 12 (Known and Suspected Teratogens), women who are pregnant or considering pregnancy should abstain from using any alcoholic beverages. The CDC analyzed data from the Behavioral Risk Factor Surveillance System from 2011 to 2013 and estimated that 10 percent of pregnant women used alcohol. It is estimated that 3.3 million women are at risk for such exposure (Green, 2016). The American College of Obstetricians and Gynecologists (2016b) in collaboration with the CDC has developed the *Fetal Alcohol Spectrum Disorders (FASD) Prevention Program*, which provides resources for providers and is available at: http://www.acog.org/alcohol.

Illicit Drugs

It is estimated that 10 percent of fetuses are exposed to one or more illicit drugs. Agents may include heroin and other opiates, cocaine, amphetamines, barbiturates, and marijuana (American Academy of Pediatrics, 2017; American College of Obstetricians and Gynecologists, 2015a, 2017d). As discussed in Chapter 12 (Warfarin), chronic use of most of these in large quantities is harmful to the fetus (Metz, 2015). Well-documented sequelae include fetal-growth restriction, low birthweight, and drug withdrawal soon after birth. Adverse effects of marijuana are less convincing. Women who use such drugs frequently do not seek prenatal care, which in itself is associated with risks for preterm and low-birthweight newborns (El-Mohandes, 2003; Eriksen, 2016).

For women who abuse heroin, methadone maintenance can be initiated within a registered methadone treatment program to reduce complications of illicit opioid use and narcotic withdrawal, to encourage prenatal care, and to avoid drug culture risks (American College of Obstetricians and Gynecologists, 2017f). Available programs can be found through the treatment locator of the Substance Abuse and Mental Health Services Administration at www.samhsa.gov. Methadone dosages usually are initiated at 10 to 30 mg daily and titrated as needed. In some women, careful methadone taper may be an appropriate option (Stewart, 2013). Although less commonly used, buprenorphine alone or in combination with naloxone may also be offered and managed by physicians with specific credentialing.

Intimate-Partner Violence

This term refers to a pattern of assault and coercive behavior that may include physical injury, psychological abuse, sexual assault, progressive isolation, stalking, deprivation, intimidation, and reproductive coercion (American College of Obstetricians and Gynecologists, 2012). Such violence has been recognized as a major public health problem. Unfortunately, most abused women continue to be victimized during pregnancy. With the possible exception of preeclampsia, domestic violence is more prevalent than any major medical condition detectable through routine prenatal screening (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2017). The prevalence during pregnancy is estimated to range between 4 and 8 percent. Intimate-partner violence is associated with an increased risk of several adverse perinatal outcomes including preterm delivery, fetal-growth restriction, and perinatal death (Chap. 47, Trauma).

The American College of Obstetricians and Gynecologists (2012) has provided methods for domestic violence screening and recommends their use at the first prenatal visit, then again at least once per trimester, and again at the postpartum visit. Such screening should be done privately and away from family members and friends. Patient self-administered or computerized screenings appear to be as effective for disclosure as clinician-directed interviews (Ahmad, 2009; Chen, 2007). Physicians should be familiar with state laws that may require reporting of intimate-partner violence. Coordination with social services can be invaluable in these cases. The National Domestic Violence Hotline (1–800–799-SAFE [7233]) is a nonprofit telephone referral service that provides individualized information regarding city-specific shelter locations, counseling resources, and legal advocacy.

Clinical Evaluation

A thorough, general physical examination should be completed at the initial prenatal encounter. Pelvic examination is performed as part of this evaluation. The cervix is visualized employing a speculum lubricated with warm water or water-based lubricant gel. Bluish-red passive hyperemia of the cervix is characteristic, but not of itself diagnostic, of pregnancy. Dilated, occluded cervical glands bulging beneath the ectocervical mucosa—*nabothian cysts*—may be prominent. The cervix is not normally dilated except at the external os. To identify cytological abnormalities, a Pap test is performed according to current guidelines noted in Chapter 63 (Epithelial Neoplasia). Specimens for identification of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are also obtained when indicated.

Bimanual examination is completed by palpation, with special attention given to the consistency, length, and dilatation of the cervix; to uterine and adnexal size; to the bony pelvic architecture; and to any vaginal or perineal anomalies. Later in pregnancy, fetal presentation often can also be determined. Lesions of the cervix, vagina, or vulva are further evaluated as needed by colposcopy, biopsy, culture, or dark-field examination. The perianal region is visualized, and digital rectal examination performed as required for complaints of rectal pain, bleeding, or mass.

Gestational Age Assessment

Precise knowledge of gestational age is one of the most important aspects of prenatal care because several pregnancy complications may develop for which optimal treatment will depend on fetal age. As discussed earlier and in Chapter 7 (Gestational Age), first-trimester sonographic assessment is best correlated with menstrual history. That said, gestational age can also be estimated with considerable precision by carefully performed clinical uterine size examination that is coupled with knowledge of the last menses. Uterine size similar to a small orange roughly correlates with a 6-week gestation; a large orange, with an 8-week pregnancy; and a grapefruit, with one at 12 weeks (Margulies, 2001).

Laboratory Tests

Recommended routine tests at the first prenatal encounter are listed in Table 9-1. Initial blood tests include a complete blood count, a determination of blood type with Rh status, and an antibody screen. The Institute of Medicine recommends universal human immunodeficiency virus (HIV) testing, with patient notification and right of refusal, as a routine part of prenatal care. The CDC (Branson, 2006) as well as the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2016f, 2017) continue to support this practice. If a woman declines testing, this is recorded in the prenatal record. All pregnant women are also screened for hepatitis B virus infection, syphilis, and immunity to rubella at the initial visit. Based on their prospective investigation of 1000 women, Murray and coworkers (2002) concluded that in the absence of hypertension, routine urinalysis beyond the first prenatal visit was not necessary. A urine culture is recommended by most because treating bacteruria significantly reduces the likelihood of developing symptomatic urinary tract infections in pregnancy (Chap. 53, Urinary Tract Infections).

Cervical Infections

Chlamydia trachomatis is isolated from the cervix in 2 to 13 percent of pregnant women. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that all women be screened for chlamydia during the first prenatal visit, with additional third-trimester testing for those at increased risk. Risk factors include unmarried status, recent change in sexual partner or multiple concurrent partners, age younger than 25 years, inner-city residence, history or presence of other sexually transmitted diseases, and little or no prenatal care. For those testing positive, treatment described in Chapter 65 (Chlamydial Infections) is followed by a second testing—a *test of cure*—3 to 4 weeks after treatment completion.

Neisseria gonorrhoeae typically causes lower genital tract infection in pregnancy. It also may cause septic arthritis (Bleich, 2012). Risk factors for gonorrhea are similar to those for chlamydial infection. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that pregnant women with risk factors or those living in an area of high *N gonorrhoeae* prevalence be screened at the initial prenatal visit and again in the third trimester. Treatment is given for gonorrhea and simultaneously for possible coexisting chlamydial infection (Chap. 65, Chlamydial Infections). Test of cure is also recommended following treatment.

Pregnancy Risk Assessment

Many factors can adversely affect maternal and fetal well-being. Some are evident at conception, but many become apparent during the course of pregnancy. The designation of “high-risk pregnancy” is overly vague for an individual woman and probably is best avoided if a more specific diagnosis can be assigned. Some common risk factors for which consultation is recommended by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) are shown in Table 9-3. Some conditions may require the involvement of a maternal-fetal medicine subspecialist, geneticist, pediatrician, anesthesiologist, or other medical specialist in the evaluation, counseling, and care of the woman and her fetus.

TABLE 9-3

Conditions for Which Maternal-Fetal Medicine Consultation May Be Beneficial

Medical History and Conditions
Cardiac disease—moderate to severe disorders
Diabetes mellitus with evidence of end-organ damage or uncontrolled hyperglycemia
Family or personal history of genetic abnormalities
Hemoglobinopathy
Chronic hypertension if uncontrolled or associated with renal or cardiac disease
Renal insufficiency if associated with significant proteinuria (≥500 mg/24 hour), serum creatinine ≥1.5 mg/dL, or hypertension
Pulmonary disease if severe restrictive or obstructive, including severe asthma
Human immunodeficiency virus infection
Prior pulmonary embolus or deep-vein thrombosis
Severe systemic disease, including autoimmune conditions
Bariatric surgery
Epilepsy if poorly controlled or requires more than one anticonvulsant
Cancer, especially if treatment is indicated in pregnancy
Obstetrical History and Conditions
CDE (Rh) or other blood group alloimmunization (excluding ABO, Lewis)
Prior or current fetal structural or chromosomal abnormality
Desire or need for prenatal diagnosis or fetal therapy
Periconceptional exposure to known teratogens
Infection with or exposure to organisms that cause congenital infection
Higher-order multifetal gestation
Severe disorders of amnionic fluid volume

SUBSEQUENT PRENATAL VISITS

These are traditionally scheduled at 4-week intervals until 28 weeks, then every 2 weeks until 36 weeks, and weekly thereafter. Women with complicated pregnancies—for example, with twins or diabetes—often require return visits at 1- to 2-week intervals (Luke, 2003; Power, 2013). In 1986, the Department of Health and Human Services convened an expert panel to review the content of prenatal care. This report was subsequently reevaluated and revised in 2005 (Gregory, 2006). The panel recommended, among other things, early and continuing risk assessment that is patient specific. It also endorsed flexibility in clinical visit spacing; health promotion and education, including preconceptional care; medical and psychosocial interventions; standardized documentation; and expanded prenatal care objectives—to include family health up to 1 year after birth.

The World Health Organization conducted a multicenter randomized trial with almost 25,000 women comparing routine prenatal care with an experimental model designed to minimize visits (Villar, 2001). In the new model, women were seen once in the first trimester and screened for certain risks. Those without anticipated complications—80 percent of those screened—were seen again at 26, 32, and 38 weeks. Compared with routine prenatal care, which required a median of eight visits, the new model required a median of only five. No disadvantages were attributed to the regimen with fewer visits, and these findings were consistent with other randomized trials (Clement, 1999; McDuffie, 1996).

Prenatal Surveillance

At each return visit, the well-being of mother and fetus are assessed (see Table 9-1). Fetal heart rate, growth, and activity and amnionic fluid volume are evaluated. Maternal blood pressure and weight and their extent of change are examined. Symptoms such as headache, altered vision, abdominal pain, nausea and vomiting, bleeding, vaginal fluid leakage, and dysuria are sought. After 20 weeks' gestation, uterine examination measures size from the symphysis to the fundus. In late pregnancy, vaginal examination often provides valuable information that includes confirmation of the presenting part and its station, clinical estimation of pelvic capacity and configuration, amnionic fluid volume adequacy, and cervical consistency, effacement, and dilatation (Chap. 22, Identification of Labor).

Fundal Height

Between 20 and 34 weeks' gestation, the height of the uterine fundus measured in centimeters correlates closely with gestational age in weeks (Jimenez, 1983). This measurement is used to monitor fetal growth and amnionic fluid volume. It is measured along the abdominal wall from the top of the symphysis pubis to the top of the fundus. Importantly, the bladder must be emptied before fundal measurement (Worthen, 1980). Obesity or the presence of uterine masses such as

leiomyomas may also limit fundal height accuracy. Moreover, using fundal height alone, fetal-growth restriction may be undiagnosed in up to a third of cases (American College of Obstetricians and Gynecologists, 2015b; Haragan, 2015).

Fetal Heart Sounds

Instruments incorporating Doppler ultrasound are often used to easily detect fetal heart action, and in the absence of maternal obesity, heart sounds are almost always detectable by 10 weeks with such instruments (Chap. 10, Doppler). The fetal heart rate ranges from 110 to 160 beats per minute and is typically heard as a double sound. Using a standard nonamplified stethoscope, the fetal heart is audible by 20 weeks in 80 percent of women, and by 22 weeks, heart sounds are expected to be heard in all (Herbert, 1987). Because the fetus moves freely in amnionic fluid, the site on the maternal abdomen where fetal heart sounds can be heard best will vary.

Additionally, with ultrasonic auscultation, one may hear the *funic souffle,* which is a sharp, whistling sound that is synchronous with the fetal pulse. It is caused by the rush of blood through the umbilical arteries and may not be heard consistently. In contrast, the *uterine souffle* is a soft, blowing sound that is synchronous with the maternal pulse. It is produced by the passage of blood through the dilated uterine vessels and is heard most distinctly near the lower portion of the uterus.

Sonography

Sonography provides invaluable information regarding fetal anatomy, growth, and well-being, and most women in the United States have at least one prenatal sonographic examination during pregnancy (American College of Obstetricians and Gynecologists, 2016h). Continuing trends suggest that the number of these examinations performed per pregnancy is increasing. Siddique and associates (2009) reported that the average number rose from 1.5 in 1995 through 1997 to 2.7 almost 10 years later. This trend was noted in both high- and low-risk pregnancies. The actual clinical utility of this increased use in pregnancy has not been demonstrated, and it is unclear that the cost-benefit ratio is justified (Washington State Health Care Authority, 2010). The American College of Obstetricians and Gynecologists (2016h) has concluded that sonography should be performed only when there is a valid medical indication and under the lowest possible ultrasound exposure setting. The College further states that a physician is not obligated to perform sonography without a specific indication in a low-risk patient, but that if she requests sonographic screening, it is reasonable to honor her request.

Subsequent Laboratory Tests

If initial results were normal, most tests need not be repeated. Hematocrit or hemoglobin determination, along with serology for syphilis if it is prevalent in the population, is repeated at 28 to 32 weeks (Hollier, 2003; Kiss, 2004). For women at increased risk for HIV acquisition during pregnancy, repeat testing is recommended in the third trimester, preferably before 36 weeks (American College of Obstetricians and Gynecologists, 2016f). Similarly, women who engage in behaviors that place them at high risk for hepatitis B virus infection are retested at the time of hospitalization for delivery. Women who are D (Rh) negative and are unsensitized should have an antibody screening test repeated at 28 to 29 weeks, and anti-D immunoglobulin is given if they remain unsensitized (Chap. 15, Prevention of Anti-D Alloimmunization).

Group B Streptococcal Infection

The CDC (2010b) recommends that vaginal and rectal group B streptococcal (GBS) cultures be obtained in all women between 35 and 37 weeks' gestation, and the American College of Obstetricians and Gynecologists (2016g) has endorsed this recommendation. Intrapartum antimicrobial prophylaxis is provided to those whose culture results are positive. Women with GBS bacteriuria or a previous infant with invasive disease are given empirical intrapartum prophylaxis. Trials are in progress to test an investigational vaccine (Donders, 2016; Schrag, 2016). These infections are described further in Chapter 64 (Bacterial Infections).

Gestational Diabetes

All pregnant women are screened for gestational diabetes mellitus, whether by history, clinical factors, or routine laboratory testing. Although laboratory testing between 24 and 28 weeks' gestation is the most sensitive approach, there may be pregnant women at low risk who are less likely to benefit from testing (American College of Obstetricians and Gynecologists, 2017c). Gestational diabetes is discussed in Chapter 57 (Gestational Diabetes).

Neural-Tube Defect and Genetic Screening

Serum screening for neural-tube defects is offered at 15 to 20 weeks. Fetal aneuploidy screening may be performed at 11 to 14 weeks' gestation and/or at 15 to 20 weeks, depending on the protocol selected (Rink, 2016). Additionally, screening for certain genetic abnormalities is offered to women at increased risk based on family history, ethnic or racial background, or age (American College of Obstetricians and Gynecologists, 2017h). These are discussed in greater detail in Chapter 14 (Historical Perspective). Some examples include testing for Tay-Sachs disease for persons of Eastern European Jewish or French Canadian ancestry; β-thalassemia for those of Mediterranean, Southeast Asian, Indian, Pakistani, or African ancestry; α-thalassemia for individuals of Southeast Asian or African ancestry; sickle-cell anemia for people of African, Mediterranean, Middle Eastern, Caribbean, Latin American, or Indian descent; and trisomy 21 for those with advanced maternal age.

NUTRITIONAL COUNSELING

Weight Gain Recommendations

In 2009, the Institute of Medicine and National Research Council revised guidelines for weight gain in pregnancy and continued to stratify suggested weight gain ranges based on prepregnancy body mass index (BMI) (Table 9-4). The new guidelines included a specific, relatively narrow range of recommended weight gains for obese women. Also, the same recommendations apply to adolescents, short women, and women of all racial and ethnic groups. The American College of Obstetricians and Gynecologists (2016i) has endorsed these measures.

TABLE 9-4

Recommendations for Total and Rate of Weight Gain During Pregnancy

Category (BMI)	Total Weight Gain Range (lb)[a]	Weight Gain in 2nd and 3rd Trimesters Mean in lb/wk (range)
Underweight (<18.5)	28–40	1 (1–1.3)
Normal weight (18.5–24.9)	25–35	1 (0.8–1)
Overweight (25.0–29.9)	15–25	0.6 (0.5–0.7)
Obese (≥30.0)	11–20	0.5 (0.4–0.6)

[a]Empirical recommendations for weight gain in twin pregnancies include: normal BMI, 37–54 lb; overweight women, 31–50 lb; and obese women, 25–42 lb.

BMI = body mass index.

Modified from the Institute of Medicine and National Research Council, 2009.

When the Institute of Medicine guidelines were formulated, concern focused on low-birthweight newborns, however, current emphasis is directed to the obesity epidemic (Catalano, 2007). This explains renewed interest in *lower* weight gains during pregnancy. Obesity is associated with significantly greater risks for gestational hypertension, preeclampsia, gestational diabetes, macrosomia, cesarean delivery, and other complications (Chap. 48, Maternal Morbidity). The risk appears "dose related" to prenatal weight gain. In a population-based cohort of more than 120,000 obese pregnant women, those who gained *<15 lb* had the lowest rates of preeclampsia, large-for-gestational age neonates, and cesarean delivery (Kiel, 2007). Among 100,000 women with normal prepregnancy BMI, DeVader and colleagues (2007) found that those who gained <25 lb during pregnancy had a lower risk for preeclampsia, failed induction, cephalopelvic disproportion, cesarean delivery, and large-for-gestational age neonates. This cohort, however, had an increased risk for small-for-gestational age newborns. Lifestyle intervention during pregnancy can result in less weight gain (Sagedal, 2017).

There is irrefutable evidence that maternal weight gain during pregnancy influences birthweight. Martin and coworkers (2009) studied this using birth certificate data for 2006. Approximately 60 percent of women gained 26 lb or more during pregnancy, and maternal weight gain positively correlated with birthweight. Moreover, women with the greatest risk— 14 percent—for delivering a newborn weighing <2500 g were those with weight gain <16 lb. Nearly 20 percent of births to women with such low weight gains were preterm.

Severe Undernutrition

Meaningful studies of nutrition in human pregnancy are exceedingly difficult to design because experimental dietary deficiency is not ethical. In those instances in which severe nutritional deficiencies have been induced as a consequence of social, economic, or political disaster, coincidental events have often created many variables, the effects of which are not amenable to quantification. Some past experiences suggest, however, that in otherwise healthy women, a state of near starvation is required to establish clear differences in pregnancy outcome.

During the severe European winter of 1944 to 1945, nutritional deprivation of known intensity prevailed in a well-circumscribed area of The Netherlands occupied by the German military (Kyle, 2006). At the lowest point during this Dutch Hunger Winter, rations reached 450 kcal/d, with generalized rather than selective malnutrition. Smith (1947) analyzed the outcomes of pregnancies that were in progress during this 6-month famine. Median neonatal birthweights declined approximately 250 g and rose again after food became available. This indicated that birthweight can be influenced significantly by starvation during later pregnancy. The perinatal mortality rate, however, was not altered. Moreover, the incidence of fetal malformations or preeclampsia did not rise significantly. Parenthetically, weight loss in obese women during pregnancy is also associated with an increased risk for low-birthweight neonates (Cox Bauer, 2016).

Evidence of impaired brain development has been obtained in some animal fetuses whose mothers had been subjected to intense dietary deprivation. Subsequent intellectual development was studied by Stein and associates (1972) in young male adults whose mothers had been starved during pregnancy in the aforementioned Hunger Winter. The comprehensive study was made possible because all males at age 19 underwent compulsory examination for military service. It was concluded that severe dietary deprivation during pregnancy caused no detectable effects on subsequent mental performance.

Several studies of the long-term consequences to this cohort of children born to nutritionally deprived women have been performed and have been reviewed by Kyle and Pichard (2006). Progeny deprived in mid to late pregnancy were lighter, shorter, and thinner at birth, and they had a higher incidences of subsequent hypertension, reactive airway disease, dyslipidemia, diminished glucose tolerance, and coronary artery disease. Early pregnancy deprivation was associated with greater obesity rates in adult women but not men. Early starvation was also linked to higher rates of central nervous system anomalies, schizophrenia, and schizophrenia-spectrum personality disorders.

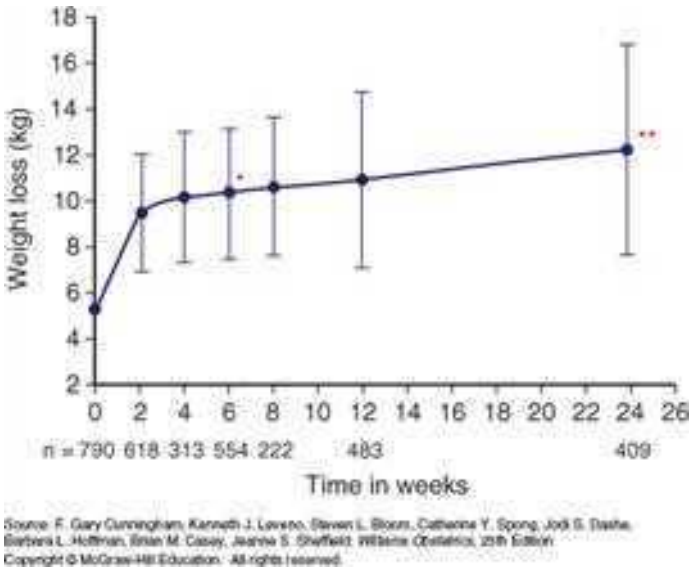
These observations and others have led to the concept of *fetal programming* by which adult morbidity and mortality are related to fetal health. Known widely as the *Barker hypothesis*, as promulgated by Barker and colleagues (1989), this concept is discussed in Chapter 44 (Placental Abnormalities).

Weight Retention after Pregnancy

Not all the weight gained during pregnancy is lost during and immediately after delivery. Schauberger and coworkers (1992) studied prenatal and postpartum weights in 795 women. Their average weight gain was 28.6 lb or 12.9 kg. As shown in Figure 9-4, most maternal weight loss was at delivery—approximately 12 lb or 5.4 kg—and in the ensuing 2 weeks—approximately 9 lb or 4 kg. An additional 5.5 lb or 2.5 kg was lost between 2 weeks and 6 months postpartum. Thus, average retained pregnancy weight was 2.1 lb or 1 kg. Excessive weight gain is manifest by accrual of fat and may be partially retained as long-term fat (Berggren, 2016; Widen, 2015). Overall, the more weight that was gained during pregnancy, the more that was lost postpartum. Interestingly, there is no relationship between prepregnancy BMI or prenatal weight gain and weight retention.

FIGURE 9-4

Cumulative weight loss from last antepartum visit to 6 months postpartum. *Significantly different from 2-week weight loss; **Significantly different from 6-week weight loss. (Redrawn from Schauberger CW, Rooney BL, Brimer LM: Factors that influence weight loss in the puerperium. Obstet Gynecol 79:424, 1992.)



Dietary Reference Intakes—Recommended Allowances

Periodically, the Institute of Medicine (2006, 2011) publishes recommended dietary allowances, including those for pregnant or lactating women. The latest recommendations are summarized in Table 9-5. Certain prenatal vitamin–mineral supplements may lead to intakes well in excess of the recommended allowances. Moreover, the use of excessive supplements, which often are self-prescribed, has led to concern regarding nutrient toxicities during pregnancy. *Those with potentially toxic effects include iron, zinc, selenium, and vitamins A, B_6, C, and D.*

TABLE 9-5

Recommended Daily Dietary Allowances for Pregnant and Lactating Women

	Pregnant	Lactating
Fat-Soluble Vitamins		
Vitamin A	770 µg	1300 µg
Vitamin D[a]	15 µg	15 µg
Vitamin E	15 mg	19 mg
Vitamin K[a]	90 µg	90 µg
Water-Soluble Vitamins		
Vitamin C	85 mg	120 mg
Thiamine	1.4 mg	1.4 mg
Riboflavin	1.4 mg	1.6 mg
Niacin	18 mg	17 mg
Vitamin B_6	1.9 mg	2 mg
Folate	600 µg	500 µg
Vitamin B_{12}	2.6 µg	2.8 µg
Minerals		
Calcium[a]	1000 mg	1000 mg
Sodium[a]	1.5 g	1.5 g
Potassium[a]	4.7 g	5.1 g
Iron	27 mg	9 mg
Zinc	11 mg	12 mg
Iodine	220 µg	290 µg
Selenium	60 µg	70 µg
Other		
Protein	71 g	71 g
Carbohydrate	175 g	210 g
Fiber[a]	28 g	29 g

[a]Recommendations measured as adequate intake.

From the Institute of Medicine, 2006, 2011.

Calories

As shown in Figure 9-5, pregnancy requires an additional 80,000 kcal, mostly during the last 20 weeks. To meet this demand, a caloric increase of 100 to 300 kcal/d is recommended during pregnancy (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2017). This greater intake, however, should not be divided equally during the course of pregnancy. The Institute of Medicine (2006) recommends adding 0, 340, and 452 kcal/d to the estimated nonpregnant energy requirements in the first, second, and third trimesters, respectively. The addition of 1000 kcal/d or more results in fat accrual (Jebeile, 2015).

FIGURE 9-5
Cumulative kilocalories required for pregnancy. (Redrawn from Chamberlain G, Broughton-Pipkin F (eds): Clinical Physiology in Obstetrics, 3rd ed. Oxford, Blackwell Science, 1998.)

Calories are necessary for energy. Whenever caloric intake is inadequate, protein is metabolized rather than being spared for its vital role in fetal growth and development. Total physiological requirements during pregnancy are not necessarily the sum of ordinary nonpregnant requirements plus those specific to pregnancy. For example, the additional energy required during pregnancy may be compensated in whole or in part by reduced physical activity (Hytten, 1991).

Protein

Protein requirements rise to meet the demands for growth and remodeling of the fetus, placenta, uterus, and breasts, and for increased maternal blood volume (Chap. 4, Protein Metabolism). During the second half of pregnancy, approximately 1000 g of protein are deposited, amounting to 5 to 6 g/d (Hytten, 1971). To accomplish this, protein intake that approximates 1 g/kg/d is recommended (see Table 9-5). Data suggest this should be doubled in late gestation (Stephens, 2015). Most amino-acid levels in maternal plasma fall markedly, including ornithine, glycine, taurine, and proline (Hytten, 1991). Exceptions during pregnancy are glutamic acid and alanine, the concentrations of which rise.

Preferably, most protein is supplied from animal sources, such as meat, milk, eggs, cheese, poultry, and fish. These furnish amino acids in optimal combinations. Milk and dairy products are considered nearly ideal sources of nutrients, especially protein and calcium, for pregnant or lactating women. Ingestion of specific fish and potential methylmercury toxicity are discussed in Common Concerns.

Minerals

The intakes recommended by the Institute of Medicine (2006) for various minerals are listed in Table 9-5. With the exception of iron and iodine, practically all diets that supply sufficient calories for appropriate weight gain will contain enough minerals to prevent deficiency.

Iron requirements are greatly increased during pregnancy, and reasons for this are discussed in Chapter 4 (Iron Metabolism). Of the approximately 300 mg of iron transferred to the fetus and placenta and the 500 mg incorporated into the expanding maternal hemoglobin mass, nearly all is used after midpregnancy. During that time, iron requirements imposed by pregnancy and maternal excretion total approximately 7 mg/d (Pritchard, 1970). Few women have sufficient iron stores or dietary intake to supply this amount. Thus, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) endorse the recommendation by the National Academy of Sciences that at least 27 mg of elemental iron be supplemented daily to pregnant women. This amount is contained in most prenatal vitamins.

Scott and coworkers (1970) established that as little as 30 mg of elemental iron, supplied as ferrous gluconate, sulfate, or fumarate and taken daily throughout the latter half of pregnancy, provides sufficient iron to meet pregnancy requirements and protect preexisting iron stores. This amount will also provide for iron requirements of lactation. The pregnant woman may benefit from 60 to 100 mg of elemental iron per day if she is large, has a multifetal gestation, begins supplementation late in pregnancy, takes iron irregularly, or has a somewhat depressed hemoglobin level. The woman who is overtly anemic from iron deficiency responds well to oral supplementation with iron salts. In response, serum ferritin levels rise more than the hemoglobin concentration (Daru, 2016).

Iodine is also needed, and the recommended iodine allowance is 220 µg/d (see Table 9-5). The use of iodized salt and bread products is recommended during pregnancy to offset the increased fetal requirements and maternal renal losses of iodine. Despite this, iodine intake has declined substantially in the past 15 years, and in some areas it is probably inadequate (Casey, 2017). Severe maternal iodine deficiency predisposes offspring to endemic cretinism, which is

characterized by multiple severe neurological defects. In parts of China and Africa where this condition is common, iodide supplementation very early in pregnancy prevents some cretinism cases (Cao, 1994). To obviate this, many prenatal supplements now contain various quantities of iodine.

Calcium is retained by the pregnant woman during gestation and approximates 30 g. Most of this is deposited in the fetus late in pregnancy (Pitkin, 1985). This amount of calcium represents only approximately 2.5 percent of total maternal calcium, most of which is in bone and can readily be mobilized for fetal growth. As another potential use, routine calcium supplementation to prevent preeclampsia has not proved effective (Chap. 40, Antihypertensive Drugs).

Zinc deficiency if severe may lead to poor appetite, suboptimal growth, and impaired wound healing. During pregnancy, the recommended daily intake approximates 12 mg. But, the safe level of zinc supplementation for pregnant women has not been clearly established. Vegetarians have lower zinc intakes (Foster, 2015). The bulk of studies support zinc supplementation only in zinc-deficient women in poor-resource countries (Nossier, 2015; Ota, 2015).

Magnesium deficiency as a consequence of pregnancy has not been recognized. Undoubtedly, during prolonged illness with no magnesium intake, the plasma level might become critically low, as it would in the absence of pregnancy. We have observed magnesium deficiency during pregnancies in some with previous intestinal bypass surgery. As a preventive agent, Sibai and coworkers (1989) randomly assigned 400 normotensive primigravid women to 365-mg elemental magnesium supplementation or placebo tablets from 13 to 24 weeks' gestation. Supplementation did not improve any measures of pregnancy outcome.

Trace metals include copper, selenium, chromium, and manganese, which all have important roles in certain enzyme functions. In general, most are provided by an average diet. Selenium deficiency is manifested by a frequently fatal cardiomyopathy in young children and reproductive-aged women. Conversely, selenium toxicity resulting from oversupplementation also has been observed. Selenium supplementation is not needed in American women.

Potassium concentrations in maternal plasma decline by approximately 0.5 mEq/L by midpregnancy (Brown, 1986). Potassium deficiency develops in the same circumstances as in nonpregnant individuals—a common example is hyperemesis gravidarum.

Fluoride metabolism is not altered appreciably during pregnancy (Maheshwari, 1983). Horowitz and Heifetz (1967) concluded that no additional offspring benefits accrued from maternal ingestion of fluoridated water if the newborn ingested such water from birth. Sa Roriz Fonteles and associates (2005) studied microdrill biopsies of deciduous teeth and concluded that antenatal fluoride provided no additional fluoride uptake compared with postnatal fluoride alone. Finally, supplemental fluoride ingested by lactating women does not raise the fluoride concentration in breast milk (Ekstrand, 1981).

Vitamins

The increased requirements for most vitamins during pregnancy shown in Table 9-5 usually are supplied by any general diet that provides adequate calories and protein. The exception is folic acid during times of unusual requirements, such as pregnancy complicated by protracted vomiting, hemolytic anemia, or multiple fetuses. That said, in impoverished countries, routine multivitamin supplementation reduced the incidence of low-birthweight and growth-restricted fetuses, but did not alter preterm delivery or perinatal mortality rates (Fawzi, 2007).

Folic acid supplementation in early pregnancy can lower neural-tube defect risks (Chap. 13, Genetic Tests). Namely, the CDC (2004) estimated that the number of affected pregnancies had decreased from 4000 pregnancies per year to approximately 3000 per year after mandatory fortification of cereal products with folic acid in 1998. Perhaps more than half of all neural-tube defects can be prevented with daily intake of 400 µg of folic acid throughout the periconceptional period. Evidence also suggests that folate insufficiency has a global effect on brain development (Ars, 2016). Putting 140 µg of folic acid into each 100 g of grain products may increase the folic acid intake of the average American woman of childbearing age by 100 µg/d. Because nutritional sources alone are insufficient, however, folic acid supplementation is still recommended (American College of Obstetricians and Gynecologists, 2016e). Likewise, the U.S. Preventive Services Task Force (2009) recommends that all women planning or capable of pregnancy take a daily supplement containing 400 to 800 µg of folic acid.

A woman with a prior child with a neural-tube defect can reduce the 2- to 5-percent recurrence risk by more than 70 percent with a daily 4-mg folic acid supplement taken during the month before conception and during the first trimester. As emphasized by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), this dose should be consumed as a separate supplement and not as multivitamin tablets. This practice avoids excessive intake of fat-soluble vitamins.

Vitamin A, although essential, has been associated with congenital malformations when taken in high doses (>10,000 IU/d) during pregnancy. These malformations are similar to those produced by the vitamin A derivative isotretinoin (Accutane*)*, which is a potent teratogen (Chap. 12, Retinoids). Beta-carotene, the precursor of vitamin A found in fruits and vegetables, has not been shown to produce vitamin A toxicity. Most prenatal vitamins contain vitamin A in doses considerably below the teratogenic threshold. Dietary intake of vitamin A in the United States appears to be adequate, and additional supplementation is not routinely recommended. In contrast, vitamin A deficiency is an endemic nutritional problem in the developing world (McCauley, 2015). Vitamin A deficiency, whether overt or subclinical, is associated with night blindness and with an increased risk of maternal anemia and spontaneous preterm birth (West, 2003).

Vitamin B_{12} plasma levels drop in normal pregnancy, mostly as a result of reduced plasma levels of their carrier proteins—*transcobalamins*. Vitamin B_{12} occurs naturally only in foods of animal origin, and strict vegetarians may give birth to neonates whose B_{12} stores are low. Likewise, because breast milk of a vegetarian mother contains little vitamin B_{12}, the deficiency may become profound in the breastfed infant (Higginbottom, 1978). Excessive ingestion of vitamin C also can lead to a functional deficiency of vitamin B_{12}. Although its role is still controversial, vitamin B_{12} deficiency preconceptionally, similar to folate, may elevate the risk of neural-tube defects (Molloy, 2009).

Vitamin B_6, which is pyridoxine, does not require supplementation in most gravidas (Salam, 2015). For women at high risk for inadequate nutrition, a daily 2-mg supplement is recommended. As discussed in Caffeine, vitamin B_6, when combined with the antihistamine *doxylamine,* is helpful in many cases of nausea and vomiting of pregnancy.

Vitamin C allowances during pregnancy are 80 to 85 mg/d—approximately 20 percent more than when nonpregnant (see Table 9-5). A reasonable diet should readily provide this amount, and supplementation is not necessary (Rumbold, 2015). Maternal plasma levels decline during pregnancy, whereas cord-blood levels are higher, a phenomenon observed with most water-soluble vitamins.

Vitamin D is a fat-soluble vitamin. After being metabolized to its active form, it boosts the efficiency of intestinal calcium absorption and promotes bone mineralization and growth. Unlike most vitamins that are obtained exclusively from dietary intake, vitamin D is also synthesized endogenously with exposure to sunlight. Vitamin D deficiency is common during pregnancy. This is especially true in high-risk groups such as women with limited sun exposure, vegetarians, and ethnic minorities—particularly those with darker skin (Bodnar, 2007). Maternal deficiency can cause disordered skeletal homeostasis, congenital rickets, and fractures in the newborn (American College of Obstetricians and Gynecologists, 2017k). Vitamin D supplementation to women with asthma may decrease the likelihood of childhood asthma in their fetuses (Litonjua, 2016). The Food and Nutrition Board of the Institute of Medicine (2011) established that an adequate intake of vitamin D during pregnancy and lactation was 15 µg/d (600 IU/d). In women suspected of having vitamin D deficiency, serum levels of 25-hydroxyvitamin D can be obtained. Even then, the optimal levels in pregnancy have not been established (De-Regil, 2016).

Pragmatic Nutritional Surveillance

Although researchers continue to study the ideal nutritional regimen for the pregnant woman and her fetus, basic tenets for the clinician include:

1. Advise the pregnant woman to eat food types she wants in reasonable amounts and salted to taste.
2. Ensure that food is amply available for socioeconomically deprived women.
3. Monitor weight gain, with a goal of approximately 25 to 35 lb in women with a normal BMI.
4. Explore food intake by dietary recall periodically to discover the occasional nutritionally errant diet.
5. Give tablets of simple iron salts that provide at least 27 mg of elemental iron daily. Give folate supplementation before and in the early weeks of pregnancy. Provide iodine supplementation in areas of known dietary insufficiency.
6. Recheck the hematocrit or hemoglobin concentration at 28 to 32 weeks' gestation to detect significant anemia.

COMMON CONCERNS

Employment

More than half of the children in the United States are born to working mothers. Federal law prohibits employers from excluding women from job categories on the basis that they are or might become pregnant. The Family and Medical Leave Act of 1993 requires that covered employers must grant up to 12 work weeks of unpaid leave to an employee for the birth and care of a newborn child (Jackson, 2015). In the absence of complications, most women can continue to work until the onset of labor (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2017).

Some types of work, however, may increase pregnancy complication risks. Mozurkewich and colleagues (2000) reviewed 29 studies that involved more than 160,000 pregnancies. With physically demanding work, women had 20- to 60-percent higher rates of preterm birth, fetal-growth restriction, or gestational hypertension. In a prospective study of more than 900 healthy nulliparas, women who worked had a fivefold risk of preeclampsia (Higgins, 2002). Newman and coworkers (2001) reported outcomes in more than 2900 women with singleton pregnancies. Occupational fatigue—estimated by the number of hours standing, intensity of physical and mental demands, and environmental stressors—was associated with an increased risk of preterm premature membrane rupture. For women reporting the highest degrees of fatigue, the risk was 7.4 percent.

Thus, any occupation that subjects the gravida to severe physical strain should be avoided. Ideally, no work or play is continued to the extent that undue fatigue develops. Adequate periods of rest should be provided. It seems prudent to advise women with prior pregnancy complications that commonly recur to minimize physical work.

Exercise

In general, pregnant women do not need to limit exercise, provided they do not become excessively fatigued or risk injury (Davenport, 2016). Clapp and associates (2000) reported that both placental size and birthweight were significantly greater in women who exercised. Duncombe and coworkers (2006) reported similar findings in 148 women. In contrast, Magann and colleagues (2002) prospectively analyzed exercise behavior in 750 healthy women and found that working women who exercised had smaller infants and more dysfunctional labors.

The American College of Obstetricians and Gynecologists (2017g) advises a thorough clinical evaluation before recommending an exercise program. In the absence of contraindications listed in Table 9-6, pregnant women are encouraged to engage in regular, moderate-intensity physical activity for at least 150 minutes each week. Each activity should be reviewed individually for its potential risk. Examples of safe activities are walking, running, swimming, stationary

cycling, and low-impact aerobics. However, they should refrain from activities with a high risk of falling or abdominal trauma. Similarly, scuba diving is avoided because the fetus is at increased risk for decompression sickness.

TABLE 9-6

Some Contraindications to Exercise During Pregnancy

Significant cardiovascular or pulmonary disease
Significant risk for preterm labor: cerclage, multifetal gestation, significant bleeding, threatened preterm labor, prematurely ruptured membranes
Obstetrical complications: preeclampsia, placenta previa, anemia, poorly controlled diabetes or epilepsy, morbid obesity, fetal-growth restriction

Summarized from American College of Obstetricians and Gynecologists, 2017g.

In the setting of certain pregnancy complications, it is wise to abstain from exercise and even limit physical activity. For example, some women with pregnancy-associated hypertensive disorders, preterm labor, placenta previa, or severe cardiac or pulmonary disease may gain from being sedentary. Also, those with multiple or suspected growth-restricted fetuses may be served by greater rest.

Seafood Consumption

Fish are an excellent source of protein, are low in saturated fats, and contain omega-3 fatty acids. The Avon Longitudinal Study of Parents and Children reported beneficial effects on pregnancy outcomes in women who consumed 340 g or more of seafood weekly (Hibbeln, 2007). Because nearly all fish and shellfish contain trace amounts of mercury, pregnant and lactating women are advised to avoid specific types of fish with potentially high methylmercury levels. These include shark, swordfish, king mackerel, and tile fish. It is further recommended that pregnant women ingest 8 to 12 ounces of fish weekly, but no more than 6 ounces of albacore or "white" tuna (U.S. Environmental Protection Agency, 2014). If the mercury content of locally caught fish is unknown, then overall fish consumption should be limited to 6 ounces per week (American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2017).

Lead Screening

Maternal lead exposure has been associated with several adverse maternal and fetal outcomes across a range of maternal blood lead levels (Taylor, 2015). These include gestational hypertension, miscarriage, low birthweight, and neurodevelopmental impairments in exposed pregnancies (American College of Obstetricians and Gynecologists, 2016c). The levels at which these risks rise remains unclear. However, recognizing that such exposure remains a significant health issue for reproductive-aged women, the CDC (2010a) has issued guidance for screening and managing exposed pregnant and lactating women. These guidelines, which have been endorsed by the American College of Obstetricians and Gynecologists (2016c), recommend blood lead testing only if a risk factor is identified. If the levels are >5 µg/dL, then counseling is completed, and the lead source is sought and removed. Subsequent blood levels are obtained. Blood lead levels >45 µg/dL are consistent with lead poisoning, and women in this group may be candidates for chelation therapy. Affected pregnancies are best managed in consultation with lead poisoning treatment experts. National and state resources are available at the CDC website: www.cdc.gov/nceh/lead/.

Automobile and Air Travel

Pregnant women are encouraged to wear properly positioned three-point restraints as protection against automobile crash injury (Chap. 47, Other Blunt Trauma). The lap portion of the restraining belt is placed under the abdomen and across her upper thighs. The belt should be comfortably snug. The shoulder belt also is firmly positioned between the breasts. Airbags should not be disabled for the pregnant woman.

In general, air travel in a properly pressurized aircraft has no harmful effect on pregnancy (Aerospace Medical Association, 2003). Thus, in the absence of obstetrical or medical complications, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2016a, 2017) have concluded that pregnant women can safely fly up to 36 weeks' gestation. It is recommended that pregnant women observe the same precautions for air travel as the general population. Seatbelts are used while seated. Periodic lower extremity movement and at least hourly ambulation help lower the venous thromboembolism threat. Significant risks with travel, especially international travel, are infectious disease acquisition and development of complications remote from adequate health-care resources (Ryan, 2002).

Coitus

In healthy pregnant women, sexual intercourse usually is not harmful. Whenever miscarriage, placenta previa, or preterm labor threatens, however, coitus is avoided. Nearly 10,000 women enrolled in a prospective investigation by the Vaginal Infection and Prematurity Study Group were interviewed regarding sexual activity (Read, 1993). They reported a decreased frequency of coitus with advancing gestation. By 36 weeks, 72 percent had intercourse less than once weekly. The decline is attributed to lower desire and fear of harming the pregnancy (Bartellas, 2000; Staruch, 2016).

Intercourse specifically late in pregnancy is not harmful. Grudzinskas and coworkers (1979) noted no association between gestational age at delivery and coital frequency during the last 4 weeks of pregnancy. Sayle and colleagues (2001) reported no increased—and actually a decreased—risk of delivery within 2 weeks of

intercourse. Tan and associates (2007) studied women scheduled for nonurgent labor induction and found that spontaneous labor ensued at equal rates in groups either participating in or abstaining from intercourse.

Oral-vaginal intercourse is occasionally hazardous. Aronson and Nelson (1967) described a fatal air embolism late in pregnancy as a result of air blown into the vagina during cunnilingus. Other near-fatal cases have been described (Bernhardt, 1988).

Dental Care

Examination of the teeth is included in the prenatal examination, and good dental hygiene is encouraged. Indeed, periodontal disease has been linked to preterm labor. Unfortunately, although its treatment improves dental health, it does not prevent preterm birth (Michalowicz, 2006). Dental caries are not aggravated by pregnancy. Importantly, pregnancy is not a contraindication to dental treatment including dental radiographs (Giglio, 2009).

Immunization

Current recommendations for immunization during pregnancy are summarized in Table 9-7. Well-publicized concerns regarding a causal link between childhood exposure to the thimerosal preservative in some vaccines and neuropsychological disorders have led to some parents to vaccine prohibition. Although controversy continues, these associations have proven groundless (Sugarman, 2007; Thompson, 2007; Tozzi, 2009). Thus, many vaccines may be used in pregnancy. The American College of Obstetricians and Gynecologists (2016b) stresses the importance of integrating an effective vaccine strategy into the care of both obstetrical and gynecological patients. The College further emphasizes that information on the safety of vaccines given during pregnancy is subject to change, and recommendations can be found on the CDC website at www.cdc.gov/vaccines.

TABLE 9-7

Recommendations for Immunization During Pregnancy

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Live Attenuated Virus Vaccines			
Measles	Contraindicated—see immune globulins	Single dose SC, preferably as MMR[a]	Vaccinate susceptible women postpartum. Breastfeeding is not a contraindication
Mumps	Contraindicated	Single dose SC, preferably as MMR	Vaccinate susceptible women postpartum
Rubella	Contraindicated, but congenital rubella syndrome has never been described after vaccine	Single dose SC, preferably as MMR	Teratogenicity of vaccine is theoretical and not confirmed to date; vaccinate susceptible women postpartum
Poliomyelitis oral = live attenuated; injection = enhanced-potency inactivated virus	Not routinely recommended for women in the United States, except women at increased risk of exposure[b]	Primary: Two doses of enhanced-potency inactivated virus SC at 4- to 8-week intervals and a 3rd dose 6–12 months after 2nd dose Immediate protection: One dose oral polio vaccine (in outbreak setting)	Vaccine indicated for susceptible women traveling in endemic areas or in other high-risk situations
Yellow fever	Travel to high-risk areas	Single dose SC	Limited theoretical risk outweighed by risk of yellow fever
Varicella	Contraindicated, but no adverse outcomes reported in pregnancy	Two doses needed: 2nd dose given 4–8 weeks after 1st dose	Teratogenicity of vaccine is theoretical. Vaccination of susceptible women should be considered postpartum
Smallpox (vaccinia)	Contraindicated in pregnant women and in their household contacts	One dose SC, multiple pricks with lancet	Only vaccine known to cause fetal harm
Other			
Influenza	All pregnant women, regardless of trimester during flu season (October–May)	One dose IM every year	Inactivated virus vaccine
Rabies	Indications for prophylaxis not altered by pregnancy; each case considered individually	Public health authorities to be consulted for indications, dosage, and route of administration	Killed-virus vaccine
Human papillomavirus	Not recommended	Three-dose series IM at 0, 1, and 6 months	Polyvalent vaccines available containing inactivated virus. No teratogenicity has been observed
Hepatitis B	Preexposure and postexposure for women at risk of infection, e.g., chronic liver or kidney disease	Three-dose series IM at 0, 1, and 6 months	Used with hepatitis B immune globulin for some exposures. Exposed newborn needs birth-dose vaccination and immune globulin as soon as possible. All infants should receive birth dose of vaccine
Hepatitis A	Preexposure and postexposure if at risk (international travel); chronic liver disease	Two-dose schedule IM, 6 months apart	Inactivated virus
Inactivated Bacterial Vaccines			

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Pneumococcus	Indications not altered by pregnancy. Recommended for women with asplenia; metabolic, renal, cardiac, or pulmonary diseases; immunosuppression; or smokers	In adults, one dose only; consider repeat dose in 6 years for high-risk women	Polyvalent polysaccharide vaccine; safety in the first trimester has not been evaluated
Meningococcus	Indications not altered by pregnancy; vaccination recommended in unusual outbreaks	One dose; tetravalent vaccine; two doses for asplenia	Antimicrobial prophylaxis if significant exposure
Typhoid	Not recommended routinely except for close, continued exposure or travel to endemic areas	Killed Primary: 2 injections IM 4 weeks apart Booster: One dose; schedule not yet determined	Killed, injectable vaccine or live attenuated oral vaccine. Oral vaccine preferred
Anthrax	Chapter 64 (Mycotic Infections)	Six-dose primary vaccination, then annual booster vaccination	Preparation from cell-free filtrate of *B anthracis*. No dead or live bacteria. Teratogenicity of vaccine theoretical
Toxoids			
Tetanus-diphtheria-acellular pertussis (Tdap)	Recommended in every pregnancy, preferably between 27 and 36 weeks to maximize passive antibody transfer	Primary: Two doses IM at 1–2 month interval with 3rd dose 6–12 months after the 2nd Booster: Single dose IM every 10 years, as a part of wound care if ≥ 5 years since last dose, or once per pregnancy	Combined tetanus-diphtheria toxoids with acellular pertussis (Tdap) preferred. Updating immune status should be part of antepartum care
Specific Immune Globulins			
Hepatitis B	Postexposure prophylaxis	Depends on exposure (Chap. 55, Pregnancy and Hepatitis B)	Usually given with hepatitis B virus vaccine; exposed newborn needs immediate prophylaxis
Rabies	Postexposure prophylaxis	Half dose at injury site, half dose in deltoid	Used in conjunction with rabies killed-virus vaccine
Tetanus	Postexposure prophylaxis	One dose IM	Used in conjunction with tetanus toxoid
Varicella	Should be considered for exposed pregnant women to protect against maternal, not congenital, infection	One dose IM within 96 hours of exposure	Indicated also for newborns or women who developed varicella within 4 days before delivery or 2 days following delivery
Standard Immune Globulins			
Hepatitis A: Hepatitis A virus vaccine should be used with hepatitis A immune globulin	Postexposure prophylaxis and those at high risk	0.02 mL/kg IM in one dose	Immune globulin should be given as soon as possible and within 2 weeks of exposure; infants born to women who are incubating the virus or are acutely ill at delivery should receive one dose of 0.5 mL as soon as possible after birth

[a]Two doses necessary for students entering institutions of higher education, newly hired medical personnel, and travel abroad.

[b]Inactivated polio vaccine recommended for nonimmunized adults at increased risk.

ID = intradermally; IM = intramuscularly; MMR = measles, mumps, rubella; PO = orally; SC = subcutaneously.

From the Centers for Disease Control and Prevention, 2011; Kim, 2016.

The frequency of pertussis infection has substantially risen in the United States. Young infants are at increased risk for death from pertussis and are entirely dependent on passive immunization from maternal antibodies until the infant vaccine series is initiated at age 2 months. For this reason, a three-agent tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended and is safe for pregnant women (Centers for Disease Control and Prevention, 2013b, 2016; Morgan, 2015). However, as demonstrated by Healy and coworkers (2013), maternal antipertussis antibodies are relatively short-lived, and Tdap administration before pregnancy—or even in the first half of the current pregnancy—is not likely to provide a high level of newborn antibody protection. Thus, to maximize passive antibody transfer to the fetus, a dose of Tdap is ideally given to gravidas between 27 and 36 weeks' gestation (American College of Obstetricians and Gynecologists, 2017j; Centers for Disease Control and Prevention, 2013b, 2016).

All women who will be pregnant during influenza season should be offered vaccination, regardless of gestational age. Those with underlying medical conditions that increase the risk for influenza complications are provided the vaccine before flu season starts. In addition to maternal protection against infection, prenatal maternal vaccination in one study reduced the infant influenza incidence in the first 6 months of life by 63 percent (Zaman, 2008). Moreover, it reduced all febrile respiratory illnesses in these infants by a third.

Women who are susceptible to rubella during pregnancy should receive measles, mumps, rubella (MMR) vaccination postpartum. Although this vaccine is not recommended during pregnancy, congenital rubella syndrome has never resulted from its inadvertent use. Breastfeeding is compatible with MMR vaccination (Centers for Disease Control and Prevention, 2011).

Caffeine

Whether adverse pregnancy outcomes are related to caffeine consumption is somewhat controversial. As summarized from Chapter 18 (Paternal Factors), heavy intake of coffee each day—about five cups or 500 mg of caffeine—slightly raises the miscarriage risk. Studies of "moderate" intake—less than 200 mg daily—did not find a higher risk.

It is unclear if caffeine consumption is associated with preterm birth or impaired fetal growth. Clausson and coworkers (2002) found no association between moderate caffeine consumption of less than 500 mg/d and low birthweight, fetal-growth restriction, or preterm delivery. Bech and associates (2007) randomly assigned more than 1200 pregnant women who drank at least three cups of coffee per day to caffeinated versus decaffeinated coffee. They found no difference in birthweight or gestational age at delivery between groups. The CARE Study Group (2008), however, evaluated 2635 low-risk pregnancies and reported a 1.4-fold risk for fetal-growth restriction among those whose daily caffeine consumption was >200 mg/d compared with those who consumed <100 mg/d. The American College of Obstetricians and Gynecologists (2016d) concludes that moderate consumption of caffeine—less than 200 mg/d—does not appear to be associated with miscarriage or preterm birth, but that the relationship between caffeine consumption and fetal-growth restriction remains unsettled. The American Dietetic Association (2008) recommends that caffeine intake during pregnancy be limited to less than 300 mg/d, which approximates three 5-oz cups of percolated coffee.

Nausea and Heartburn

Nausea and vomiting are common complaints during the first half of pregnancy. These vary in severity and usually commence between the first and second missed menstrual period and continue until 14 to 16 weeks' gestation. Although nausea and vomiting tend to be worse in the morning—thus erroneously termed *morning sickness*—both symptoms frequently continue throughout the day. Lacroix and coworkers (2000) found that nausea and vomiting were reported by three fourths of pregnant women and lasted an average of 35 days. Half had relief by 14 weeks, and 90 percent by 22 weeks. In 80 percent of these women, nausea lasted all day.

Treatment of pregnancy-associated nausea and vomiting seldom provides complete relief, but symptoms can be minimized. Eating small meals at frequent intervals is valuable. One systematic literature search reported that the herbal remedy ginger was likely effective (Borrelli, 2005). Mild symptoms usually respond to vitamin B_6 given along with doxylamine, but some women require phenothiazine or H_1-receptor blocking antiemetics (American College of Obstetricians and Gynecologists, 2015c). In some with *hyperemesis gravidarum,* vomiting is so severe that dehydration, electrolyte and acid-base disturbances, and starvation ketosis become serious problems.

Heartburn is another common complaint of gravidas and is caused by gastric content reflux into the lower esophagus. The greater frequency of regurgitation during pregnancy most likely results from upward displacement and compression of the stomach by the uterus, combined with relaxation of the lower esophageal sphincter. Avoiding bending over or lying flat is preventive. In most pregnant women, symptoms are mild and relieved by a regimen of more frequent but smaller meals. Antacids may provide considerable relief (Phupong, 2015). Specifically, aluminum hydroxide, magnesium trisilicate, or magnesium hydroxide is given alone or in combination. Management of heartburn or nausea that does not respond to simple measures is discussed in Chapter 54 (Management).

Pica and Ptyalism

The craving of pregnant women for strange foods is termed pica. Worldwide, its prevalence is estimated to be 30 percent (Fawcett, 2016). At times, nonfoods such as ice—pagophagia, starch—amylophagia, or clay—geophagia may predominate. This desire is considered by some to be triggered by severe iron deficiency. Although such cravings usually abate after deficiency correction, not all pregnant women with pica are iron deficient. Indeed, if strange "foods" dominate the diet, iron deficiency will be aggravated or will develop eventually.

Patel and coworkers (2004) prospectively completed a dietary inventory on more than 3000 women during the second trimester. The prevalence of pica was 4 percent. The most common nonfood items ingested were starch in 64 percent, dirt in 14 percent, sourdough in 9 percent, and ice in 5 percent. The prevalence of

anemia was 15 percent in women with pica compared with 6 percent in those without it. Interestingly, the rate of spontaneous preterm birth before 35 weeks was twice as high in women with pica.

Women during pregnancy are occasionally distressed by profuse salivation—*ptyalism*. Although usually unexplained, ptyalism sometimes appears to follow salivary gland stimulation by the ingestion of starch.

Headache or Backache

At least 5 percent of pregnancies are estimated to be complicated by new-onset or new-type headache (Spierings, 2016). Common headaches are virtually universal. Acetaminophen is suitable for most of these, and an in-depth discussion is found in Chapter 60 (Headache).

Low back pain to some extent is reported by nearly 70 percent of gravidas (Liddle, 2015; Wang, 2004). Minor degrees follow excessive strain or significant bending, lifting, or walking. It can be reduced by squatting rather than bending when reaching down, by using a back-support pillow when sitting, and by avoiding high-heeled shoes. Back pain complaints increase with progressing gestation and are more prevalent in obese women and those with a history of low back pain. In some cases, troublesome pain may persist for years after the pregnancy (Norén, 2002).

Severe back pain should not be attributed simply to pregnancy until a thorough orthopedic examination has been conducted. Severe pain has other uncommon causes that include pregnancy-associated osteoporosis, disc disease, vertebral osteoarthritis, or septic arthritis (Smith, 2008). More commonly, muscular spasm and tenderness are classified clinically as acute strain or fibrositis. Although evidence-based clinical research directing care in pregnancy is limited, low back pain usually responds well to analgesics, heat, and rest. Acetaminophen may be used chronically as needed. Nonsteroidal antiinflammatory drugs may also be beneficial but are used only in short courses to avoid fetal effects (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Muscle relaxants that include cyclobenzaprine or baclofen may be added when needed. Once acute pain is improved, stabilizing and strengthening exercises provided by physical therapy help improve spine and hip stability, which is essential for the increased load of pregnancy. For some, a support belt that stabilizes the sacroiliac joint may be helpful (Gutke, 2015).

Varicosities and Hemorrhoids

Venous leg varicosities have a congenital predisposition and accrue with advancing age. They can be aggravated by factors that raise lower extremity venous pressures, such as an enlarging uterus. Femoral venous pressures in the supine gravida rise from 8 mm Hg in early pregnancy to 24 mm Hg at term. Thus, leg varicosities typically worsen as pregnancy advances, especially with prolonged standing. Symptoms vary from cosmetic blemishes and mild discomfort at the end of the day to severe discomfort that requires prolonged rest with feet elevation. Treatment is generally limited to periodic rest with leg elevation, elastic stockings, or both. Surgical correction during pregnancy generally is not advised, although rarely the symptoms may be so severe that injection, ligation, or even stripping of the veins is necessary.

Vulvar varicosities frequently coexist with leg varicosities, but they may appear without other venous pathology. Uncommonly, they become massive and almost incapacitating. If these large varicosities rupture, blood loss can be severe. Treatment is with specially fitted pantyhose that will also minimize lower extremity varicosities. With particularly bothersome vulvar varicosities, a foam rubber pad suspended across the vulva by a belt can be used to exert pressure on the dilated veins.

Hemorrhoids are rectal vein varicosities and may first appear during pregnancy as pelvic venous pressures rise. Commonly, they are recurrences of previously encountered hemorrhoids. Up to 40 percent of pregnant women develop these (Poskus, 2014). Pain and swelling usually are relieved by topically applied anesthetics, warm soaks, and stool-softening agents. With thrombosis of an external hemorrhoid, pain can be considerable. This may be relieved by incision and removal of the clot following injection of a local anesthetic.

Sleeping and Fatigue

Beginning early in pregnancy, many women experience fatigue and need greater amounts of sleep. This likely is due to the soporific effect of progesterone but may be compounded in the first trimester by nausea and vomiting. In the latter stages, general discomforts, urinary frequency, and dyspnea can be additive. Sleep duration may be related to obesity and gestational weight gain (Facco, 2016; Lockhart, 2015). Moreover, sleep efficiency appears to progressively diminish as pregnancy advances. Wilson and associates (2011) performed overnight polysomnography and observed that women in the third trimester had poorer sleep efficiency, more awakenings, and less of both stage 4 (deep) and rapid-eye movement sleep. Women in the first trimester were also affected, but to a lesser extent. Daytime naps and mild sedatives at bedtime such as diphenhydramine (Benadryl) can be helpful.

Cord Blood Banking

Since the first successful cord blood transplantation in 1988, more than 25,000 umbilical cord blood transplantations have been performed to treat hemopoietic cancers and various genetic conditions (Butler, 2011). There are two types of cord blood banks. Public banks promote allogeneic donation, for use by a related or unrelated recipient, similar to blood product donation (Armson, 2015). Private banks were initially developed to store stem cells for future autologous use and charged fees for initial processing and annual storage. The American College of Obstetricians and Gynecologists (2015d) has concluded that if a woman requests information on umbilical cord banking, information regarding advantages and disadvantages of public versus private banking should be explained. Some states have passed laws that require physicians to inform patients about cord blood banking options. Importantly, few transplants have been performed by using cord blood stored in the absence of a known indication in the recipient (Screnci, 2016). The likelihood that cord blood would be used for the child or family member of

the donor couple is considered remote, and it is recommended that directed donation be considered when an immediate family member carries the diagnosis of a specific condition known to be treatable by hemopoietic transplantation (Chap. 56, Anemias).

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CHAPTER 10: Fetal Imaging

After discovery of the Roentgen ray and the demonstration of the various uses to which it might be put, it was thought possible that it might also afford a valuable method of investigating the shape and size of the pelvis.

—J. Whitridge Williams (1903)

INTRODUCTION

X-ray techniques were just on the horizon when the first edition of this textbook was published. The first application focused on the maternal pelvis without attention to the fetus. Thus, congenital abnormalities were routinely not discovered until birth. Subsequent radiographic efforts to evaluate the fetus were later replaced by ultrasonography and more recently by magnetic resonance (MR) imaging, techniques which have become increasingly sophisticated. The subspecialty of fetal medicine has developed only because of these advances, and today's practitioner can hardly imagine obstetrical care without them.

SONOGRAPHY IN OBSTETRICS

Prenatal sonography can be used to accurately assess gestational age, fetal number, viability, and placental location, and it can aid diagnosis of many fetal abnormalities. With improvements in resolution and image display, anomalies are increasingly detected in the first trimester, and Doppler is used to manage pregnancies complicated by growth impairment or anemia. The American College of Obstetricians and Gynecologists (2016) recommends that prenatal sonography be performed in all pregnancies and considers it an important part of obstetrical care in the United States.

Technology and Safety

The real-time image on the ultrasound screen is produced by sound waves that are reflected back from fluid and tissue interfaces of the fetus, amnionic fluid, and placenta. Sector array transducers contain groups of piezoelectric crystals working simultaneously in arrays. These crystals convert electrical energy into sound waves, which are emitted in synchronized pulses. Sound waves pass through tissue layers and are reflected back to the transducer when they encounter an interface between tissues of different densities. Dense tissue such as bone produces high-velocity reflected waves, which are displayed as bright echoes on the screen. Conversely, fluid generates few reflected waves and appears dark. Digital images generated at 50 to more than 100 frames per second undergo postprocessing that yields the appearance of real-time imaging.

Ultrasound refers to sound waves traveling at a frequency above 20,000 hertz (cycles per second). Higher-frequency transducers yield better image resolution, whereas lower frequencies penetrate tissue more effectively. Transducers use wide-bandwidth technology to perform within a range of frequencies. In early pregnancy, a 5- to 10-megahertz (MHz) transvaginal transducer usually provides excellent resolution, because the early fetus is close to the transducer. And, in the first and second trimesters, a 4- to 6-MHz transabdominal transducer is similarly close enough to the fetus to yield precise images. By the third trimester, however, a lower frequency 2- to 5-MHz transducer may be needed for tissue penetration—particularly in obese patients—and this can lead to compromised resolution.

Fetal Safety

Sonography should be performed only for a valid medical indication, using the lowest possible exposure setting to gain necessary information—the *ALARA* principle—*a*s *l*ow *a*s *r*easonably *a*chievable. Examinations are performed only by those trained to recognize fetal abnormalities and artifacts that may mimic pathology, using techniques to avoid ultrasound exposure beyond what is considered safe for the fetus (American College of Obstetricians and Gynecologists, 2016; American Institute of Ultrasound in Medicine, 2013b). No causal relationship has been demonstrated between diagnostic ultrasound and any recognized adverse effect in human pregnancy. The International Society of Ultrasound in Obstetrics and Gynecology (2016) further concludes that there is no scientifically proven association between ultrasound exposure in the first or second trimesters and autism spectrum disorder or its severity.

All sonography machines are required to display two indices: the *thermal index* and the *mechanical index*. The thermal index is a measure of the relative probability that the examination may raise the temperature, potentially high enough to induce injury. That said, fetal damage resulting from commercially available ultrasound equipment in routine practice is extremely unlikely. The potential for temperature elevation is higher with longer examination time and is greater near bone than in soft tissue. Theoretical risks are higher during organogenesis than later in gestation. The thermal index for soft tissue, *Tis*, is used before 10 weeks' gestation, and that for bone, *Tib*, is used at or beyond 10 weeks' (American Institute of Ultrasound in Medicine, 2013b). The thermal index is higher with pulsed Doppler applications than with routine B-mode scanning (Doppler). In the first trimester, if pulsed Doppler is clinically indicated, the thermal index should be ≤0.7, and the exposure time should be as brief as possible (American Institute of Ultrasound in Medicine, 2016). To document the embryonic or fetal heart rate, motion-mode (M-mode) imaging is used instead of pulsed Doppler imaging.

The mechanical index is a measure of the likelihood of adverse effects related to rarefactional pressure, such as cavitation—which is relevant only in tissues that contain air. Microbubble ultrasound contrast agents are not used in pregnancy for this reason. In mammalian tissues that do not contain gas bodies, no adverse effects have been reported over the range of diagnostically relevant exposures. Because fetuses cannot contain gas bodies, they are not considered at risk.

The use of sonography for any nonmedical purpose, such as "keepsake fetal imaging," is considered *contrary to responsible medical practice* and is not condoned by the Food and Drug Administration (2014), the American Institute of Ultrasound in Medicine (2012, 2013b), or the American College of Obstetricians and Gynecologists (2016).

Operator Safety

The reported prevalence of work-related musculoskeletal discomfort or injury among sonographers approximates 70 percent (Janga, 2012; Roll, 2012). The main risk factors for injury during transabdominal ultrasound examinations are awkward posture, sustained static forces, and various pinch grips used while maneuvering the transducer (Centers for Disease Control and Prevention, 2006). Maternal habitus can be contributory because more force is often employed when imaging obese patients.

The following guidelines may help avert injury:

1. Position the patient close to you on the examination table. As a result, your elbow is close to your body, shoulder abduction is less than 30 degrees, and your thumb is facing up.
2. Adjust the table or chair height so that your forearm is parallel to the floor.
3. If seated, use a chair with back support, support your feet, and keep ankles in neutral position. Do not lean toward the patient or monitor.
4. Face the monitor squarely and position it so that it is viewed at a neutral angle, such as 15 degrees downward.
5. Avoid reaching, bending, or twisting while scanning.
6. Frequent breaks may prevent muscle strain. Stretching and strengthening exercises can be helpful.

Gestational Age Assessment

The earlier that sonography is performed, the more accurate the gestational age assessment. Specific criteria for "re-dating" a pregnancy, that is, reassigning the gestational age and estimated date of delivery using initial sonogram findings, are shown in Table 10-1. The only exception to revising the gestational age based on early sonography is if the pregnancy resulted from assisted reproductive technology, in which case accuracy of gestational age assessment is presumed.

TABLE 10-1

Sonographic Gestational Age Assessment

Gestational Age	Parameter(s)	Threshold to Revise[a]
<9 wks	CRL	>5 d
9 to <14 wks	CRL	>7 d
14 to <16 wks	BPD, HC, AC, FL	>7 d
16 to <22 wks	BPD, HC, AC, FL	>10 d
22 to <28 wks	BPD, HC, AC, FL	>14 d
≥28 weeks	BPD, HC, AC, FL	>21 d

[a]Sonographic gestational age should be used when the LMP-derived gestational age differs from that obtained with sonography by the threshold value.

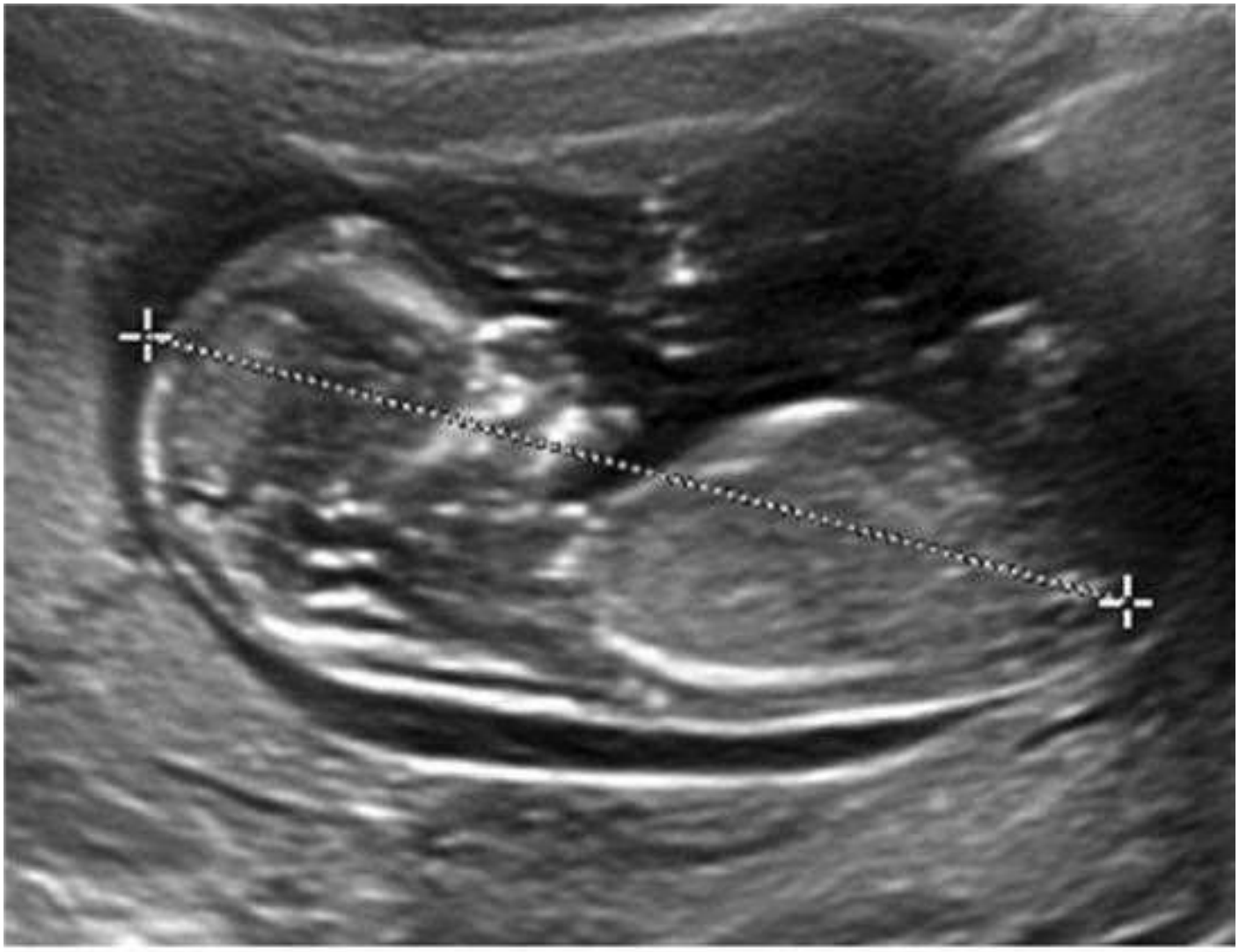
AC = abdominal circumference; BPD = biparietal diameter; CRL = crown-rump length; FL = femur length; HC = head circumference; LMP = last menstrual period.

Modified from American College of Obstetricians and Gynecologists, 2017b.

Sonographic measurement of the crown-rump length (CRL) is the most accurate method to establish or confirm gestational age (Appendix, Fetal Sonographic Measurements). As noted, transvaginal imaging typically yields higher resolution images. The CRL is measured in the midsagittal plane with the embryo or fetus in a neutral, nonflexed position so that its length can be measured in a straight line (Fig. 10-1). The measurement should include neither the yolk sac nor a limb bud. The mean of three discrete measurements is used. Until $13^{6/7}$ weeks' gestation, the CRL is accurate to within 5 to 7 days (American College of Obstetricians and Gynecologists, 2017b).

FIGURE 10-1

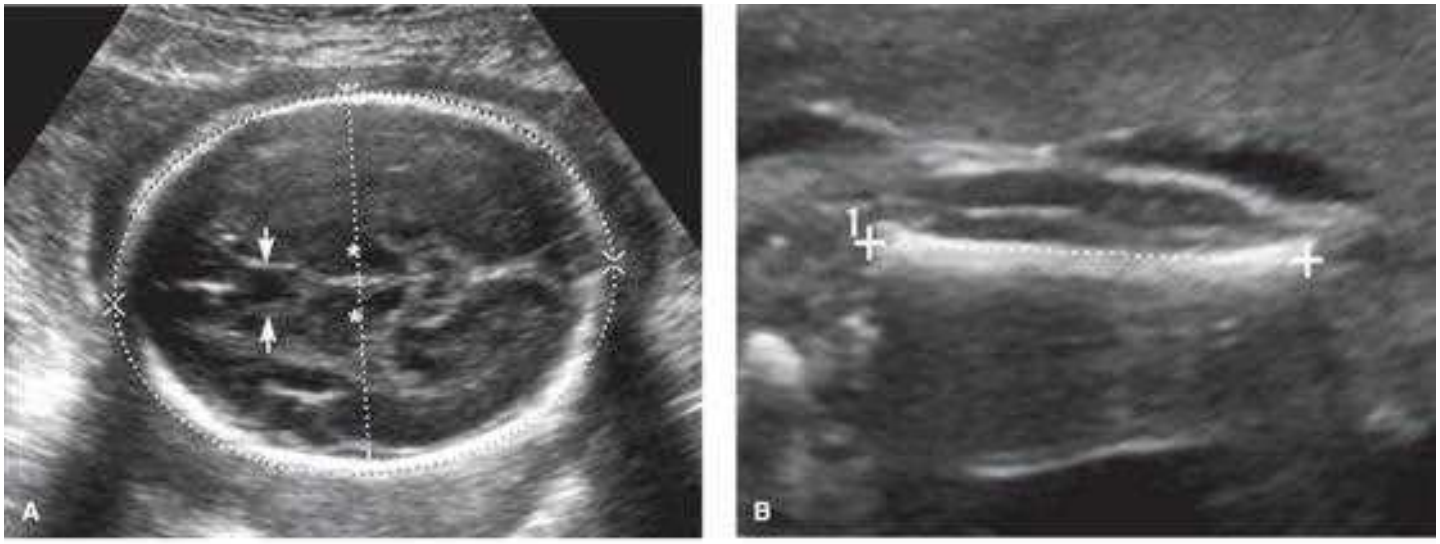
The measured crown-rump length in this 12-week 3-day fetus approximates 6 cm.



Starting at $14^{0/7}$ weeks, equipment software formulas calculate estimated gestational age and fetal weight from measurements of the biparietal diameter, head and abdominal circumference, and femur length (Fig. 10-2). The estimates are most accurate when multiple parameters are used but may over- or underestimate fetal weight by up to 20 percent (American College of Obstetricians and Gynecologists, 2016). Various nomograms for other fetal structures, including the cerebellar diameter, ear length, ocular distances, thoracic circumference, and lengths of kidney, long bones, and feet, may be used to address specific questions regarding organ system abnormalities or syndromes (Appendix, Fetal Sonographic Measurements).

FIGURE 10-2

Fetal biometry. **A.** Transthalamic view. A transverse (axial) image of the head is obtained at the level of the cavum septum pellucidum (*arrows*) and thalami (*asterisks*). The biparietal diameter is measured perpendicular to the sagittal midline, from the outer edge of the skull in the near field to the inner edge of the skull in the far field. By convention, the near field is that which is closer to the sonographic transducer. The head circumference is measured circumferentially around the outer border of the skull. **B.** Femur length. The femur is measured perpendicular to the femoral shaft, from each diaphyseal end, excluding the epiphysis. **C.** Abdominal circumference. This is a transverse measurement at the level of the stomach (*S*). The J-shaped structure (*arrowheads*) indicates the confluence of the umbilical vein and the right portal vein. Ideally, only one rib is visible on each side of the abdomen, indicating that the image was not taken at an oblique angle.



The biparietal diameter (BPD) most accurately reflects gestational age, with a variation of 7 to 10 days in the second trimester. The BPD is measured perpendicular to the midline falx in the *transthalamic view*, at the level of the thalami and cavum septum pellucidum (CSP) (see Fig. 10-2A). Calipers are placed from the outer edge of the skull in the near field to the inner edge of the skull in the far field. The head circumference (HC) is also measured in the transthalamic view. An ellipse is placed around the outer edge of the skull or the circumference is calculated using BPD and occipital-frontal diameter (OFD) values. The *cephalic index*, which is the BPD divided by the OFD, is normally 70 to 86 percent.

If the head shape is flattened—*dolichocephaly,* or rounded—*brachycephaly,* the HC is more reliable than the BPD. These head shape variants may be normal or can be secondary to fetal position or oligohydramnios. But, dolichocephaly can occur with neural-tube defects, and brachycephaly may be seen in fetuses with Down syndrome. Also, with abnormal skull shape, *craniosynostosis* and other craniofacial abnormalities are a consideration.

The femur length (FL) correlates well with both BPD and gestational age. It is measured with the beam perpendicular to the long axis of the shaft. Calipers are placed at each end of the calcified diaphysis and exclude the epiphysis. For gestational age estimation, it has a variation of 7 to 11 days in the second trimester (see Fig. 10-2B). A femur measurement that is <2.5th percentile for gestational age or that is shortened to ≤90 percent of that expected based on the measured BPD is a minor marker for Down syndrome (Chap. 14, Second-Trimester Markers—"Soft Signs"). The normal range for the FL to abdominal circumference (AC) ratio is generally 20 to 24 percent. A dramatically foreshortened FL or a FL-to-AC ratio below 18 percent prompts evaluation for a skeletal dysplasia (Skeletal Abnormalities).

Of biometric parameters, AC is most affected by fetal growth. Thus, for gestational age estimation, AC has the greatest variation, which can reach 2 to 3 weeks in the second trimester. To measure the AC, a circle is placed outside the fetal skin in a transverse image that contains the stomach and the confluence of the umbilical vein with the portal sinus (see Fig. 10-2C). The image should appear as round as possible and ideally contains no more than 1 rib on each side of the abdomen. The kidneys should not be visible in the image.

Variability of the sonographic gestational age estimate increases with advancing gestation. Accordingly, pregnancies not imaged prior to 22 weeks to confirm or revise gestational age are considered *suboptimally dated* (American College of Obstetricians and Gynecologists, 2017a). Although the estimate is improved by averaging multiple parameters, if one parameter differs significantly from the others, consideration should be given to excluding it from the calculation. The

outlier may result from poor visibility, but it could also indicate a fetal abnormality or growth problem. Reference tables such as the one in the Appendix (Fetal Sonographic Measurements) may be used to estimate fetal weight percentiles.

First-Trimester Sonography

Indications for sonography before 14 weeks' gestation are listed in Table 10-2. Early pregnancy can be evaluated using transabdominal or transvaginal sonography, or both. The components listed in Table 10-3 should be assessed. First-trimester sonography can reliably diagnose anembryonic gestation, embryonic demise, ectopic pregnancy, and gestational trophoblastic disease. The first trimester is also the ideal time to evaluate the uterus, adnexa, and cul-de-sac. Determination of chorionicity in a multifetal gestation is most accurate in the first trimester (Chap. 45, Sonographic Determination).

TABLE 10-2

Some Indications for First-Trimester Ultrasound Examination

Confirm an intrauterine pregnancy
Evaluate a suspected ectopic pregnancy
Define the cause of vaginal bleeding
Evaluate pelvic pain
Estimate gestational age
Diagnose or evaluate multifetal gestations
Confirm cardiac activity
Assist chorionic villus sampling, embryo transfer, and localization and removal of an intrauterine device
Assess for certain fetal anomalies, such as anencephaly, in high-risk patients
Evaluate maternal pelvic masses and/or uterine abnormalities
Measure nuchal translucency when part of a screening program for fetal aneuploidy
Evaluate suspected gestational trophoblastic disease

Modified from the American Institute of Ultrasound in Medicine, 2013a.

TABLE 10-3

Components of Standard Ultrasound Examination by Trimester

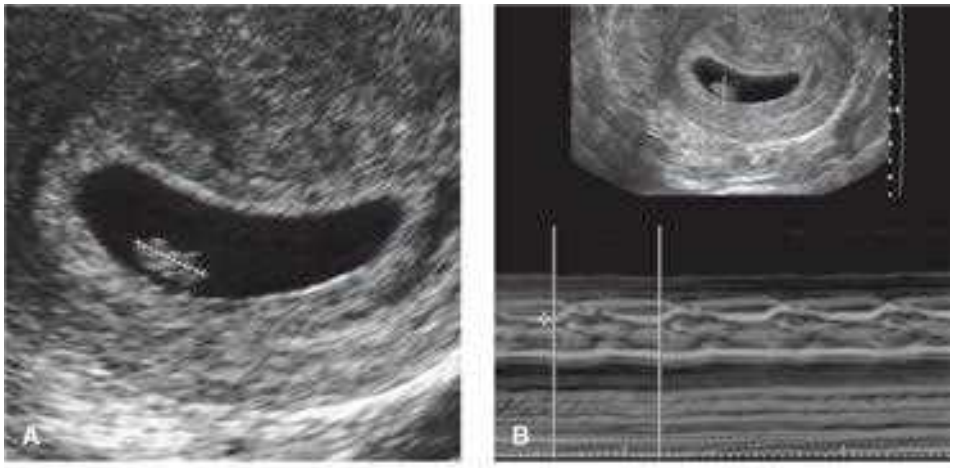
First Trimester	Second and Third Trimester
Gestational sac size, location, and number	Fetal number, including amnionicity and chorionicity of multifetal gestations
Embryo and/or yolk sac identification	Fetal cardiac activity
Crown-rump length	Fetal presentation
Fetal number, including amnionicity and chorionicity of multifetal gestations	Placental location, appearance, and relationship to the internal cervical os, with documentation of placental cord insertion site when technically possible
Embryonic/fetal cardiac activity	Amnionic fluid volume
Assessment of embryonic/fetal anatomy appropriate for the first trimester	Gestational age assessment
Evaluation of the maternal uterus, adnexa, and cul-de-sac	Fetal weight estimation
Evaluation of the fetal nuchal region, with consideration of fetal nuchal translucency assessment	Fetal anatomical survey, including documentation of technical limitations
	Evaluation of the maternal uterus, adnexa, and cervix when appropriate

Modified from the American Institute of Ultrasound in Medicine, 2013a.

An intrauterine gestational sac is reliably visualized with transvaginal sonography by 5 weeks, and an embryo with cardiac activity by 6 weeks (Fig. 10-3). The embryo should be visible transvaginally once the mean sac diameter has reached 25 mm—otherwise the gestation is *anembryonic*. Cardiac motion is usually visible with transvaginal imaging when the embryo length reaches 5 mm. In embryos <7 mm without cardiac activity, subsequent examination may be needed to determine viability (American College of Obstetricians and Gynecologists, 2016). At Parkland hospital, first-trimester demise is diagnosed if the embryo has reached 10 mm and lacks cardiac motion. Other criteria for this diagnosis are found in Chapter 18 (Table 18-3).

FIGURE 10-3

A. The measured crown-rump length is approximately 7 mm in this 6-week embryo. **B.** M-mode demonstrates embryonic cardiac activity and a heart rate of 124 beats per minute.



Nuchal Translucency

Nuchal translucency (NT) evaluation is a component of first-trimester aneuploidy screening, discussed in Chapter 14 (Traditional Aneuploidy Screening Tests). It represents the maximum thickness of the subcutaneous translucent area between the skin and soft tissue overlying the fetal spine at the back of the neck. NT is measured in the sagittal plane between 11 and 14 weeks' gestation using precise criteria (Table 10-4). When the NT measurement is increased, the risk for fetal aneuploidy and various structural anomalies—in particular heart defects—is significantly elevated.

TABLE 10-4

Guidelines for Nuchal Translucency (NT) Measurement

The margins of NT edges must be clear enough for proper caliper placement
The fetus must be in the midsagittal plane
The image must be magnified so that it is filled by the fetal head, neck, and upper thorax
The fetal neck must be in a neutral position, not flexed and not hyperextended
The amnion must be seen as separate from the NT line
Electronic calipers must be used to perform the measurement
The + calipers must be placed on the inner borders of the nuchal space with none of the horizontal crossbar itself protruding into the space
The calipers must be placed perpendicular to the long axis of the fetus
The measurement must be obtained at the widest space of the NT

From the American Institute of Ultrasound in Medicine, 2013a, with permission.

Fetal Anomaly Detection

Assessment for selected fetal abnormalities in an at-risk pregnancy is done with first-trimester sonography (see Table 10-2). Research in this area has focused on anatomy visible at 11 to 14 weeks' gestation, to coincide with sonography performed as part of aneuploidy screening. *With current technology, it is not realistic to expect that all major abnormalities detectable in the second trimester may be visualized in the first trimester.* Thus, first-trimester scanning should not replace second-trimester anatomical evaluation (American College of Obstetricians and Gynecologists, 2016).

As examples, in one study of more than 40,000 pregnancies undergoing sonographic aneuploidy screening between 11 and 14 weeks, basic anatomical evaluation yielded a detection rate of approximately 40 percent for structural abnormalities (Syngelaki, 2011). Bromley and colleagues (2014) similarly found that late first-trimester sonography identified major abnormalities in 0.5 percent of pregnancies, representing approximately 40 percent of pregnancies with anomalies detected prenatally. Detection rates are very high for anencephaly, alobar holoprosencephaly, and ventral wall defects. But, in one analysis of more than 60,000 pregnancies with these early scans, only a third of major cardiac anomalies were identified, and *no* cases of microcephaly, agenesis of the corpus callosum, cerebellar abnormalities, congenital pulmonary airway malformations, or bowel obstruction were detected (Syngelaki, 2011). In another study of low-risk or unselected pregnancies, 32 percent of anomalies were detected, whereas in pregnancies described as high-risk, anomaly detection exceeded 60 percent (Karim, 2017).

Second- and Third-Trimester Sonography

It is recommended that sonography be routinely offered to all pregnant women between 18 and 22 weeks' gestation (American College of Obstetricians and Gynecologists, 2016). This time interval permits accurate assessment of gestational age, fetal anatomy, placental location, and cervical length. Recognizing that the gestational age at which abnormalities are identified may affect pregnancy management options, providers may opt to perform the examination prior to 20 weeks. The many additional indications for second- and third-trimester sonography are listed in Table 10-5. The three examination types are *standard*, *specialized*—which includes targeted sonography, and *limited*.

TABLE 10-5

Some Indications for Second- or Third-Trimester Ultrasound Examination

Maternal Indications
Vaginal bleeding
Abdominal/pelvic pain
Pelvic mass
Suspected uterine abnormality
Suspected ectopic pregnancy
Suspected molar pregnancy
Suspected placenta previa and subsequent surveillance
Suspected placental abruption
Preterm premature rupture of membranes and/or preterm labor
Cervical insufficiency
Adjunct to cervical cerclage
Adjunct to amniocentesis or other procedure
Adjunct to external cephalic version
Fetal Indications
Gestational age estimation
Fetal-growth evaluation
Significant uterine size/clinical date discrepancy
Suspected multifetal gestation
Fetal anatomical evaluation
Fetal anomaly screening
Assessment for findings that raise the aneuploidy risk
Abnormal biochemical markers
Fetal presentation determination
Suspected hydramnios or oligohydramnios
Fetal well-being evaluation
Follow-up evaluation of a fetal anomaly
History of congenital anomaly in prior pregnancy
Suspected fetal death
Fetal condition evaluation in late registrants for prenatal care

Adapted from the American Institute of Ultrasound in Medicine, 2013a.

The standard sonogram includes evaluation of fetal number and presentation, cardiac activity, amnionic fluid volume, placental position, fetal biometry, and fetal anatomy (American Institute of Ultrasound in Medicine, 2013b). When technically feasible, the maternal cervix and adnexa are examined as clinically appropriate. Components are found in Table 10-3, and the fetal anatomical structures that should be evaluated are listed in Table 10-6. With twins or other multiples, documentation also includes the number of chorions and amnions, comparison of fetal sizes, estimation of amnionic fluid volume within each sac, and fetal sex determination (Chap. 45, Sonographic Determination).

TABLE 10-6

Components of Standard and Targeted Fetal Anatomic Surveys

Standard Sonogram	Additional Targeted (Detailed) Sonogram Components
Head, face, and neck Lateral cerebral ventricles Choroid plexus Midline falx Cavum septum pellucidum Cerebellum Cisterna magna Upper lip Consideration of nuchal skin fold measurement at 15–20 weeks	**Head, face, and neck** Integrity and shape of cranium Third ventricle[a] Fourth ventricle[a] Corpus callosum[a] Cerebellar lobes, vermis Brain parenchyma Profile Coronal nose, lips, lens[a] Palate[a], maxilla, mandible, and tongue[a] Ear position and size[a] Orbits[a] Neck
Chest Cardiac activity Four-chamber view of the heart Left ventricular outflow tract Right ventricular outflow tract	**Chest** Aortic arch Superior/inferior venae cavae 3-vessel view 3-vessel and trachea view Lungs Integrity of diaphragm Ribs[a]
Abdomen Stomach: presence, size, and situs Kidneys Urinary bladder Umbilical cord insertion into fetal abdomen Umbilical cord vessel number	**Abdomen** Small and large bowel[a] Adrenal glands[a] Gallbladder[a] Liver Renal arteries[a] Spleen[a] Integrity of abdominal wall
Spine Cervical, thoracic, lumbar, and sacral spine	**Spine** Shape and curvature Integrity of spine and overlying soft tissue
Extremities Legs and arms	**Extremities** Architecture, position, number Hands Feet Digits[a]: number, position
Fetal sex In multifetal gestations and when medically indicated	

[a]When medically indicated (determined on case-by-case basis).

Modified from the American Institute of Ultrasound in Medicine, 2013a; Wax, 2014.

The *targeted* sonogram is a type of *specialized* examination. It is performed when the risk for a fetal anatomical or genetic abnormality is elevated because of history, screening test result, or abnormal finding during standard examination (Table 10-7). Targeted sonograms include a detailed anatomical survey, the components of which are shown in Table 10-6. Because it carries the CPT code 76811, this sonogram is colloquially called the “76811 examination.” It is intended

to be indication-driven and should not be repeated later in the absence of an extenuating circumstance. Physicians who perform or interpret targeted sonograms should have expertise in fetal imaging, through both training and ongoing experience (Wax, 2014). For many of the targeted examination components, the physician determines on a case-by-case basis whether assessment is needed (American College of Obstetricians and Gynecologists, 2016). Other types of specialized examinations include fetal echocardiography, Doppler evaluation, and the biophysical profile, which is described in Chapter 17 (Acoustic Stimulation Tests).

TABLE 10-7

Indications for Targeted Fetal Anatomical Ultrasound Examination

Prior fetus or neonate with a structural or genetic/chromosomal abnormality
Current pregnancy with known or suspected fetal abnormality or confirmed growth abnormality
Increased risk for fetal structural anomaly in current pregnancy
Maternal diabetes diagnosed before 24 weeks' gestation
Assisted reproductive technology to achieve conception
Maternal prepregnancy body mass index >30 kg/m^2
Multifetal gestation (Chap. 45, Mechanisms of Multifetal Gestations)
Abnormal serum alpha-fetoprotein or estriol levels
Teratogen exposure
Nuchal translucency measurement ≥3.0 mm
Increased risk for fetal genetic/chromosomal abnormality in current pregnancy
Parental carriage of genetic/chromosomal abnormality
Maternal age ≥35 at delivery
Abnormal aneuploidy screening test result
Minor aneuploidy marker (on standard sonogram)
Nuchal translucency measurement ≥3.0 mm
Other condition affecting the fetus
Congenital infection (Chaps. 64 and 65)
Drug dependence
Alloimmunization (Chap. 15, Red Cell Alloimmunization)
Amnionic fluid abnormality (Chap. 11, Hydramnios)

Modified from Wax, 2014, 2015.

A *limited* sonogram is performed to address a specific clinical question. Examples include evaluation of fetal presentation, viability, amnionic fluid volume, or placental location. In the absence of an emergency, a limited examination is only performed if a standard sonogram has already been completed. Otherwise, provided that the gestational age is at least 18 weeks, a standard sonogram is recommended.

Fetal Anomaly Detection

With current advances in imaging technology, approximately 50 percent of major fetal abnormalities overall are detected with standard sonography (Rydberg, 2017). The sensitivity of sonography for detecting fetal anomalies varies according to factors such as gestational age, maternal habitus, fetal position, equipment features, examination type, operator skill, and the specific abnormality in question. For example, maternal obesity has been associated with a 20-percent reduction in the anomaly detection rate (Dashe, 2009).

Detection also varies considerably according to the abnormality. For example, population-based data from 18 registries comprise the EUROCAT network. Between 2011 and 2015, EUROCAT (2017) prenatal detection rates for selected fetal anomalies—excluding genetic conditions—were as follows: anencephaly, 99 percent; spina bifida, 89 percent; hydrocephaly, 78 percent; cleft lip/palate, 68 percent; hypoplastic left heart, 87 percent; transposition of the great vessels, 64 percent; diaphragmatic hernia, 74 percent; gastroschisis, 94 percent; omphalocele, 92 percent; bilateral renal agenesis, 94 percent; posterior urethral valves, 79 percent; limb-reduction defects, 57 percent; and clubfoot, 57 percent.

Importantly, however, the overall anomaly detection rate, excluding aneuploidy, was *below 40 percent.* This reflects inclusion of anomalies with minimal or no sonographic detection in the second trimester, such as microcephaly, choanal atresia, cleft palate, Hirschsprung disease, anal atresia, and congenital skin disorders. These are mentioned because clinicians tend to focus on abnormalities amenable to sonographic detection, whereas those not readily detectable may be equally devastating to families. *Therefore, every sonographic examination should include a frank discussion of examination limitations.*

Most anomalous neonates are born to women whose pregnancies are otherwise considered low-risk, that is, without an indication for targeted sonography. Thus, for standard sonographic examinations, accurate documentation and quality assurance are essential to optimize detection rates. Practice guidelines and standards established by organizations such as the American Institute of Ultrasound in Medicine (2013b) and the International Society of Ultrasound in Obstetrics and Gynecology (Salomon, 2011) have undoubtedly contributed to improvements in anomaly detection rates. Ultrasound practice accreditation is a process offered by the American Institute of Ultrasound in Medicine and the American College of Radiology that was developed to improve imaging quality and adherence to guidelines. It includes review of images and their storage, ultrasound equipment, report generation, and the qualifications of physicians and sonographers.

The Society for Maternal-Fetal Medicine (2013) recommends that whenever possible, obstetrical ultrasound examinations by maternal-fetal medicine subspecialists be performed by accredited practices.

Amnionic Fluid Volume

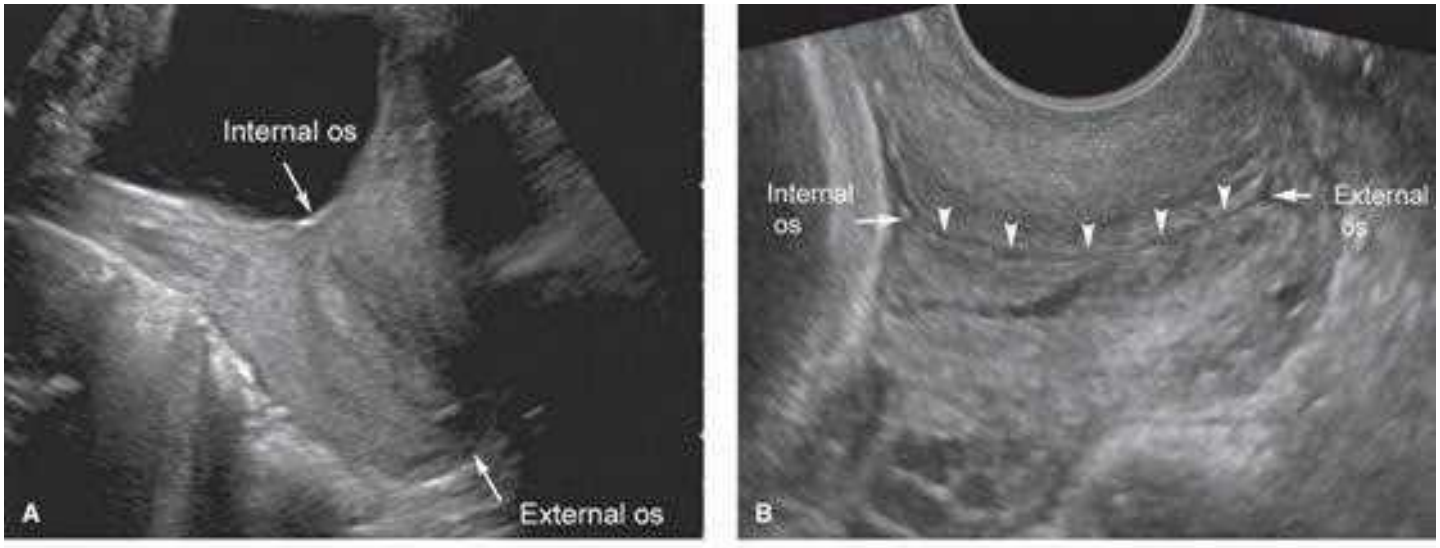
Evaluation of amnionic fluid volume is a component of every second- or third-trimester sonogram, and volumes vary with gestational age. *Oligohydramnios* indicates an amnionic fluid volume below normal range, and subjective crowding of the fetus is often noted. *Hydramnios*—also called *polyhydramnios*—defines a volume above a given normal threshold. Amnionic fluid volume is usually assessed semiquantitatively. Measurements include either the single deepest vertical fluid pocket or the sum of the deepest vertical pockets from each of four equal uterine quadrants—the *amnionic fluid index* (Phelan, 1987). Reference ranges have been established for both measurements from 16 weeks' gestation onward. The single deepest vertical pocket is normally between 2 and 8 cm, and the amnionic fluid index normally ranges between 8 and 24 cm. A further discussion and images are provided in Chapter 11 (Hydramnios).

Cervical Length Assessment

Evaluation of the relationship between the placenta and the internal cervical os is an essential component of the standard sonogram. Abnormalities of the placenta and umbilical cord are reviewed in Chapter 6 (Normal Placenta). Although the cervix may be imaged transabdominally (Fig. 10-4), this is often limited by technical factors that include maternal habitus, cervical position, or shadowing by the fetal presenting part. In addition, the maternal bladder or pressure from the transducer may artificially elongate the appearance of the cervix. As a result, values from transabdominal or transvaginal measurement of the cervix can differ significantly.

FIGURE 10-4

A. Transabdominal image of the cervix depicting the internal os and external os. **B.** Transvaginal imaging provides a more accurate evaluation of the cervix and should be used for medical decision-making. In this image, arrowheads mark the endocervical canal. (Reproduced with permission from Dr. Emily Adhikari.)



If the cervix appears shortened or if it cannot be adequately visualized during transabdominal evaluation, transvaginal assessment is considered (American Institute of Ultrasound in Medicine, 2013b). Only cervical length measurements obtained transvaginally at or beyond 16 weeks' gestation are considered sufficiently accurate for clinical decision-making (see Fig. 10-4). A foreshortened cervix is associated with an elevated risk for preterm birth, particularly in the setting of prior preterm birth, and the degree of risk rises proportionally with the degree of cervical shortening (Chap. 42, Preterm Birth Prevention).

To measure the cervix transvaginally, the imaging criteria shown in Table 10-8 are followed. The endocervical canal should be visible in its entirety, and images ideally are obtained over several minutes to allow for dynamic change. During examination, visible funneling or debris is sought. Funneling is a protrusion of amnionic membranes into a portion of the endocervical canal that has dilated (Fig. 10-5). Funneling is not an independent predictor of preterm birth, however, it is associated with cervical shortening, and transvaginal assessment is recommended if a funnel is suspected transabdominally. The cervical length is measured distal to the funnel, because the base of the funnel becomes the functional internal os. If the cervix is dilated, as with cervical insufficiency, the membranes may prolapse through the endocervical canal and into the vagina, producing an hourglass appearance. Sludge or debris represents an aggregate of particulate matter within the amnionic sac, close to the internal os. In pregnancies at risk for preterm birth, sludge is associated with a further increased risk.

TABLE 10-8

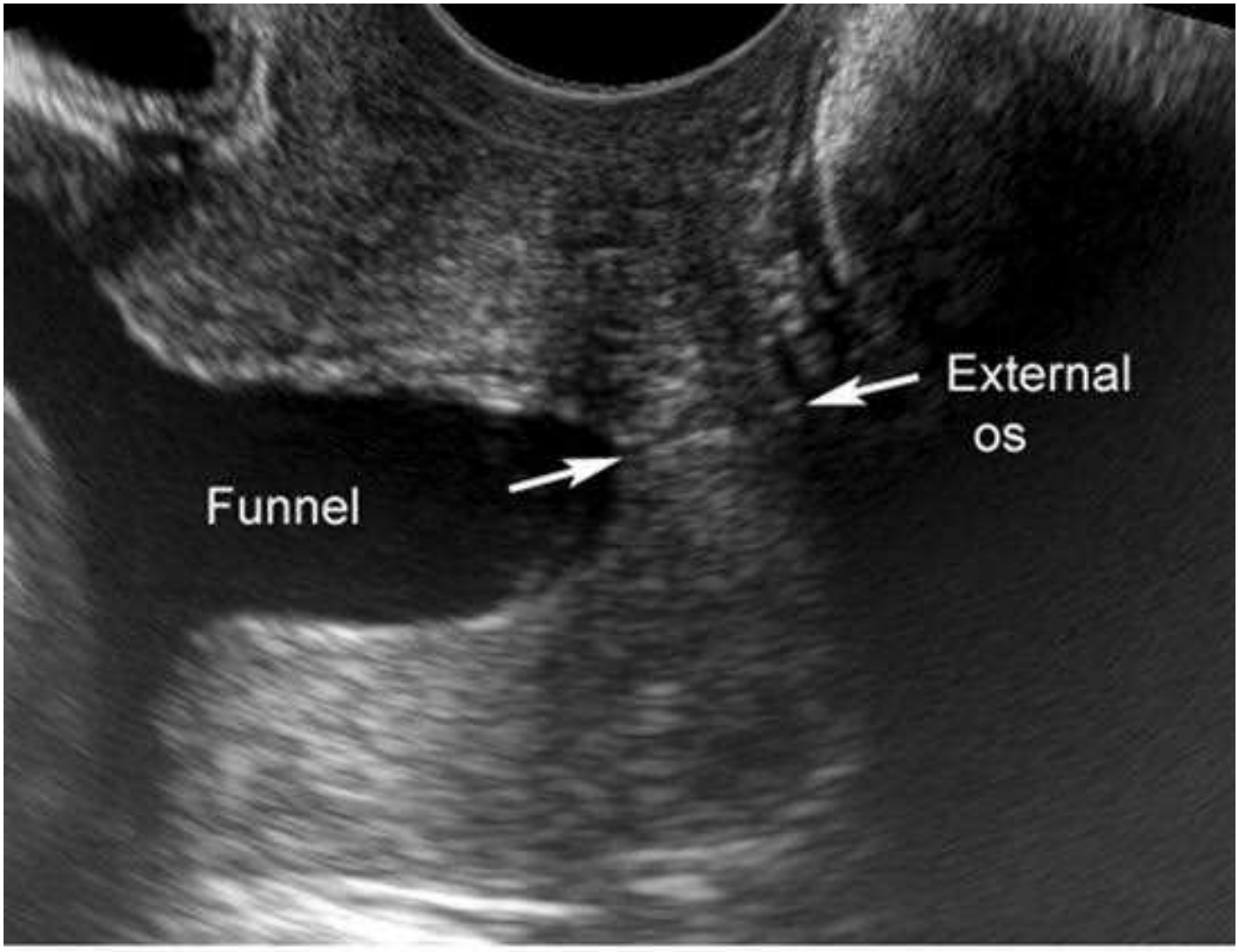
Criteria for Transvaginal Evaluation of the Cervix

Imaging the Cervix
Maternal bladder should be empty.
Transducer is inserted under real-time observation, identifying midsagittal plane, internal os, and then external os, while keeping the internal os in view.
Internal os, external os, and entire endocervical canal should be visible. The internal os may appear as a small triangular indentation at the junction of the amnionic cavity and endocervical canal.
Image is enlarged so that the cervix fills approximately 75% of the screen.
Anterior and posterior width of the cervix should be approximately equal.
Transducer is pulled back slightly until the image begins to blur, ensuring that pressure is not placed on the cervix, then inserted only enough to restore a clear image.
Images should be obtained with and without fundal or suprapubic pressure, to assess for dynamic change–or shortening on real-time imaging.
Measuring the Cervix
Calipers are placed where anterior and posterior walls of cervix meet.
Endocervical canal appears as a faint, linear echodensity.
If canal has a curved contour, a straight line between the internal and external os will deviate from the path of the endocervical canal.
If midpoint of the line between the internal and external canal deviates by ≥3 mm from the endocervical canal, measure the cervical length in two linear segments.
Funneling, sludge (debris), or dynamic change is noted.
At least three separate images are measured during a period of at least 3 minutes to allow for dynamic change. Visualization of cervical shortening on real-time imaging, with or without fundal or suprapubic pressure, raises preterm birth risks.
Shortest cervical length image that meets all criteria should be used.

Modified from Iams, 2013.

FIGURE 10-5

Transvaginal image depicting a foreshortened cervix with funneling. Funneling is a protrusion of amnionic membranes into a portion of the endocervical canal that has dilated. The distal protruding edge of the funnel becomes the functional internal os (*left arrow*). Thus, the measured cervical length, which lies between the arrows, should not include the funnel. (Reproduced with permission from Dr. Emily Adhikari.)



NORMAL AND ABNORMAL FETAL ANATOMY

Many fetal anomalies and syndromes may be characterized with targeted sonography, and selected abnormalities are discussed subsequently. This list is not intended to be comprehensive but covers abnormalities commonly detected with standard sonography and those that are potentially amenable to fetal therapy. Sonographic features of chromosomal abnormalities are reviewed in Chapters 13 and 14, and fetal therapy is discussed in Chapter 16.

Brain and Spine

Standard sonographic evaluation of the fetal brain includes three transverse (axial) views. The *transthalamic view* is used to measure the BPD and HC and includes the midline falx, cavum septum pellucidum (CSP), and thalami (see Fig. 10-1A). The CSP is the space between the two laminae that separate the frontal horns of the lateral ventricles. Inability to visualize a normal CSP may indicate a midline brain abnormality such as agenesis of the corpus callosum, lobar holoprosencephaly, or septo-optic dysplasia (de Morsier syndrome). The *transventricular view* includes the lateral ventricles, which contain the echogenic choroid plexus (Fig. 10-6). The ventricles are measured at their atrium, which is the confluence of the temporal and occipital horns. The *transcerebellar view* is obtained by angling the transducer back through the posterior fossa (Fig. 10-7). In this view, the cerebellum and cisterna magna are measured, and between 15 and about 20 weeks, the nuchal skinfold thickness may also be measured. From 15 until 22 weeks' gestation, the cerebellar diameter in millimeters is roughly equivalent to the gestational age in weeks (Goldstein, 1987). The cisterna magna normally measures between 2 and 10 mm. Effacement of the cisterna magna is present in the *Chiari II malformation*, discussed later (Ventriculomegaly).

FIGURE 10-6
The transventricular view depicts the lateral ventricles, which contain the echogenic choroid plexus (*CP*). The lateral ventricle is measured at the *atrium* (*arrows*), which is the confluence of the temporal and occipital horns. A normal measurement is between 5 and 10 mm throughout the second and third trimesters. The atria measured 6 mm in this 21-week fetus.

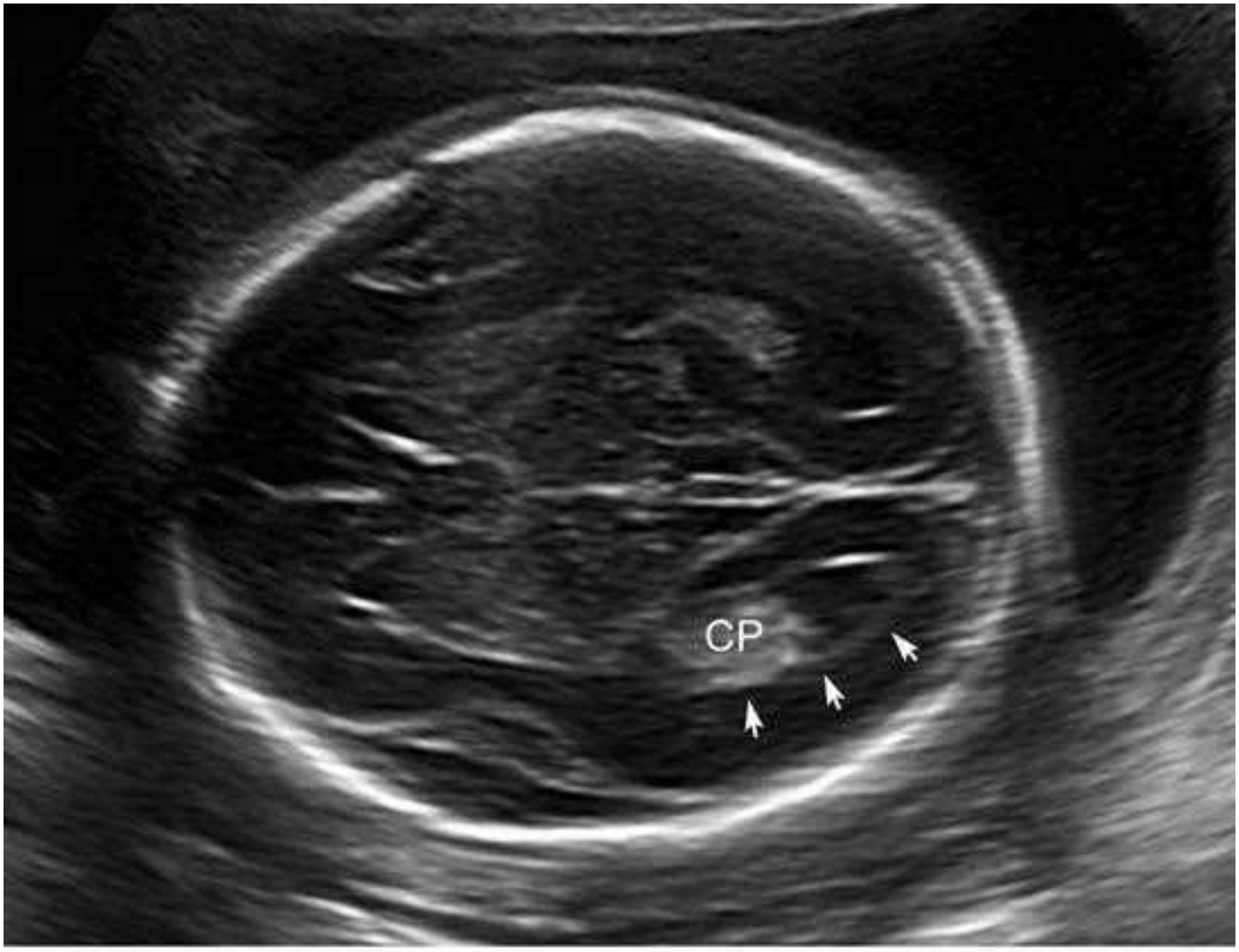
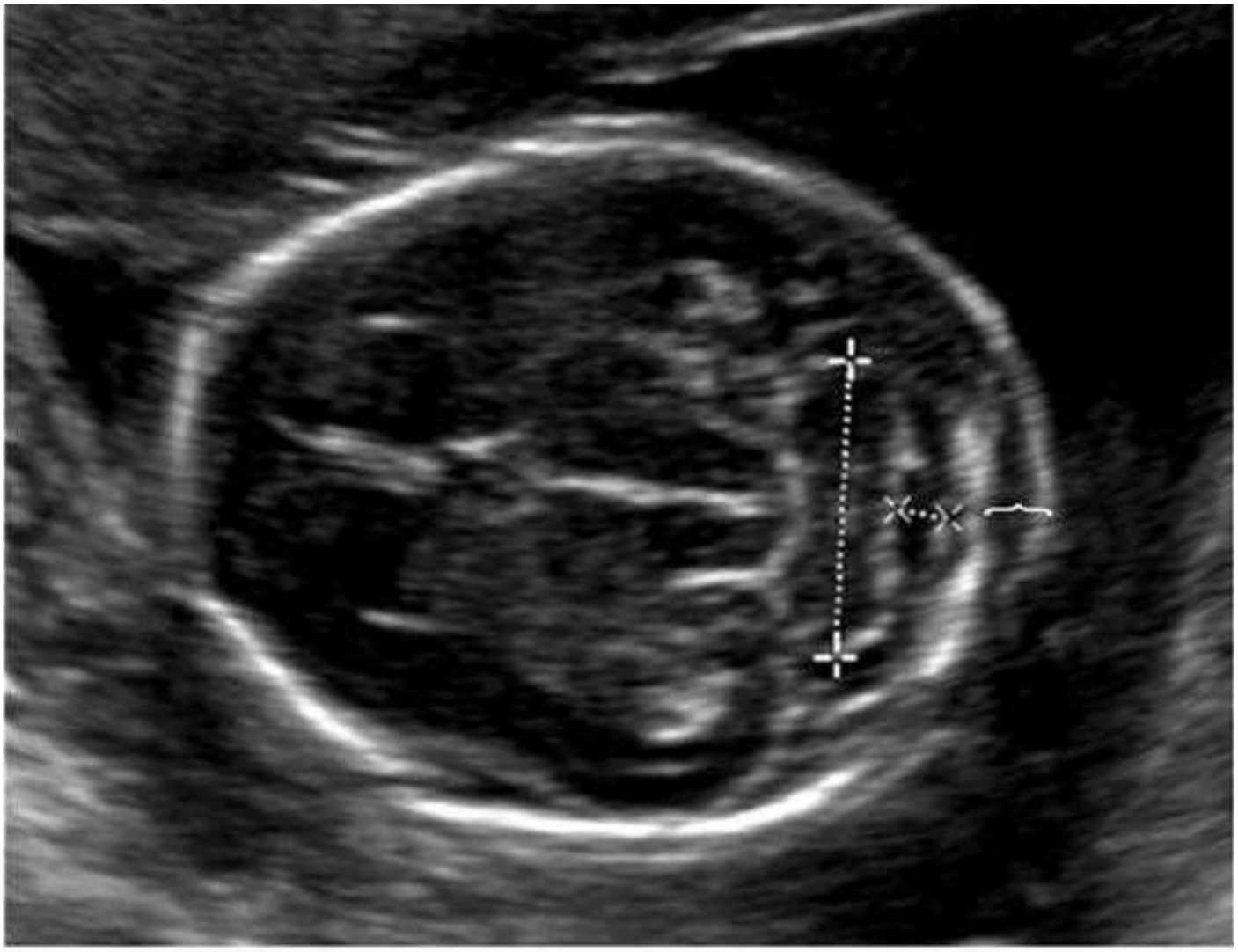


FIGURE 10-7

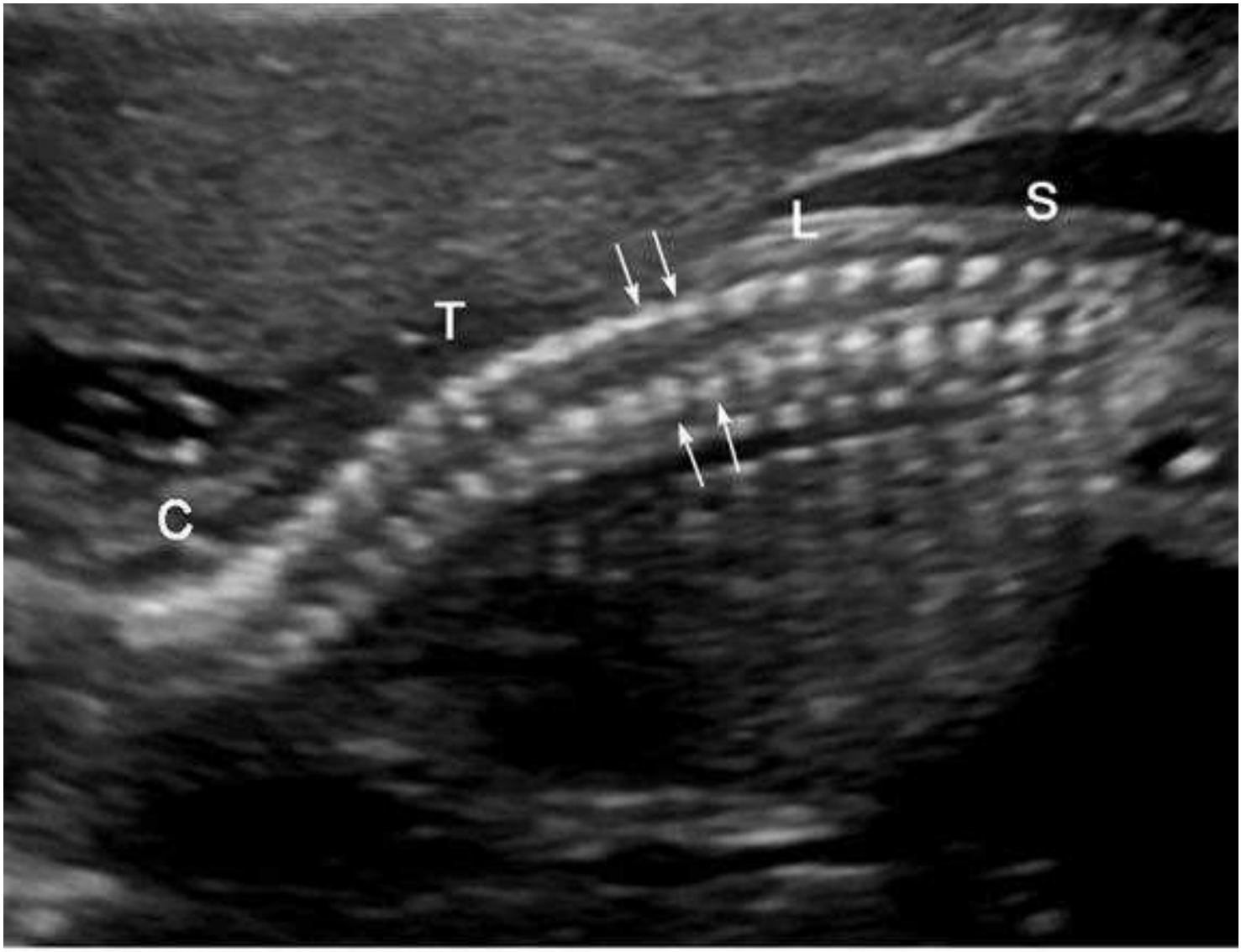
Transcerebellar view of the posterior fossa, demonstrating measurement of the cerebellum (+), cisterna magna (*x*), and nuchal fold thickness (*bracket*). Care is taken not to angle obliquely down the spine, which may artificially increase the nuchal fold measurement.



Imaging of the spine includes evaluation of the cervical, thoracic, lumbar, and sacral regions (Fig. 10-8). Representative spinal images for record keeping are often obtained in the sagittal or coronal plane, but real-time imaging of each spinal segment in the transverse plane is more sensitive for anomaly detection. Transverse images demonstrate three ossification centers. The anterior ossification center is the vertebral body, and the posterior paired ossification centers represent the junction of vertebral laminae and pedicles. Ossification of the spine proceeds in a cranial-caudal fashion, such that ossification of the upper sacrum (S_1-S_2) is not generally visible sonographically before 16 weeks' gestation, and ossification of the entire sacrum may not be visible until 21 weeks (De Biasio, 2003). Thus, detection of some spinal abnormalities can be challenging in the early second trimester.

FIGURE 10-8

Normal fetal spine. In this sagittal image of a 21-week fetus, the cervical (*C*), thoracic (*T*), lumbar (*L*), and sacral spine (*S*) are depicted. Arrows denote the parallel rows of paired posterior ossification centers—representing the junction of vertebral lamina and pedicles.



If a brain or spinal abnormality is identified, targeted sonography is indicated. The International Society of Ultrasound in Obstetrics and Gynecology (2007) has published guidelines for a "fetal neurosonogram." Fetal MR imaging may also be helpful (Fetal Anatomical Evaluation).

Neural-Tube Defects

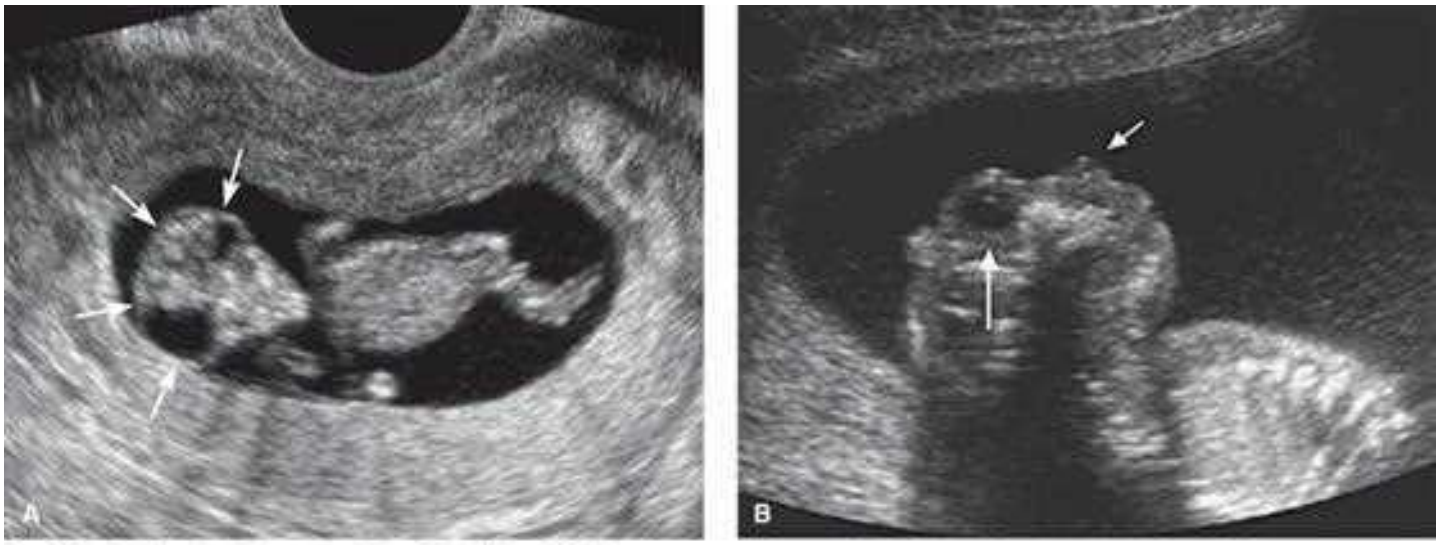
These defects include anencephaly, myelomeningocele (also called spina bifida), cephalocele, and other rare spinal fusion (or *schisis*) abnormalities. They result from incomplete closure of the neural tube by the embryonic age of 26 to 28 days. Their birth prevalence is 0.9 in 1000 in the United States and most of Europe and 1.3 in 1000 in the United Kingdom (Cragan, 2009; Dolk, 2010). Many neural-tube defects can be prevented with folic acid supplementation. When isolated, neural-tube defect inheritance is multifactorial, and the recurrence risk without periconceptional folic acid supplementation is 3 to 5 percent (Chap. 13, Genetic Tests).

Screening for neural-tube defects with maternal serum alpha-fetoprotein (MSAFP) has been offered routinely as part of prenatal care since the 1980s (Chap. 14, Maternal Serum AFP Elevation: Neural-Tube Defect Screening). Women currently have the option of neural-tube defect screening with MSAFP, sonography, or both (American College of Obstetricians and Gynecologists, 2016). Serum screening is generally performed between 15 and 20 weeks' gestation. And, if using an upper threshold of 2.5 multiples of the median (MoM), the anticipated detection rate is at least 90 percent for fetal anencephaly and 80 percent for myelomeningocele. Targeted sonography is the preferred diagnostic test, and in addition to characterizing the neural-tube defect, it may identify other abnormalities or conditions that also result in MSAFP elevation (Table 14-6).

Anencephaly is characterized by absence of the cranium and telencephalic structures above the level of the skull base and orbits (Fig. 10-9). *Acrania* is absence of the cranium with protrusion of disorganized brain tissue. Both are uniformly lethal and are generally considered together, with anencephaly as the final stage of acrania (Bronshtein, 1991). These anomalies are often diagnosed in the late first trimester, and with adequate visualization, virtually all cases may be diagnosed in the second trimester. Inability to image the BPD raises suspicion. The face often appears triangular, and sagittal images readily demonstrate absence of the ossified cranium. Hydramnios from impaired fetal swallowing is common in the third trimester.

FIGURE 10-9

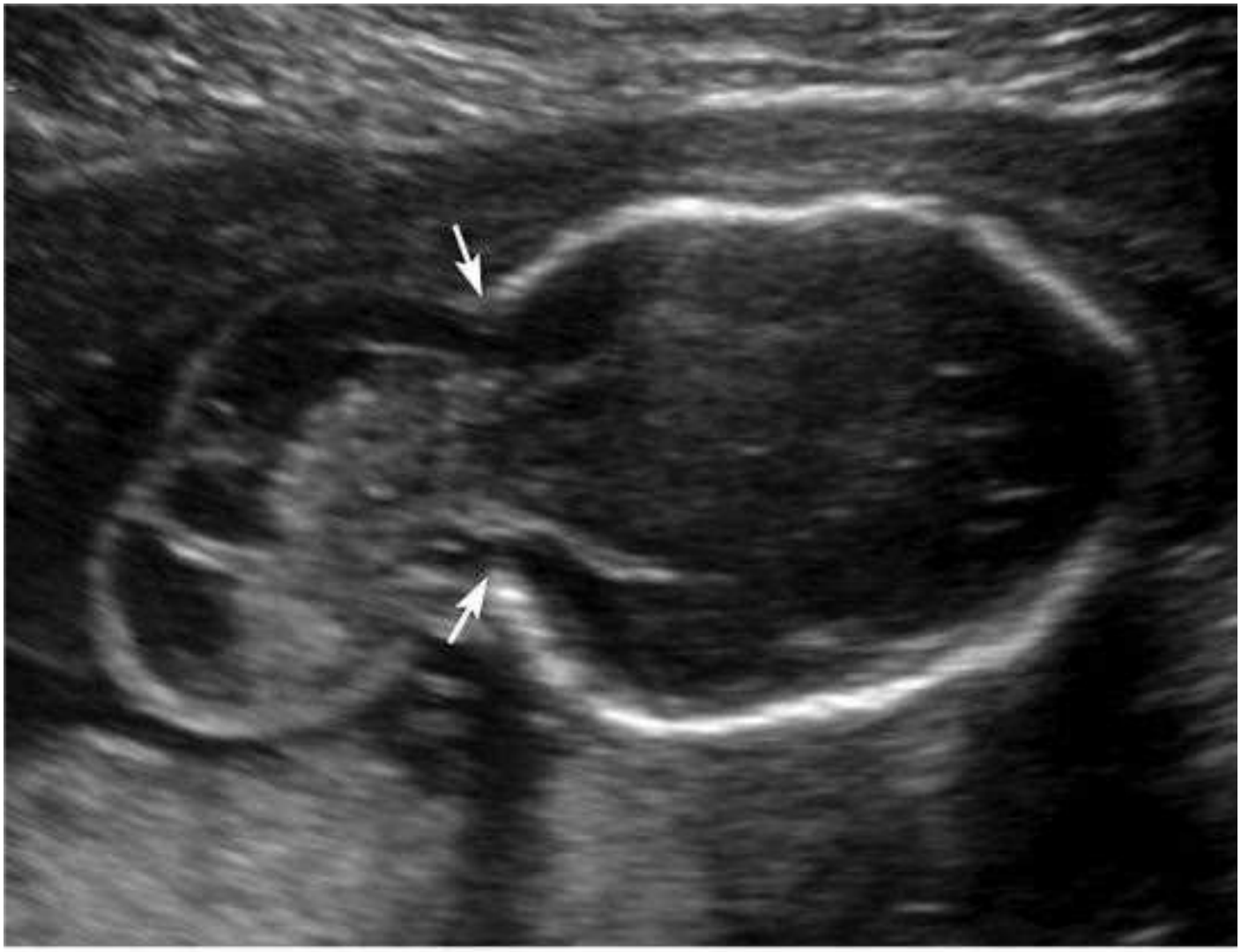
Anencephaly/acrania. **A.** Acrania. This 11-week fetus has absence of the cranium, with protrusion of a disorganized mass of brain tissue that resembles a “shower cap” (*arrows*) and a characteristic triangular facial appearance. **B.** Anencephaly. This sagittal image shows the absence of forebrain and cranium above the skull base and orbit. The long white arrow points to the fetal orbit, and the short white arrow indicates the nose.



Cephalocele is the herniation of meninges through a cranial defect, typically located in the midline occipital region (Fig. 10-10). When brain tissue herniates through the skull defect, the anomaly is termed an *encephalocele.* Herniation of the cerebellum and other posterior fossa structures constitutes a *Chiari III malformation*. Associated hydrocephalus and microcephaly are common, and survivors have a high incidence of neurological deficits and intellectual disability. Cephalocele is an important feature of the autosomal recessive *Meckel-Gruber syndrome,* which includes cystic renal dysplasia and polydactyly. A cephalocele not located in the occipital midline raises suspicion for *amnionic-band sequence* (Chap. 6, Amniochorion).

FIGURE 10-10

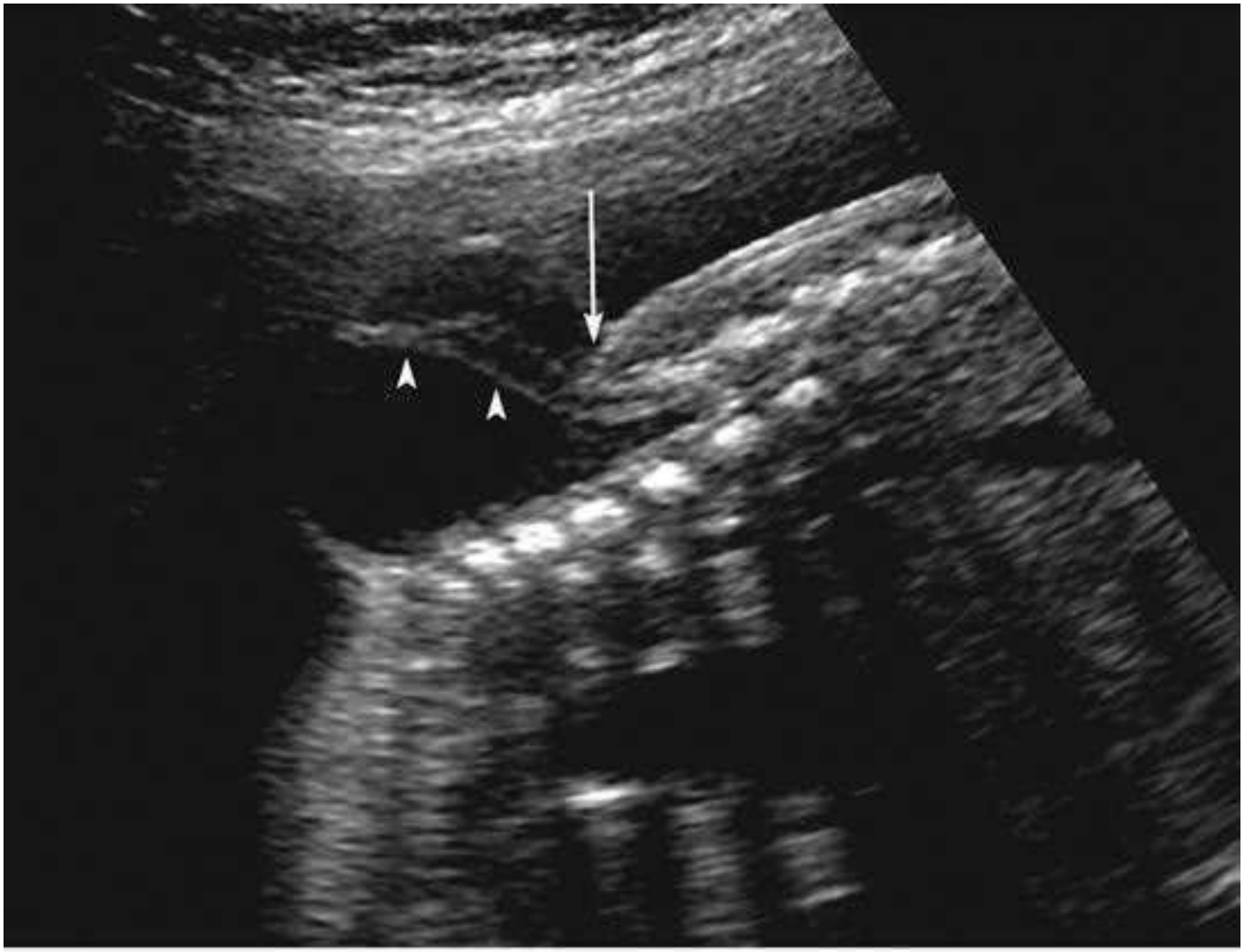
Encephalocele. This transverse image depicts a large defect in the occipital region of the cranium (*arrows*) through which meninges and brain tissue have herniated.



Spina bifida is a defect in the vertebrae, typically the dorsal arches, with exposure of the meninges and spinal cord. The birth prevalence approximates 1 in 2000 (Cragan, 2009; Dolk, 2010). Most cases are *open spina bifida*—the defect includes the skin and soft tissues. Herniation of a meningeal sac containing neural elements is termed a *myelomeningocele* (Fig. 10-11). When only a meningeal sac is present, the defect is a *meningocele.* Although the sac may be easier to image in the sagittal plane, transverse images more readily demonstrate separation or splaying of the lateral processes.

FIGURE 10-11

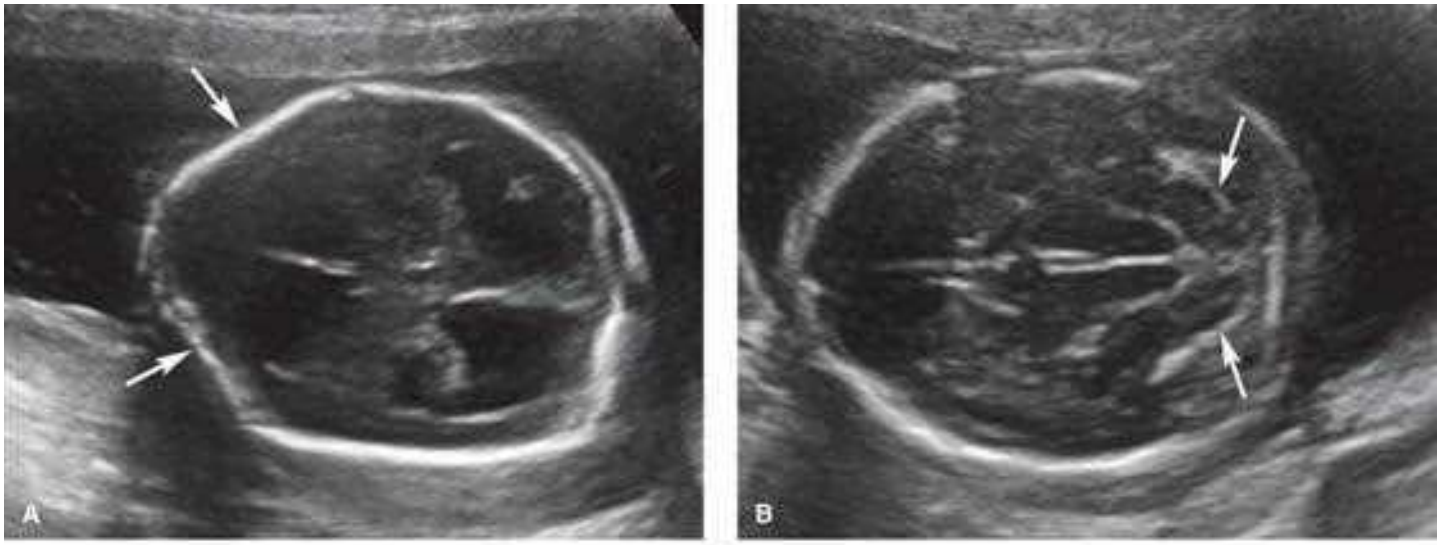
Myelomeningocele. In this sagittal image of a lumbosacral myelomeningocele, the arrowheads indicate nerve roots within the anechoic herniated sac. The overlying skin is visible above the level of the spinal defect but abruptly stops at the defect (*arrow*).



Detection of spina bifida is aided by two characteristic cranial findings (Nicolaides, 1986). Scalloping of the frontal bones is termed the *lemon sign*, and anterior curvature of the cerebellum with effacement of the cisterna magna is the *banana sign* (Fig. 10-12). These findings are manifestations of the Chiari II malformation, also called the *Arnold-Chiari malformation*. This develops when downward displacement of the spinal cord pulls a portion of the cerebellum through the foramen magnum and into the upper cervical canal. *Ventriculomegaly* is another frequent associated sonographic finding, particularly after midgestation. More than 80 percent of infants with open spina bifida require ventriculoperitoneal shunt placement. A small BPD is often present as well. Children with spina bifida require multidisciplinary care to address problems related to the defect, therapeutic shunting, and deficits in swallowing, bladder and bowel function, and ambulation. Fetal myelomeningocele surgery is discussed in Chapter 16 (Open Fetal Surgery).

FIGURE 10-12

Cranial findings in myelomeningocele. **A.** Image of a fetal head at the level of the lateral ventricles demonstrates inward bowing or scalloping of the frontal bones (*arrows*)—the lemon sign. **B.** Image of a fetal head at the level of the posterior fossa shows anterior curvature of the cerebellum (*arrows*) with effacement of the cisterna magna—the banana sign.

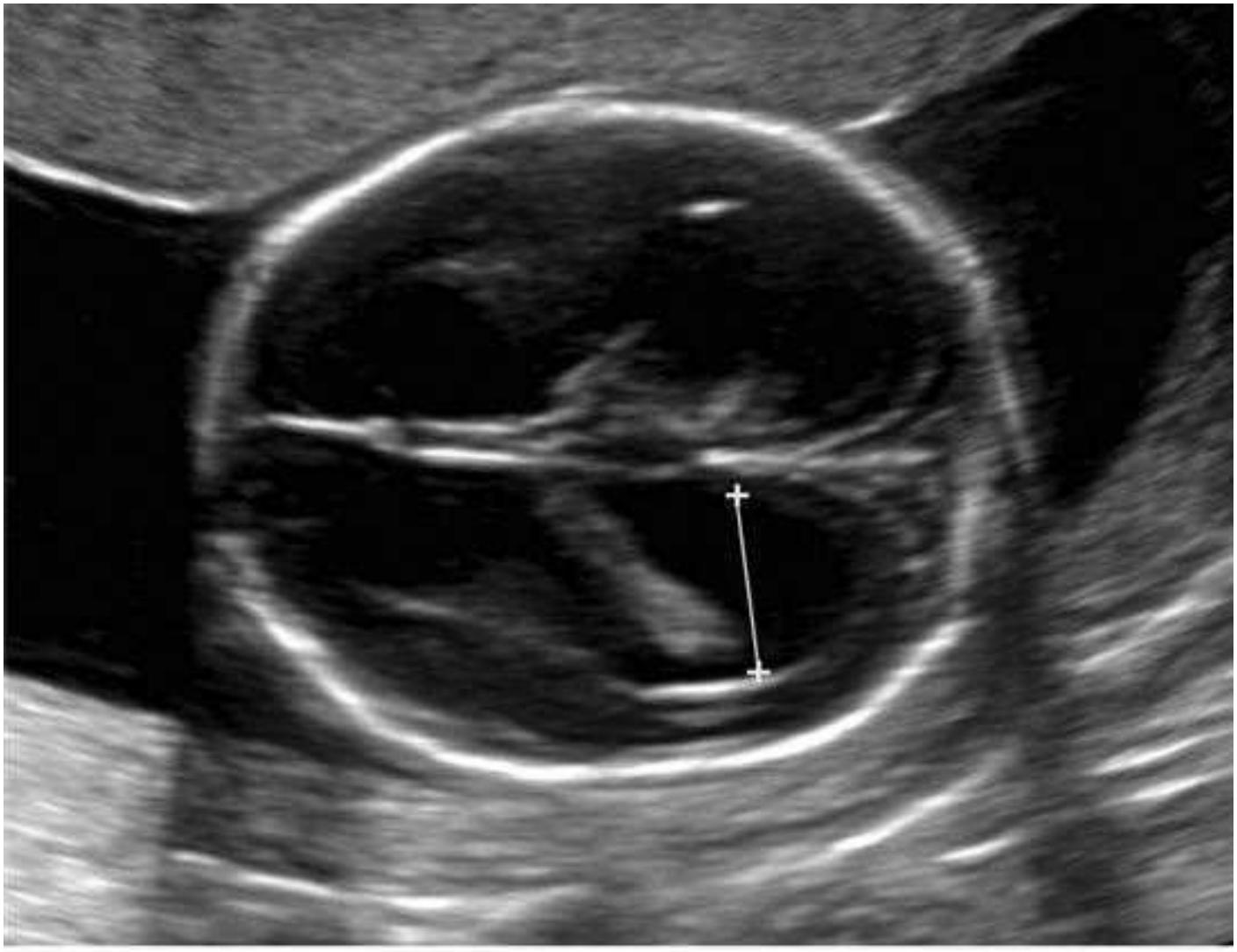


Ventriculomegaly

Characterized by distention of the cerebral ventricles by cerebrospinal fluid (CSF), this finding is a nonspecific marker of abnormal brain development (Pilu, 2011). The atrium normally measures between 5 and 10 mm from 15 weeks' gestation until term (see Fig. 10-6). Mild ventriculomegaly is diagnosed when the atrial width measures 10 to 15 mm (Fig. 10-13), and overt or severe ventriculomegaly when it exceeds 15 mm. The larger the atrium, the greater the likelihood of an abnormal outcome (Gaglioti, 2009; Joó, 2008). CSF is produced within the ventricles by the *choroid plexus*, which is composed of loose connective tissue surrounding an epithelium-lined capillary core. The choroid plexus often appears to *dangle* within the ventricle when severe ventriculomegaly is present.

FIGURE 10-13

Ventriculomegaly. In this transverse view of the cranium, the white line depicts measurement of the atrium of the lateral ventricle, which measured 12 mm, consistent with mild ventriculomegaly.



Ventriculomegaly may be caused by various genetic and environmental insults. It may be due to other central nervous system (CNS) abnormalities—such as Dandy-Walker malformation or holoprosencephaly, to an obstructive process—such as aqueductal stenosis, or to a destructive process—such as porencephaly or an intracranial teratoma. Initial evaluation includes a targeted examination of fetal anatomy, testing for congenital infections such as cytomegalovirus and toxoplasmosis, and chromosomal microarray analysis, which is described in Chapter 13 (Chromosomal Microarray Analysis). Fetal MR imaging should be considered to assess for associated abnormalities that may not be detectable sonographically.

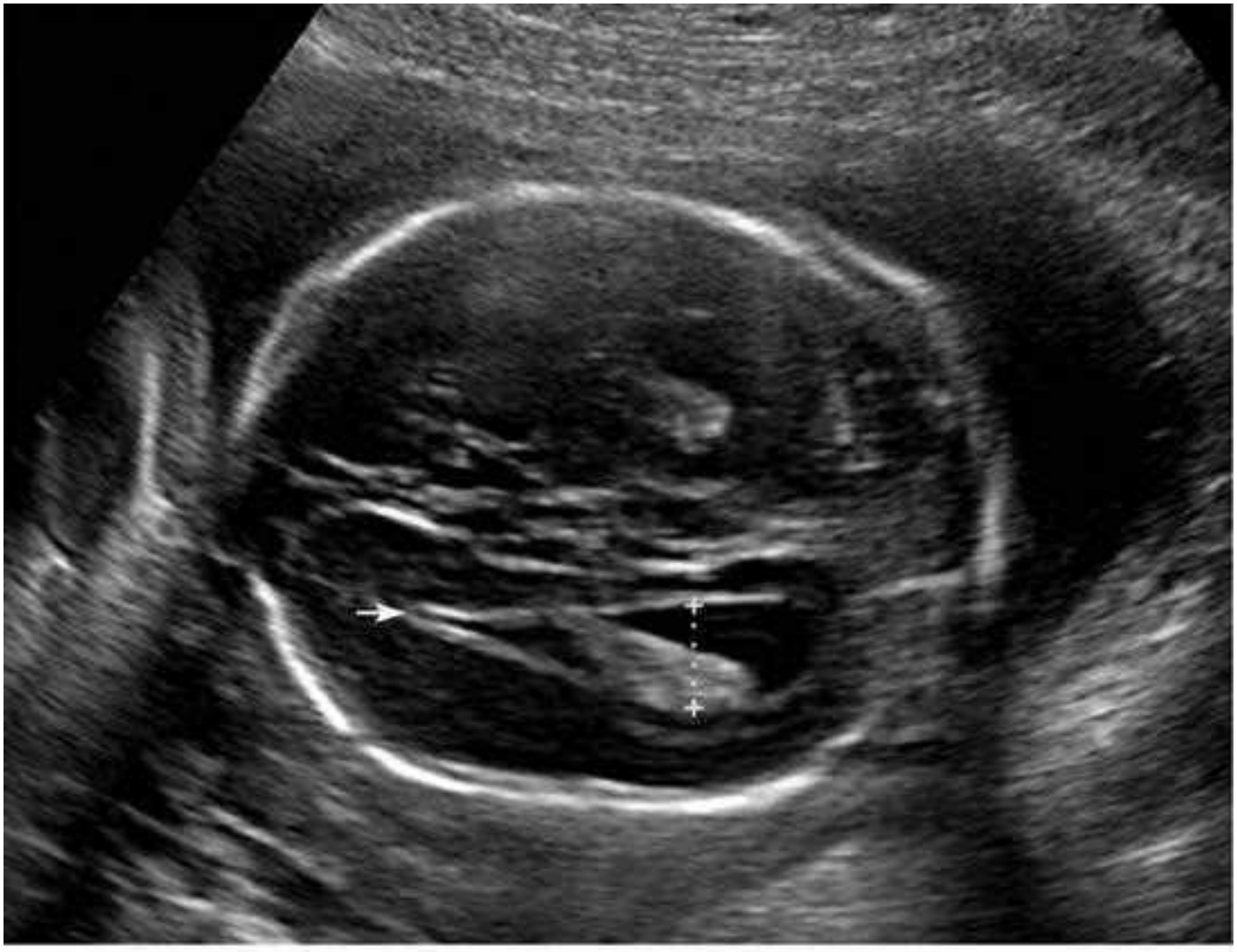
Prognosis is generally determined by etiology, severity, and rate of progression. However, even with mild-appearing and isolated ventriculomegaly, prognosis can vary widely. In a systematic review of nearly 1500 mild-to-moderate cases, 1 to 2 percent were associated with congenital infection, 5 percent with aneuploidy, and 12 percent with neurological abnormality (Devaseelan, 2010). A neurological abnormality was significantly more common if ventriculomegaly progressed with advancing gestation.

Agenesis of the Corpus Callosum

The corpus callosum is the major fiber bundle connecting reciprocal regions of the cerebral hemispheres. With complete agenesis of the corpus callosum, a normal cavum septum pellucidum cannot be visualized sonographically. Also, the frontal horns are displaced laterally, and the atria show mild enlargement posteriorly—such that the ventricle has a characteristic “teardrop” appearance (Fig. 10-14). Callosal dysgenesis involves only the caudal portions—the body and splenium—and consequently may be more difficult to detect prenatally.

FIGURE 10-14

Agenesis of the corpus callosum. This image demonstrates a “teardrop” shaped ventricle with mild ventriculomegaly (*dotted line*) and laterally displaced frontal horns (*arrow*). A normal cavum septum pellucidum cannot be visualized.



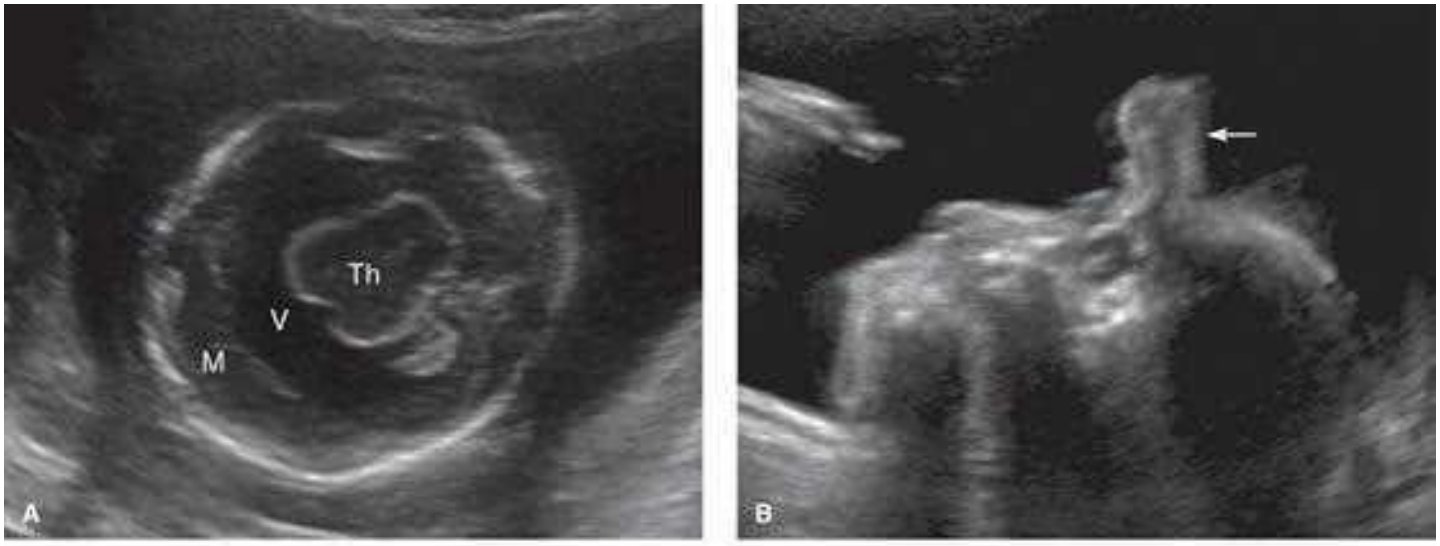
In population-based studies, agenesis of the corpus callosum has a prevalence of 1 in 5000 births (Glass, 2008; Szabo, 2011). In a review of apparently isolated cases, fetal MR imaging identified additional brain abnormalities in more than 20 percent (Sotiriadis, 2012). If the anomaly was still considered isolated following MR imaging, normal developmental outcome was reported in 75 percent of cases, but severe disability occurred in 12 percent. Agenesis of the corpus callosum is associated with other anomalies, aneuploidy, and more than 200 genetic syndromes. Thus, genetic counseling can be challenging.

Holoprosencephaly

In early normal brain development, the prosencephalon or forebrain divides as it becomes the telencephalon and diencephalon. With holoprosencephaly, the prosencephalon fails to divide completely into two separate cerebral hemispheres and underlying paired diencephalic structures. Main forms of holoprosencephaly are a continuum that contains, with decreasing severity, *alobar*, *semilobar*, and *lobar* types. In the most severe form—*alobar holoprosencephaly*—a single monoventricle, with or without a covering mantle of cortex, surrounds fused central thalami (Fig. 10-15). In *semilobar holoprosencephaly*, partial separation of the hemispheres occurs. *Lobar holoprosencephaly* is characterized by a variable degree of fusion of frontal structures and should be considered when a normal CSP cannot be seen.

FIGURE 10-15

Alobar holoprosencephaly. **A.** Transverse cranial image of a fetus with alobar holoprosencephaly, depicting fused thalami (*Th*) encircled by a monoventricle (*V*) with a covering mantle *(M)* of cortex. The midline falx is absent. (Reproduced with permission from Rafael Levy, RDMS.) **B.** In this profile view of the face, a soft tissue mass—a proboscis (*arrow*), protrudes from the region of the forehead.



Differentiation into two cerebral hemispheres is induced by prechordal mesenchyme, which is also responsible for differentiation of the midline face. Thus, holoprosencephaly may be associated with anomalies of the orbits and eyes—hypotelorism, cyclopia, or micro-ophthalmia; lips—median cleft; or nose—ethmocephaly, cebocephaly, or arhinia with proboscis (see Fig. 10-15).

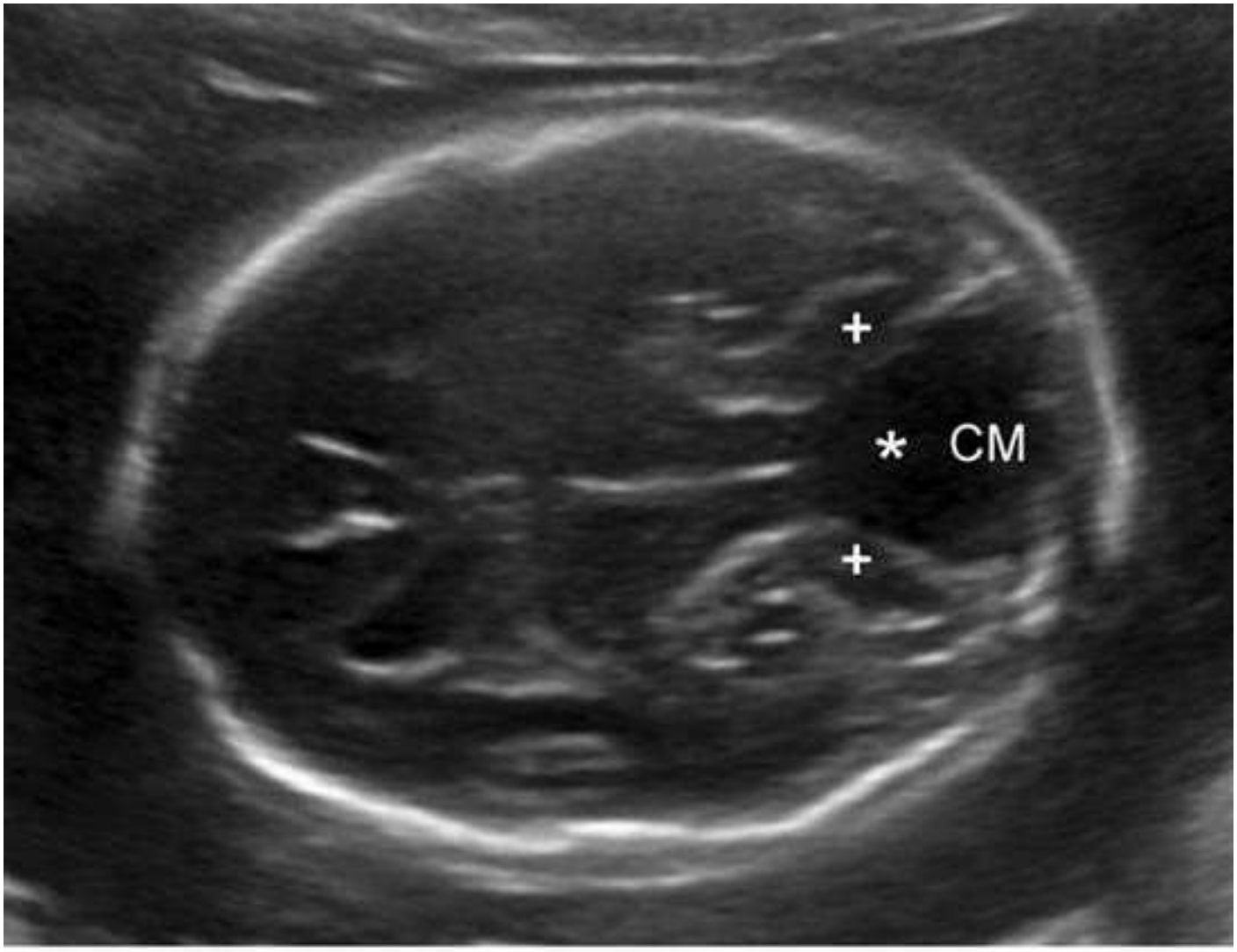
The birth prevalence of holoprosencephaly is only 1 in 10,000 to 15,000. However, the abnormality has been identified in nearly 1 in 250 early abortuses, which attests to the extremely high in-utero lethality (Orioli, 2010; Yamada, 2004). The alobar form accounts for 40 to 75 percent of cases, and 30 to 40 percent have a numerical chromosomal abnormality, particularly trisomy 13 (Orioli, 2010; Solomon, 2010). Conversely, two thirds of trisomy 13 cases are found to have holoprosencephaly. Fetal karyotype or chromosomal microarray analysis should be offered when this anomaly is identified.

Dandy-Walker Malformation—Vermian Agenesis

This posterior fossa abnormality is characterized by agenesis of the cerebellar vermis, posterior fossa enlargement, and elevation of the tentorium. Sonographically, fluid in the enlarged cisterna magna visibly communicates with the fourth ventricle through the cerebellar vermis defect, with visible separation of the cerebellar hemispheres (Fig. 10-16). The birth prevalence approximates 1 in 12,000 (Long, 2006). Associated anomalies and aneuploidy are common. These include ventriculomegaly in 30 to 40 percent, other anomalies in approximately 50 percent, and aneuploidy in 40 percent (Ecker, 2000; Long, 2006). Dandy-Walker malformation is also associated with numerous genetic and sporadic syndromes, congenital viral infections, and teratogen exposure, all of which greatly affect the prognosis. Thus, the initial evaluation mirrors that for ventriculomegaly (Ventriculomegaly).

FIGURE 10-16

Dandy-Walker malformation. This transcerebellar image demonstrates agenesis of the cerebellar vermis. The cerebellar hemispheres (+) are widely separated by a fluid collection that connects the 4th ventricle (*asterisk*) to the enlarged cisterna magna (*CM*).



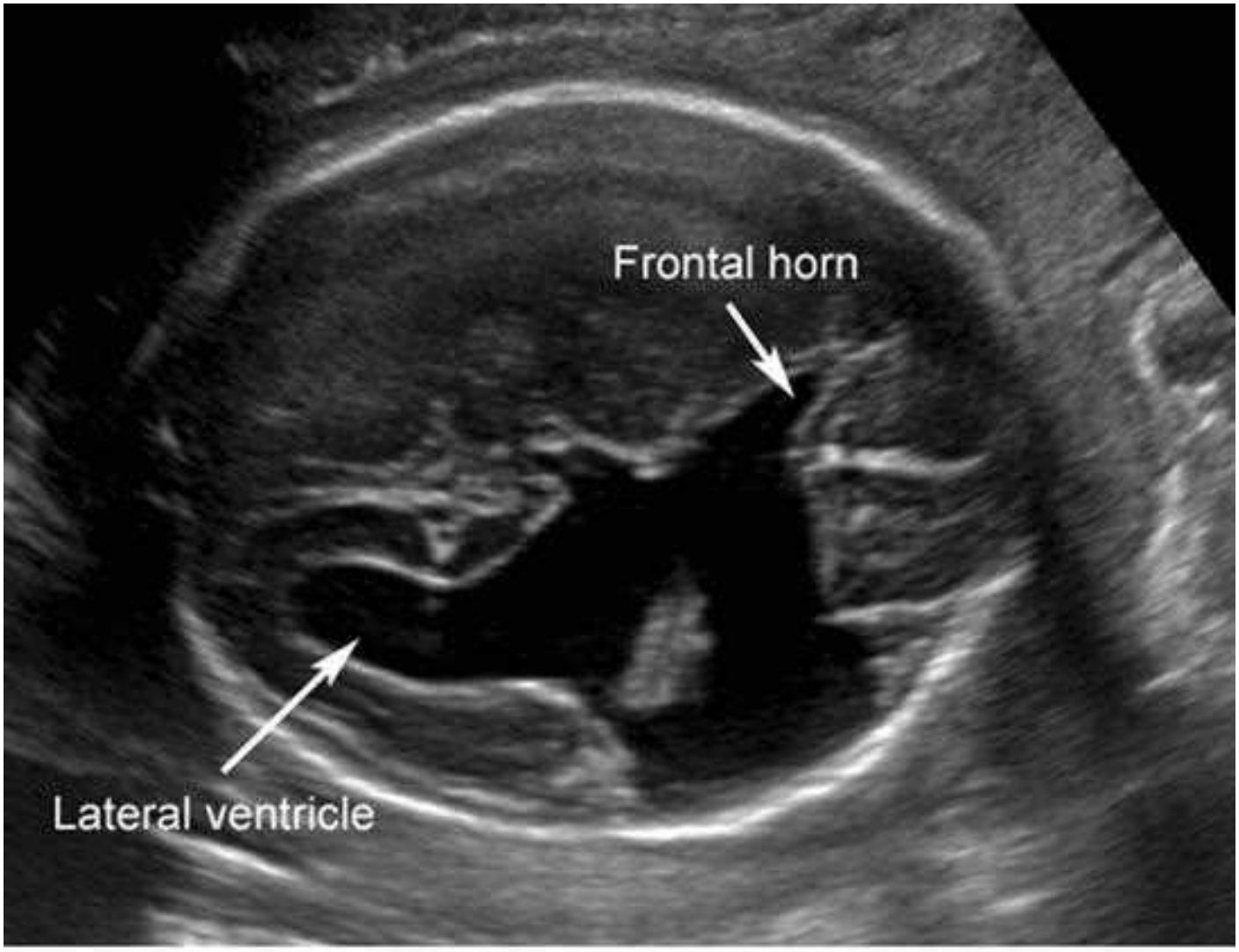
Inferior vermian agenesis, also called *Dandy-Walker variant*, is a term used when only the inferior portion of the vermis is absent. But, even when vermian agenesis appears to be partial and relatively subtle, the prevalence of associated anomalies and aneuploidy is still high, and the prognosis is often poor (Ecker, 2000; Long, 2006).

Schizencephaly and Porencephaly

Schizencephaly is a rare brain abnormality characterized by clefts in one or both cerebral hemispheres, typically involving the perisylvian fissure. The cleft is lined by heterotopic gray matter and communicates with the ventricle, extending through the cortex to the pial surface (Fig. 10-17). Schizencephaly is believed to be an abnormality of neuronal migration, which explains its typically delayed recognition until after midpregnancy (Howe, 2012). It is associated with absence of the cavum septum pellucidum, resulting in the frontal horn communication shown in the image below.

FIGURE 10-17

Schizencephaly. This transverse image of the fetal head shows a large cleft that extends from the right lateral ventricle through the cortex. Because the borders of the cleft are separate, the defect is termed *open-lipped*. (Reproduced with permission from Michael Davidson, RDMS.)



In contrast, porencephaly is a cystic space within the brain that is lined by white matter and may or may not communicate with the ventricular system. It is generally considered to be a destructive lesion and may develop following intracranial hemorrhage in the setting of neonatal alloimmune thrombocytopenia or following death of a monochorionic co-twin (Fig. 45-20). Fetal MR imaging should be considered when either of these CNS anomalies is identified.

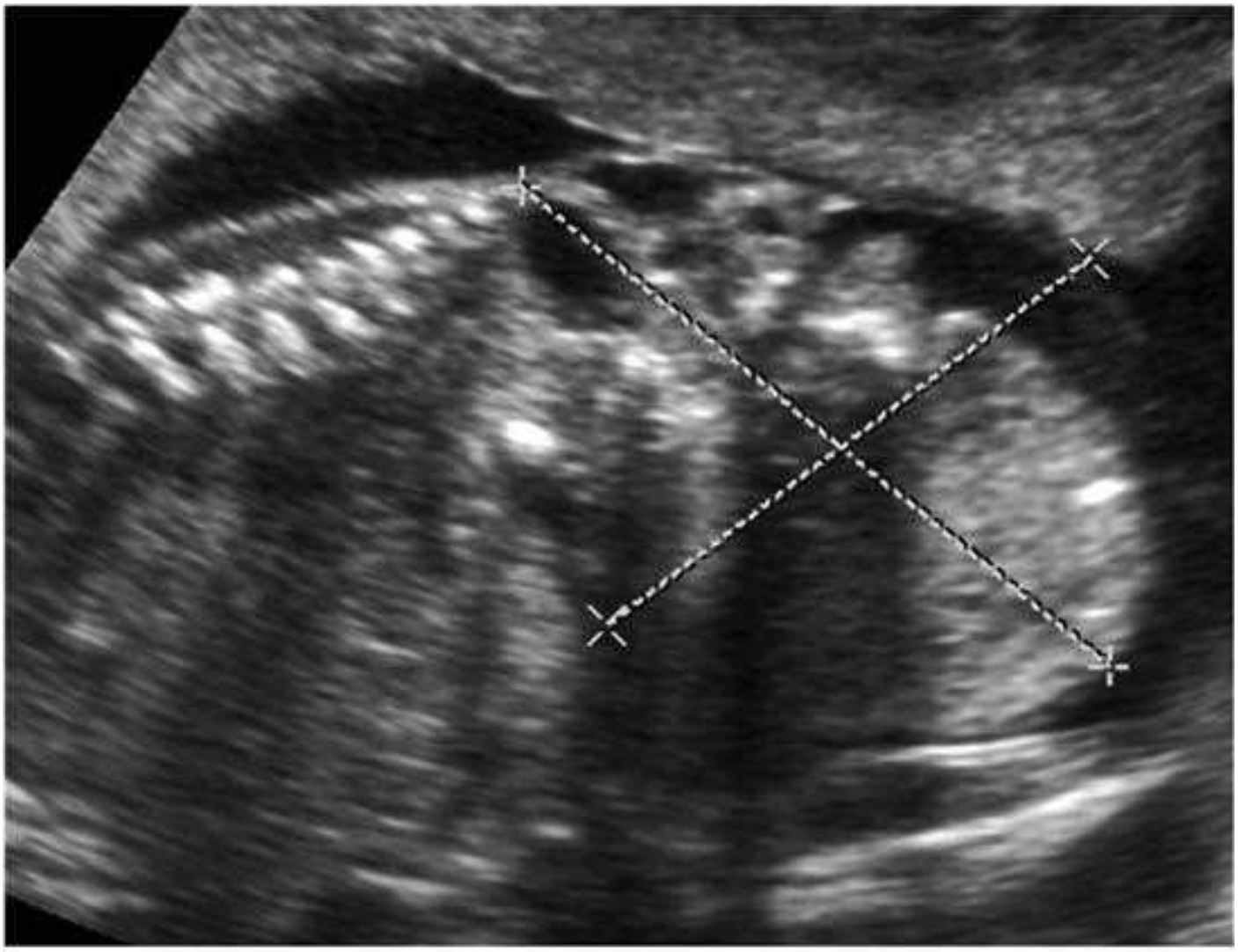
Sacrococcygeal Teratoma

This germ cell tumor is one of the most common tumors in neonates, with a birth prevalence of approximately 1 in 28,000 (Derikx, 2006; Swamy, 2008). It is thought to arise from the totipotent cells along Hensen node, anterior to the coccyx. Classification of sacrococcygeal teratoma (SCT) includes four types (Altman, 1974). Type 1 is predominantly external with a minimal presacral component; type 2 is predominantly external but with a significant intrapelvic component; type 3 is predominantly internal but with abdominal extension; and type 4 is entirely internal with no external component. The tumor histological type may be mature, immature, or malignant.

Sonographically, SCT appears as a solid and/or cystic mass that arises from the anterior sacrum and usually extends inferiorly and externally as it grows (Fig. 10-18). Solid components often have varying echogenicity, appear disorganized, and may enlarge rapidly with advancing gestation. Internal pelvic components may be more challenging to visualize, and fetal MR imaging should be considered. Hydramnios is frequent, and hydrops may develop from high-output cardiac failure, either as a consequence of tumor vascularity or secondary to bleeding within the tumor and resultant anemia. Mentioned throughout this chapter, hydrops is more fully described in Chapter 15 (Hydrops Fetalis). Fetuses with tumors >5 cm often require cesarean delivery, and classical hysterotomy may be needed (Gucciardo, 2011). As shown in Figure 16-3, fetal surgery is suitable for some SCT cases.

FIGURE 10-18

Sacrococcygeal teratoma. Sonographically, this tumor appears as a solid and/or cystic mass that arises from the anterior sacrum and tends to extend inferiorly and externally as it grows. In this image, a 7 × 6 cm inhomogeneous solid mass is visible below the normal-appearing sacrum. There is also an internal component to the tumor.



Caudal Regression Sequence—Sacral Agenesis

This rare anomaly is characterized by absence of the sacral spine and often portions of the lumbar spine. It is approximately 25 times more common in diabetic pregnancies (Garne, 2012). Sonographic findings include a spine that appears abnormally short, lacks normal lumbosacral curvature, and terminates abruptly above the level of the iliac wings. Because the sacrum does not lie between the iliac wings, they are abnormally close together and may appear "shield-like." There may also be abnormal positioning of the lower extremities and lack of normal local soft tissue development. Caudal regression should be differentiated from *sirenomelia*, which is a rare anomaly characterized by a single fused lower extremity that occupies the midline.

Face and Neck

Normal fetal lips and nose are shown in Figure 10-19. A fetal profile is not a required component of standard examination but may be helpful in identifying cases of *micrognathia*—an abnormally small jaw (Fig. 10-20). Micrognathia should be considered in the evaluation of hydramnios (Chap. 11, Hydramnios). Use of the *ex-utero intrapartum treatment (EXIT)* procedure for severe micrognathia is discussed in Chapter 16 (Ex-Utero Intrapartum Treatment).

FIGURE 10-19

Midline face. This view demonstrates the integrity of the upper lip.

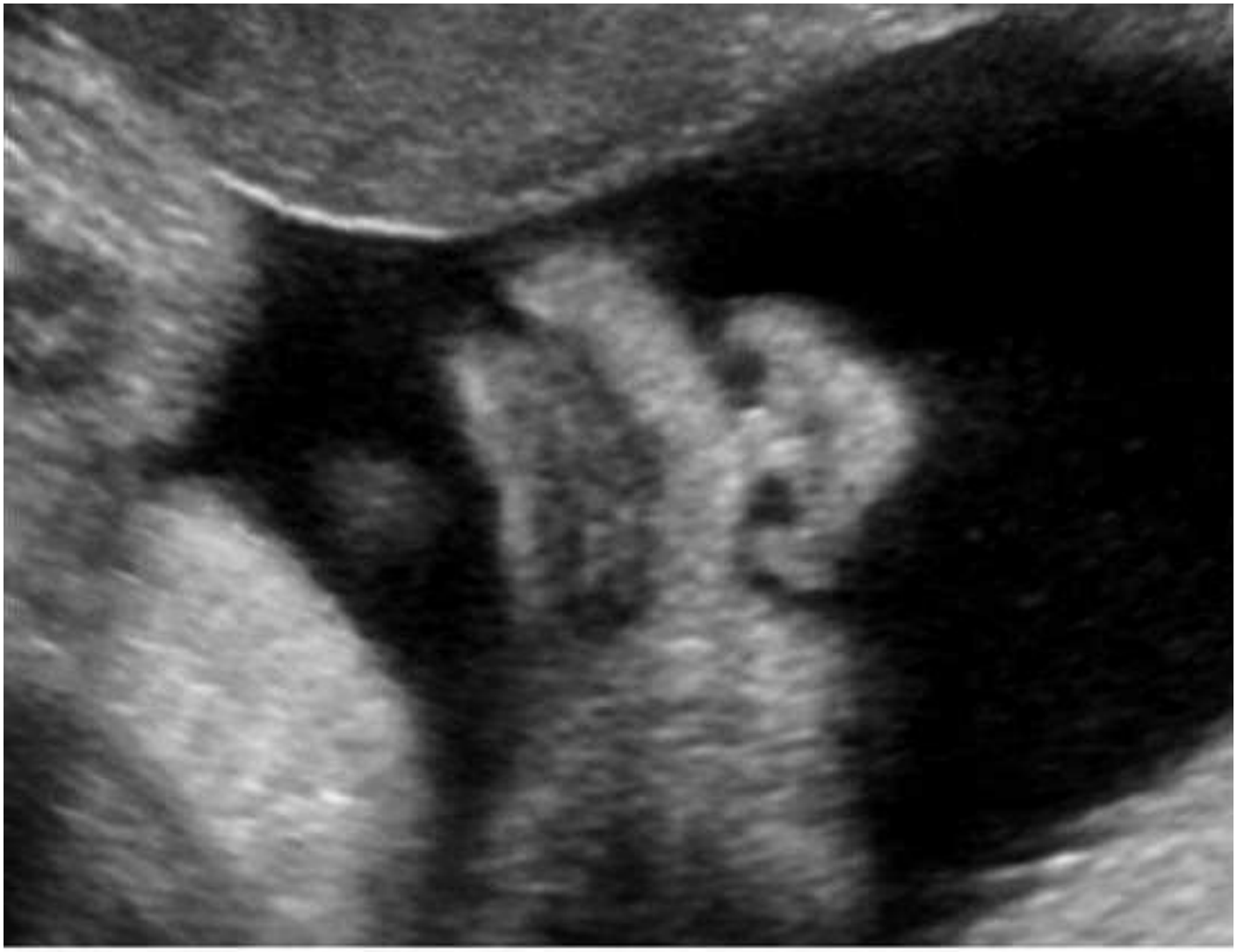
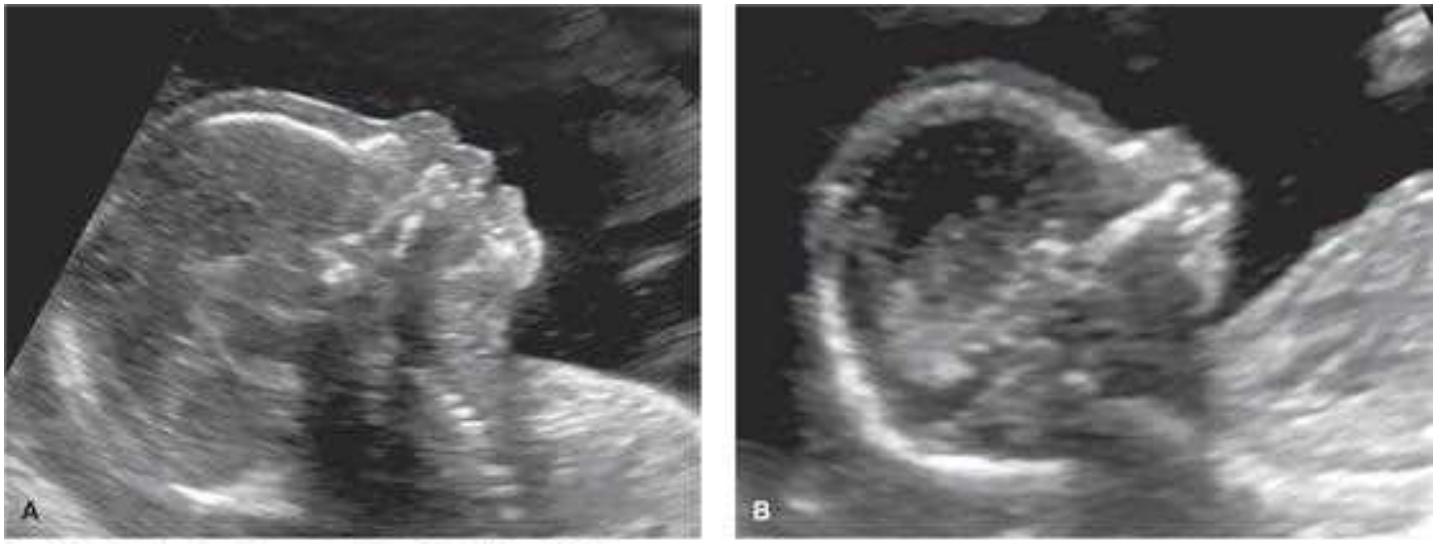


FIGURE 10-20

Fetal profile. **A.** This image depicts a normal fetal profile. **B.** This fetus has severe micrognathia, which creates a severely recessed chin.



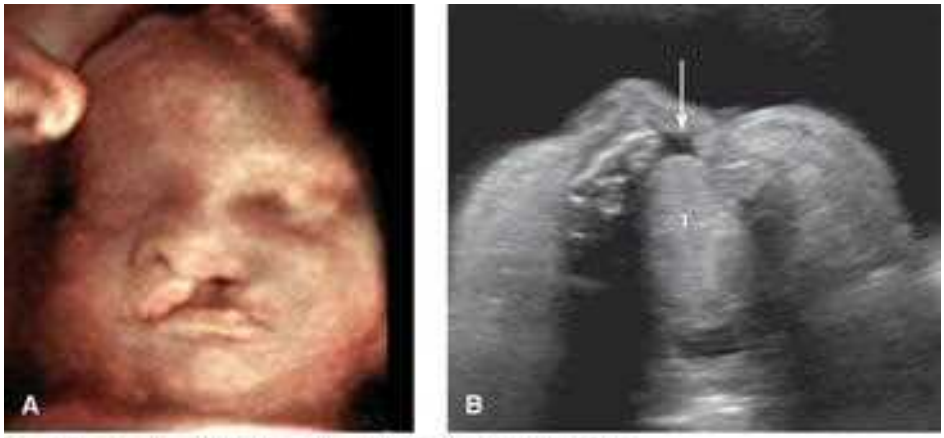
Facial Clefts

There are three main types of clefts. The first type, *cleft lip and palate*, always involves the lip, may also involve the hard palate, can be unilateral or bilateral, and has a birth prevalence that approximates 1 in 1000 (Cragan, 2009; Dolk, 2010). If isolated, the inheritance is multifactorial—with a recurrence risk of 3 to 5 percent

for one prior affected child. If a cleft is visible in the upper lip, a transverse image at the level of the alveolar ridge may demonstrate that the defect also involves the primary palate (Fig. 10-21).

FIGURE 10-21

Cleft lip/palate. **A.** This fetus has a prominent unilateral (left-sided) cleft lip. **B.** Transverse view of the palate in the same fetus demonstrates a defect in the alveolar ridge (*arrow*). The tongue (*T*) is also visible.



In one systematic review of low-risk pregnancies, cleft lip was identified sonographically in only about half of cases (Maarse, 2010). Approximately 40 percent of those detected in prenatal series are associated with other anomalies or syndromes, and aneuploidy is common (Maarse, 2011; Offerdal, 2008). The rate of associated anomalies is highest for bilateral defects that involve the palate. Using data from the Utah Birth Defect Network, Walker and associates (2001) identified aneuploidy in 1 percent with cleft lip alone, 5 percent with unilateral cleft lip and palate, and 13 percent with bilateral cleft lip and palate. It is reasonable to offer fetal chromosomal microarray analysis when a cleft is identified.

The second type of cleft is *isolated cleft palate.* It begins at the uvula, may involve the soft palate, and occasionally involves the hard palate—but does not involve the lip. The birth prevalence approximates 1 in 2000 (Dolk, 2010). Identification of isolated cleft palate has been described using specialized 2- and 3-dimensional sonography (Ramos, 2010; Wilhelm, 2010). However, it is not expected to be visualized during a standard sonographic examination (Maarse, 2011; Offerdal, 2008).

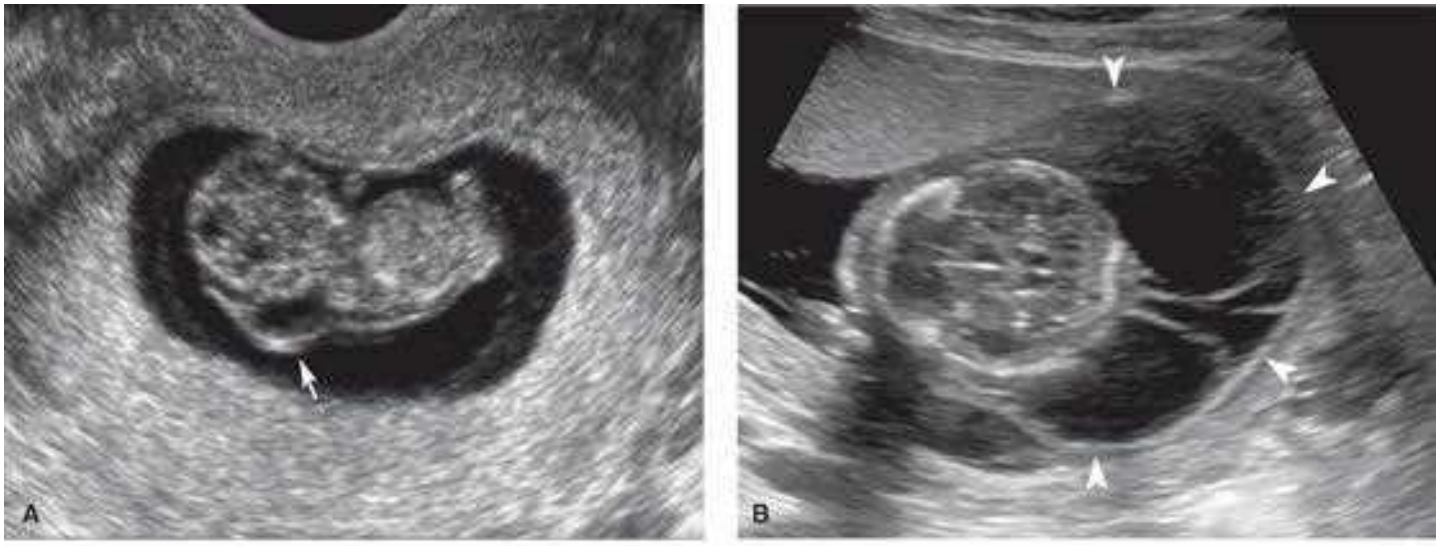
A third type of cleft is *median cleft lip,* which is found in association with several conditions. These include agenesis of the primary palate, hypotelorism, and holoprosencephaly. Median clefts may also be associated with hypertelorism and frontonasal hyperplasia, formerly called the *median cleft face syndrome*.

Cystic Hygroma

This venolymphatic malformation is characterized by fluid-filled sacs that extend from the posterior neck (Fig. 10-22). Cystic hygromas may be diagnosed as early as the first trimester and vary widely in size. They are believed to develop when lymph from the head fails to drain into the jugular vein and accumulates instead in jugular lymphatic sacs. Their birth prevalence approximates 1 in 5000. But, reflecting the high in-utero lethality of the condition, the first-trimester incidence exceeds 1 in 300 (Malone, 2005).

FIGURE 10-22

Cystic hygromas. **A.** This 9-week fetus with a cystic hygroma (*arrow*) was later found to have Noonan syndrome. **B.** Massive multiseptated hygromas (*arrowheads*) in the setting of hydrops fetalis at 15 weeks' gestation.



Up to 70 percent of cystic hygromas are associated with aneuploidy. When cystic hygromas are diagnosed in the first trimester, trisomy 21 is the most common aneuploidy, followed by 45,X and trisomy 18 (Kharrat, 2006; Malone, 2005). First-trimester fetuses with cystic hygromas are five times more likely to be aneuploid than fetuses with a thickened nuchal translucency. When cystic hygromas are diagnosed in the second trimester, approximately 75 percent of aneuploid cases are 45,X—*Turner syndrome* (Johnson, 1993; Shulman, 1992).

Even in the absence of aneuploidy, cystic hygromas confer a significantly greater risk for other anomalies, particularly cardiac anomalies that are flow-related. These include hypoplastic left heart and coarctation of the aorta. Cystic hygromas also may be part of a genetic syndrome. One is *Noonan syndrome,* an autosomal dominant disorder that shares several features with Turner syndrome, including short stature, lymphedema, high-arched palate, and often pulmonary valve stenosis.

Large cystic hygromas are usually associated with hydrops fetalis, rarely resolve, and carry a poor prognosis. Small hygromas may undergo spontaneous resolution, and provided that fetal karyotype and echocardiography results are normal, the prognosis *may* be good. The likelihood of a nonanomalous liveborn neonate with normal karyotype following identification of first-trimester hygroma is approximately 1 in 6 (Kharrat, 2006; Malone, 2005).

Thorax

The lungs appear homogeneous and surround the heart. In the four-chamber view of the heart, they comprise approximately two thirds of the area, with the heart occupying the remaining third. The thoracic circumference is measured at the skin line in a transverse plane at the level of the four-chamber view. In cases of suspected pulmonary hypoplasia secondary to a small thorax, such as with severe skeletal dysplasia, comparison with a reference table may be helpful (Appendix, Fetal Sonographic Measurements). Various abnormalities may appear sonographically as cystic or solid space-occupying lesions or as an effusion outlining the heart or lung(s). Fetal therapy for thoracic abnormalities is discussed in Chapter 16 (Percutaneous Procedures).

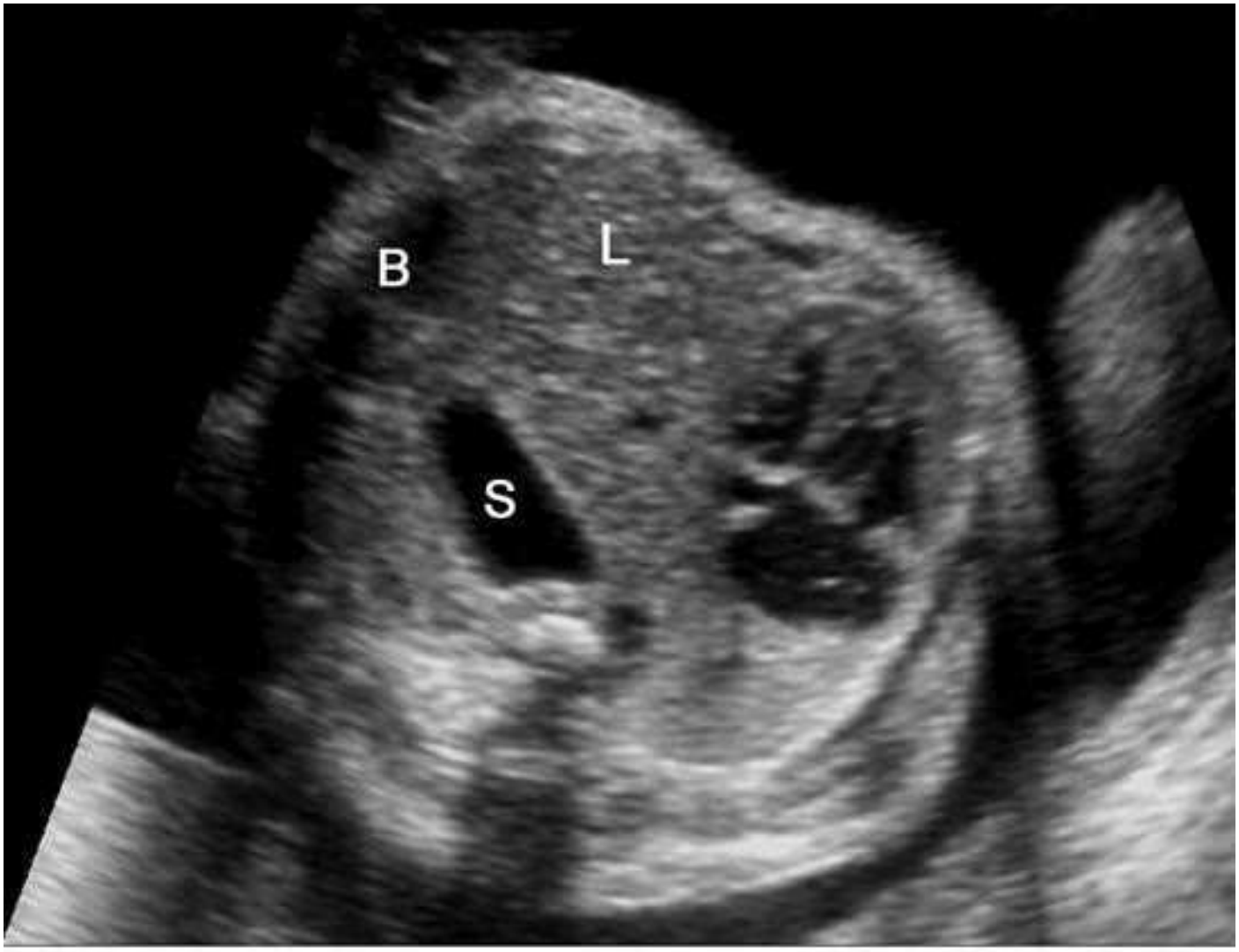
Congenital Diaphragmatic Hernia

This is a defect in the diaphragm through which abdominal organs herniate into the thorax. It is left-sided in approximately 75 percent of cases, right-sided in 20 percent, and bilateral in 5 percent (Gallot, 2007). The prevalence of congenital diaphragmatic hernia (CDH) is 1 in 3000 to 4000 births (Cragan, 2009; Dolk, 2010). Associated anomalies and aneuploidy are found in 40 percent of cases (Gallot, 2007; Stege, 2003). With suspected CDH, targeted sonography and fetal echocardiography should be performed, and fetal chromosomal microarray analysis should be offered. In population-based series, the presence of an associated abnormality reduces the overall survival rate of neonates with CDH from approximately 50 percent to about 20 percent (Colvin, 2005; Gallot, 2007). If there are no associated abnormalities, the major causes of neonatal mortality are pulmonary hypoplasia and pulmonary hypertension.

Sonographically, left-sided CDH typically shows dextroposition of the heart toward the right side of the thorax and a cardiac axis pointing toward the midline (Fig. 10-23). Associated findings include the stomach bubble or bowel peristalsis in the chest and a wedge-shaped mass—the liver—located anteriorly in the left hemithorax. Liver herniation complicates at least 50 percent of cases and is associated with a 30-percent reduction in the survival rate (Mullassery, 2010). With large lesions, impaired swallowing and mediastinal shift may result in hydramnios and hydrops, respectively.

FIGURE 10-23

Congenital diaphragmatic hernia. In this transverse view of the thorax, the heart is shifted to the far right side of the chest by a left-sided diaphragmatic hernia containing stomach (*S*), liver (*L*), and bowel (*B*).



Efforts to reduce neonatal mortality rates and need for extracorporeal membrane oxygenation (ECMO) have focused on indicators such as the sonographic lung-to-head ratio, MR imaging measurements of lung volume, and the degree of liver herniation (Jani, 2012; Oluyomi-Obi, 2016; Worley, 2009). These and fetal therapy for CDH are reviewed in Chapter 16 (Congenital Diaphragmatic Hernia).

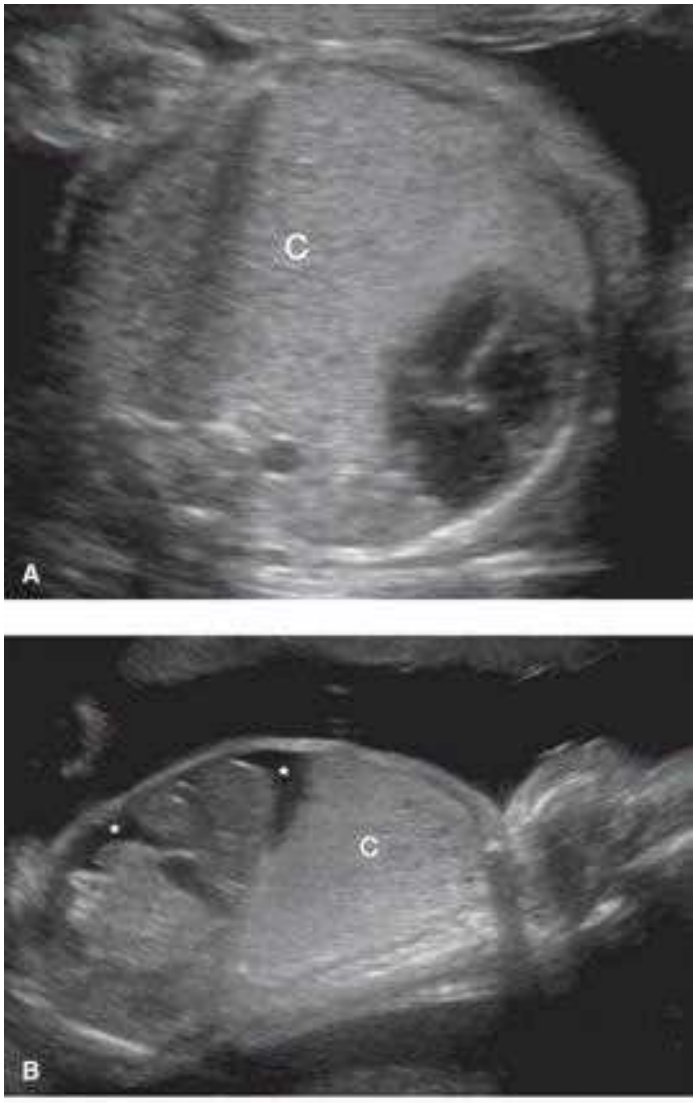
Congenital Cystic Adenomatoid Malformation

This abnormality represents a hamartomatous overgrowth of terminal bronchioles that communicates with the tracheobronchial tree. It is also called *congenital pulmonary airway malformation (CPAM),* based on an understanding that not all histopathological types are *cystic* or *adenomatoid* (Azizkhan, 2008; Stocker, 1977, 2002). The estimated prevalence is 1 in 6000 to 8000 births, and this rate is rising because of improved sonographic detection of milder cases (Burge, 2010; Duncombe, 2002).

Sonographically, congenital cystic adenomatoid malformation (CCAM) is a well-circumscribed thoracic mass that may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 10-24). It usually involves one lobe, has blood supply from the pulmonary artery, and drains into the pulmonary veins. Lesions with cysts ≥5 mm are generally termed *macrocystic*, and lesions with cysts <5 mm are termed *microcystic* (Adzick, 1985).

FIGURE 10-24

Transverse **(A)** and sagittal **(B)** images of a 26-week fetus with a very large left-sided microcystic congenital cystic adenomatoid malformation (CCAM). The mass (*C*) fills the thorax and has shifted the heart to the far right side of the chest, with development of ascites (*asterisks*). Fortunately, the mass did not continue to grow, the ascites resolved, and the neonate was delivered at term and did well following resection.



In a review of 645 CCAM cases, the overall survival rate exceeded 95 percent, and 30 percent of cases demonstrated apparent prenatal resolution. The other 5 percent of cases—typically very large lesions with associated mediastinal shift—were complicated by hydrops, and the prognosis was poor (Cavoretto, 2008). CCAMs often become less conspicuous with advancing gestation. However, a subset of CCAMs demonstrates rapid growth between 18 and 26 weeks' gestation. Corticosteroid therapy has been used for large microcystic lesions to forestall growth and potentially ameliorate hydrops (Curran, 2010; Peranteau, 2016). If a large dominant cyst is present, thoracoamnionic shunt placement may lead to hydrops resolution. Fetal therapy for CCAM is discussed in Chapter 16 (Percutaneous Procedures).

Pulmonary Sequestration

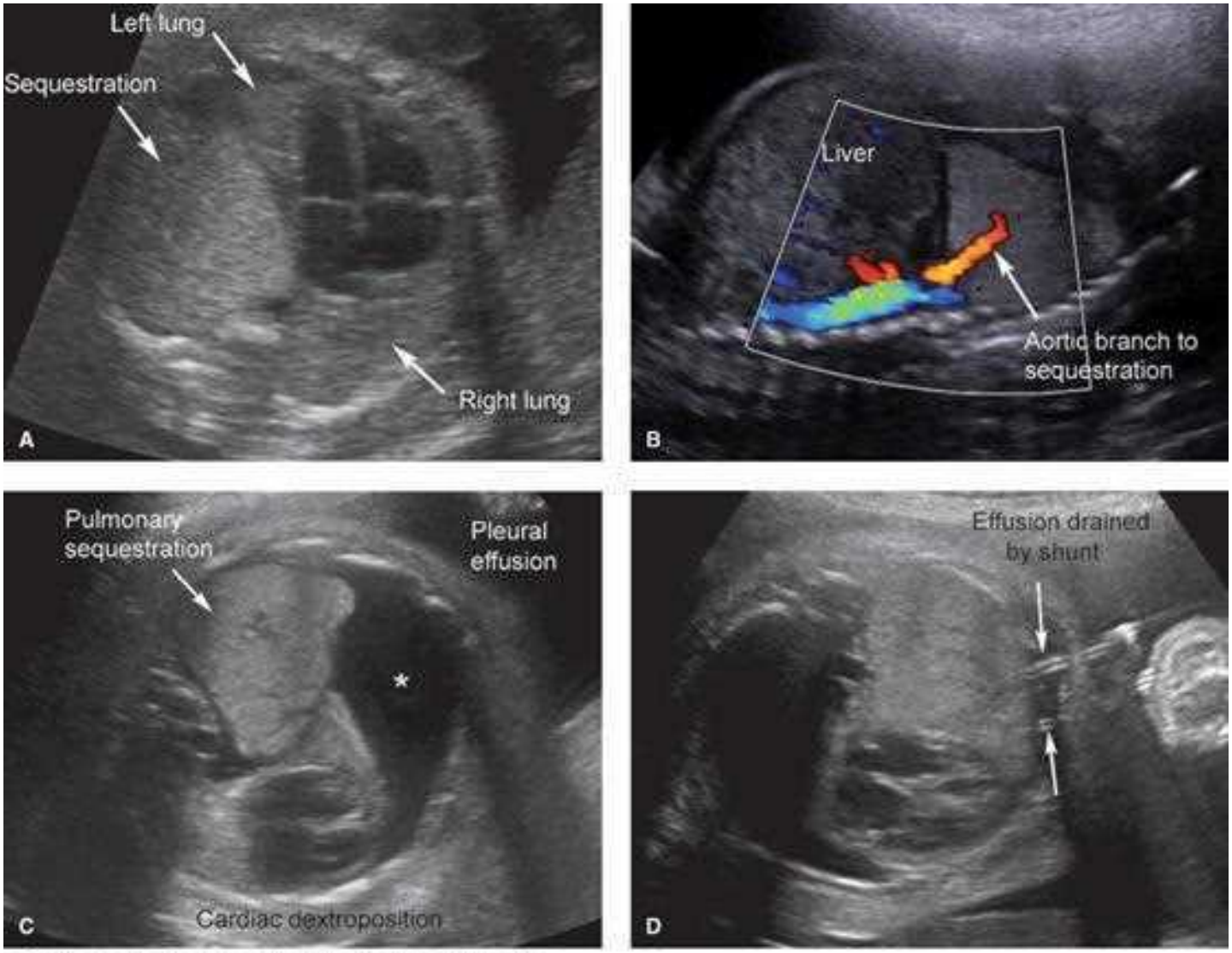
Also called a *bronchopulmonary sequestration*, this abnormality is an accessory lung bud "sequestered" from the tracheobronchial tree, that is, a mass of nonfunctioning lung tissue. Most cases diagnosed prenatally are *extralobar,* which means they are enveloped in their own pleura. Overall, however, most sequestrations present in adulthood and are *intralobar*—within the pleura of another lobe. Extralobar pulmonary sequestration is considered significantly less common than CCAM, and no precise prevalence has been reported. Lesions have a left-sided predominance and most often involve the left lower lobe. Of cases, 10 to 20 percent are located below the diaphragm, and associated anomalies have been reported in approximately 10 percent of cases (Yildirim, 2008).

Sonographically, pulmonary sequestration presents as a homogeneous, echogenic thoracic mass (Fig. 10-25A). Thus, it may resemble a microcystic CCAM. However, the blood supply is from the systemic circulation—from the aorta rather than the pulmonary artery (see Fig. 10-25B). In 5 to 10 percent with pulmonary sequestration, a large ipsilateral pleural effusion develops, and without treatment, this may result in pulmonary hypoplasia or hydrops (see Fig. 10-25C,D). Therapeutic thoracoamnionic shunting of effusions is discussed in Chapter 16 (Percutaneous Procedures). Hydrops may also result from mediastinal shift or high-output cardiac failure due to the left-to-right shunt imposed by the mass. In the absence of a pleural effusion, the reported survival rate exceeds 95 percent, and 40 percent of cases demonstrate apparent prenatal resolution (Cavoretto, 2008).

FIGURE 10-25

Pulmonary sequestration. **A.** This transverse image at the level of the 4-chamber view of the heart depicts a pulmonary sequestration involving the left lower lobe in a 25-week fetus. Mass effect leads to dextroposition of the heart to the right side of the chest. **B.** A sagittal image shows the pulmonary sequestration supplied by a branch of the abdominal aorta. **C.** Over the next 3 weeks, a large ipsilateral pleural effusion develops (*asterisk*), resulting in mediastinal shift and

dextroposition of the heart to the far right thorax. **D.** Following placement of a double-pigtail shunt through the chest wall and into the effusion, the effusion drained and the lung significantly reexpanded. Arrows points to coils of the pigtail shunt. (Reproduced with permission from Dr. Elaine Duryea.)

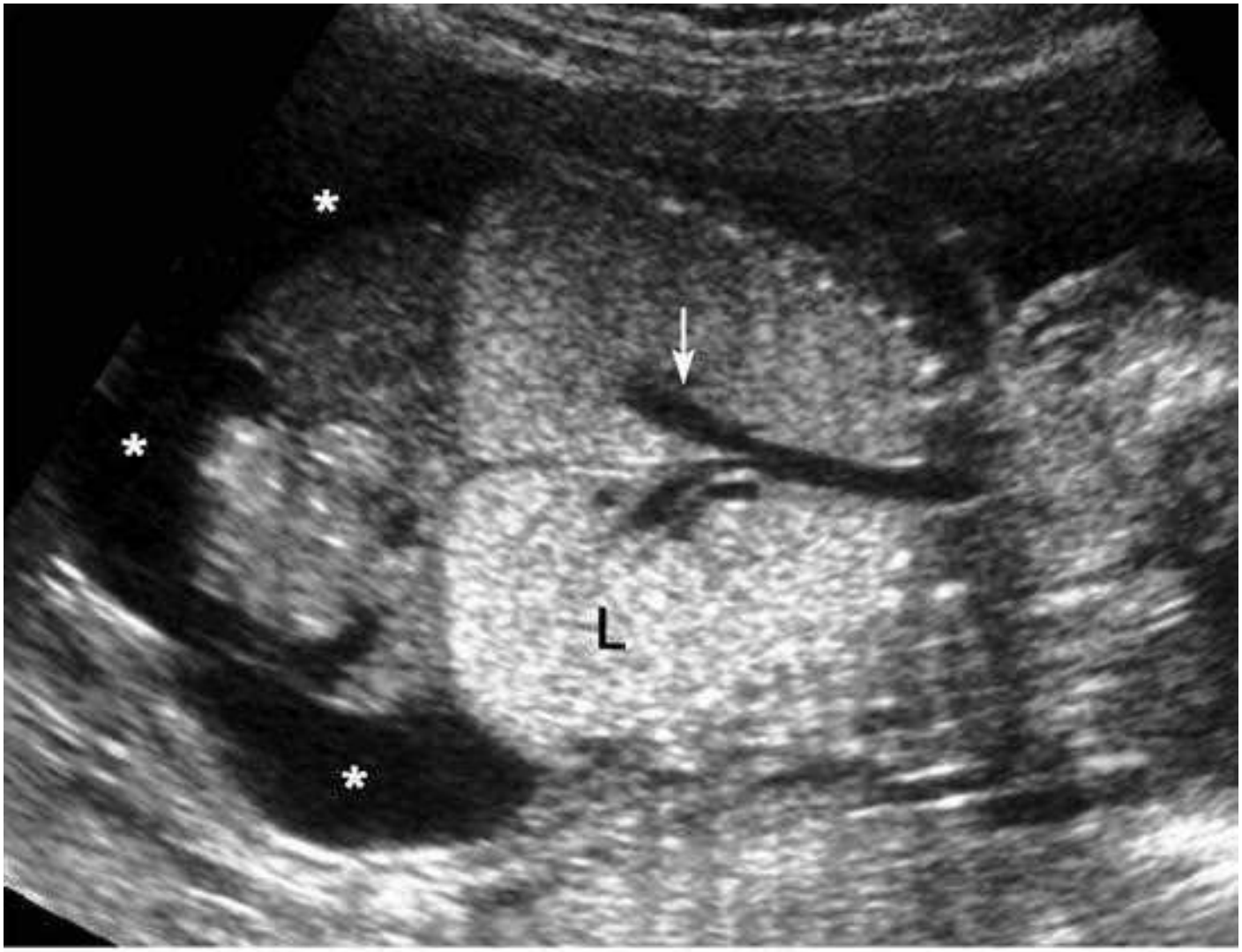


Congenital High Airway Obstruction Sequence

This rare anomaly usually results from laryngeal or tracheal atresia. The normal egress of lung fluid is obstructed, and the tracheobronchial tree and lungs become massively distended. Sonographically, the lungs appear brightly echogenic, the bronchi are dilated, the diaphragm is flattened or everted, and the heart is compressed (Fig. 10-26). Venous return is impaired and ascites develops, typically followed by hydrops. In one review of 118 cases, associated anomalies were identified in more than 50 percent (Sanford, 2012). Congenital high airway obstruction sequence (CHAOS) is a feature of the autosomal recessive *Fraser syndrome* and has been associated with the 22q11.2 deletion syndrome. In some cases, the obstructed airway spontaneously perforates, which potentially confers a better prognosis. The EXIT procedure has significantly improved outcome in selected cases (Chap. 16, Ex-Utero Intrapartum Treatment).

FIGURE 10-26

Congenital high airway obstruction sequence (CHAOS). The lungs appear brightly echogenic, and one is marked by an “L.” The bronchi, one of which is noted by an arrow, are dilated with fluid. Flattening and eversion of the diaphragm is common, as is ascites (*asterisks*).



Heart

Cardiac malformations are the most common class of congenital anomalies, and their overall prevalence is 8 in 1000 births (Cragan, 2009). Almost 90 percent of cardiac defects are multifactorial or polygenic in origin, another 1 to 2 percent result from a single-gene disorder or gene-deletion syndrome, and 1 to 2 percent stem from exposure to a teratogen such as isotretinoin, hydantoin, or maternal diabetes. Based on data from population-based registries, approximately 1 in 8 liveborn and stillborn neonates with a congenital heart defect has a chromosomal abnormality (Dolk, 2010; Hartman, 2011). Of chromosomal abnormalities associated with cardiac anomalies, trisomy 21 accounts for more than 50 percent of cases. Others are trisomy 18, 22q11.2 deletion, trisomy 13, and monosomy X (Hartman, 2011). Of these aneuploid fetuses, 50 to 70 percent also have extracardiac anomalies. Chromosomal microarray analysis should be offered when cardiac defects are found.

Traditionally, detection of congenital cardiac anomalies is more challenging than for anomalies of other organ systems. Routine second-trimester sonography identifies approximately 40 percent of those with major cardiac anomalies before 22 weeks' gestation, and specialized sonography may identify 80 percent (Romosan, 2009; Trivedi, 2012). For selected anomalies, prenatal detection may improve neonatal survival. This may be particularly true for *ductal-dependent* lesions—those requiring prostaglandin infusion after birth to keep the ductus arteriosus open (Franklin, 2002; Mahle, 2001; Tworetzky, 2001).

Basic Cardiac Examination

Standard cardiac assessment includes a four-chamber view, evaluation of rate and rhythm, and evaluation of the left and right ventricular outflow tracts (Figs. 10–27 and 10-28A–C). Examination of the cardiac outflow tracts aids detection of abnormalities that might not be appreciated in the four-chamber view. These include tetralogy of Fallot, transposition of the great vessels, and truncus arteriosus.

FIGURE 10-27

The four-chamber view. **A.** Diagram demonstrating measurement of the cardiac axis from the four-chamber view of the fetal heart. **B.** Sonogram of the four-chamber view at 22 weeks' gestation shows the normal symmetry of the atria and ventricles, normal position of the mitral and triscuspid valves, pulmonary veins entering the left atrium, and descending aorta (*Ao*). L = left; LA = left atrium; LV = left ventricle; R = right; RA = right atrium; RV = right ventricle.

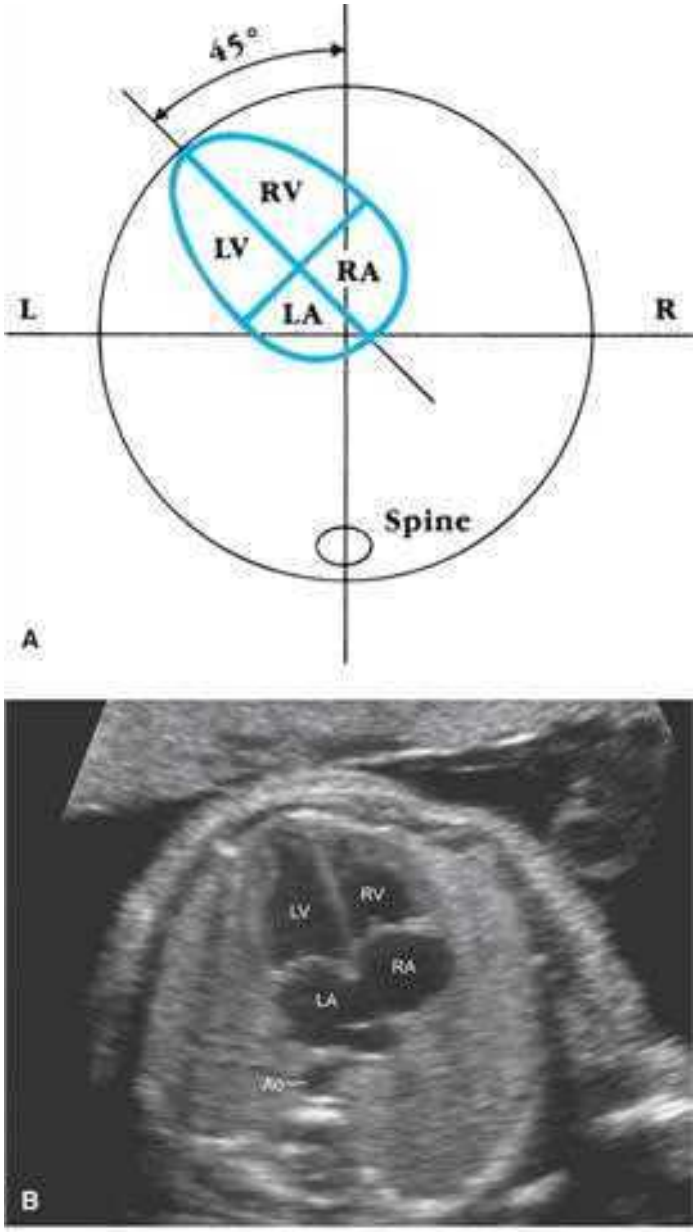
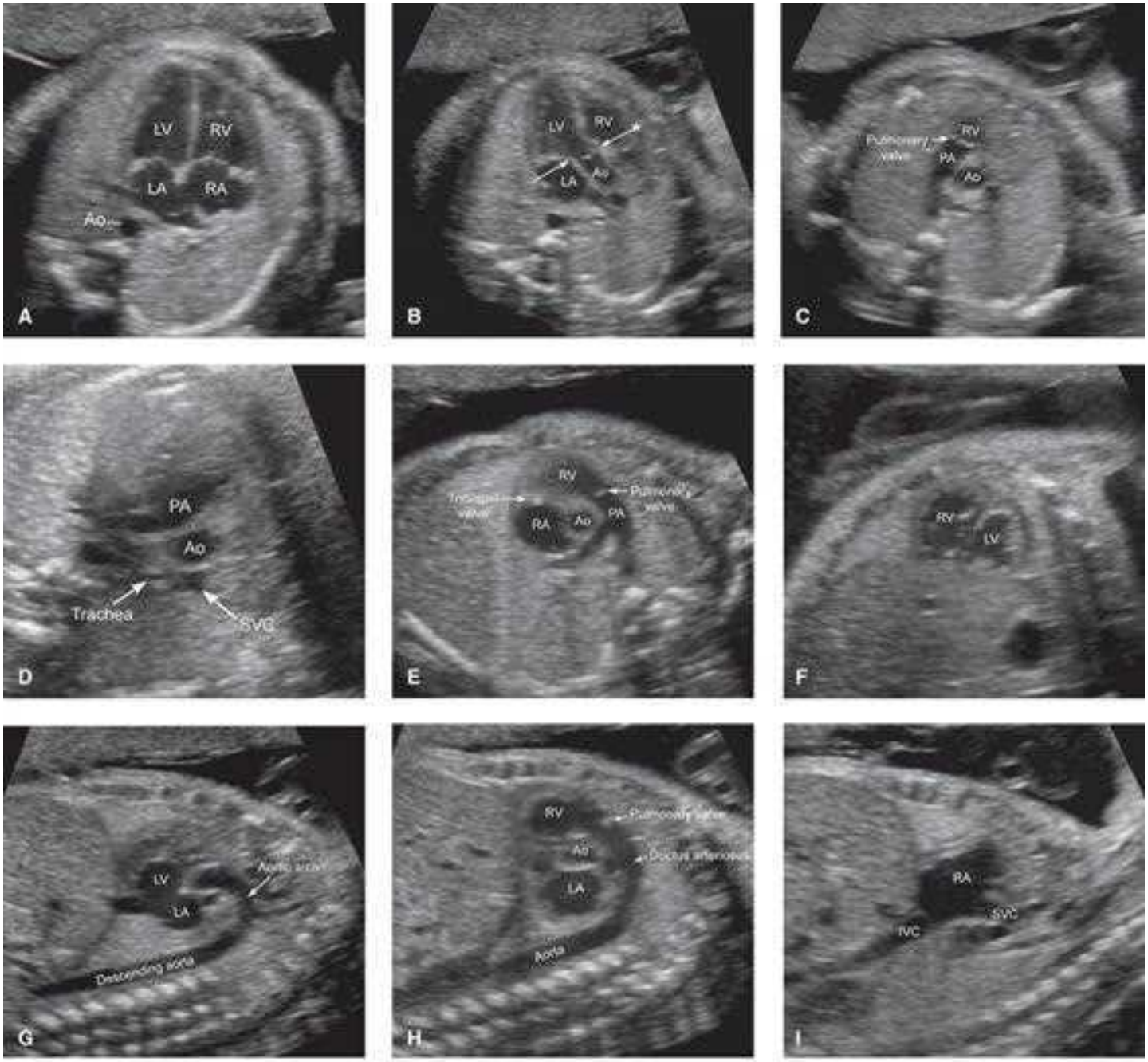


FIGURE 10-28

Fetal echocardiography gray-scale imaging planes. **A.** Four-chamber view. **B.** Left ventricular outflow tract view. The white arrow illustrates the mitral valve becoming the wall of the aorta. The arrow with asterisk marks the interventricular septum becoming the opposing aortic wall. **C.** Right ventricular outflow tract view. **D.** Three vessel and trachea view. **E.** High short-axis view (outflow tracts). **F.** Low short-axis view (ventricles). **G.** Aortic arch view. **H.** Ductal arch view. **I.** Superior and inferior vena cavae views. Ao = aorta; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; SVC = superior vena cava.

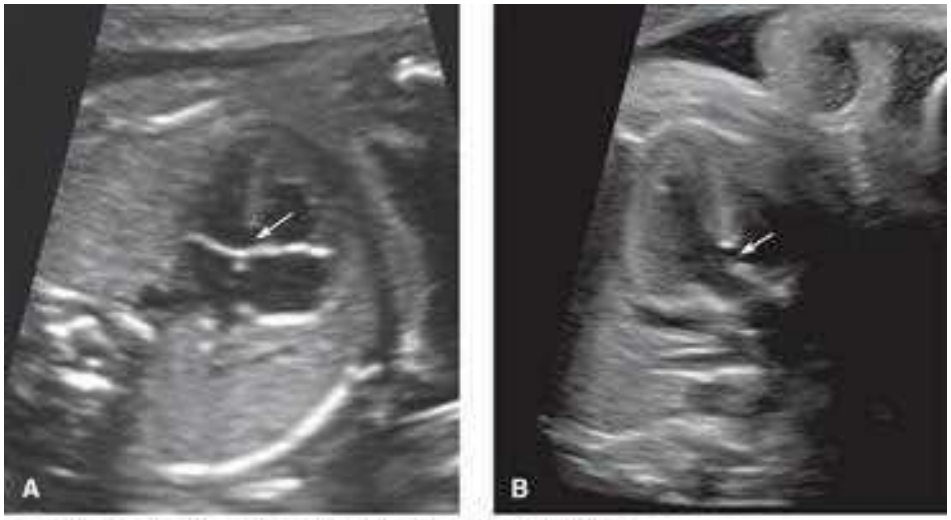


The *four-chamber view* is a transverse image of the fetal thorax at a level immediately above the diaphragm. It allows evaluation of cardiac size, position in the thorax, cardiac axis, atria and ventricles, foramen ovale, atrial septum primum, interventricular septum, and atrioventricular valves (see Fig. 10–27). The atria and ventricles should be similar in size, and the apex of the heart should form a 45-degree angle with the left anterior chest wall. Abnormalities of cardiac axis are frequently encountered with structural cardiac anomalies and occur in more than a third (Shipp, 1995).

The *left ventricular outflow tract view* is a transverse image just above the diaphragm and demonstrates that the ascending aorta arises entirely from the left ventricle. The interventricular septum is shown to be in continuity with the anterior wall of the aorta, and the mitral valve in continuity with the posterior wall of the aorta (see Fig. 10–28B). Ventricular septal defects and outflow tract abnormalities are often visible in this view (Fig. 10–29).

FIGURE 10-29

Ventricular septal defect. **A.** In this four-chamber view of a 22-week fetus, a defect (*arrow*) is noted in the superior (membranous) portion of the interventricular septum. **B.** The left-ventricular outflow tract view of the same fetus demonstrates a break (*arrow*) in continuity between the interventricular septum and the anterior wall of the aorta.



The *right ventricular outflow tract view* shows the right ventricle giving rise to the pulmonary artery (see Fig. 10–28C). Together, the left and right outflow tract views demonstrate the normal perpendicular orientation of the aorta and pulmonary artery, and the comparable size of these great arteries. Structures visible in the right ventricular outflow tract view include the right ventricle and the main pulmonary artery, which subsequently branches into the right and left pulmonary arteries. These structures are also visible in the short axis view, shown in Figure 10–28E.

Fetal Echocardiography

This is a specialized examination of fetal cardiac structure and function designed to identify and characterize abnormalities. Guidelines for its performance have been developed collaboratively by the American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, American Society of Echocardiography, and American College of Radiology. Echocardiography indications include suspected fetal cardiac anomaly, extracardiac anomaly, or chromosomal abnormality; fetal arrhythmia; hydrops; thick nuchal translucency; monochorionic twin gestation; first-degree relative to the fetus with a congenital cardiac defect; in vitro fertilization; maternal anti-Ro or anti-La antibodies; exposure to a medication associated with cardiac defects; and maternal metabolic disease associated with cardiac defects—such as pregestational diabetes or phenylketonuria (American Institute of Ultrasound in Medicine, 2013a). Components of the examination are listed in Table 10-9, and examples of nine required gray-scale imaging views are shown in Figure 10-28. Examples of selected cardiac anomalies are reviewed below.

TABLE 10-9

Components of Fetal Echocardiography

Basic imaging parameters
Evaluation of atria
Evaluation of ventricles
Evaluation of great vessels
Cardiac and visceral situs
Atrioventricular junctions
Ventriculoarterial junctions
Scanning planes, gray scale
Four-chamber view
Left ventricular outflow tract
Right ventricular outflow tract
Three-vessel and trachea view
Short-axis view, low (ventricles)
Short-axis view, high (outflow tracts)
Aortic arch
Ductal arch
Superior and inferior vena cavae
Color Doppler evaluation
Systemic veins (vena cavae and ductus venosus[a])
Pulmonary veins
Foramen ovale
Atrioventricular valves[a]
Atrial and ventricular septae
Aortic and pulmonary valves[a]
Ductus arteriosus
Aortic arch
Umbilical artery and vein (optional)[a]
Cardiac rate and rhythm assessment

[a]Pulsed-wave Doppler sonography should be used as an adjunct to evaluate these structures.

Cardiac biometry and functional assessment are optional but should be considered for suspected structural/functional abnormalities.

Adapted from the American Institute of Ultrasound in Medicine, 2013b.

Ventricular Septal Defect

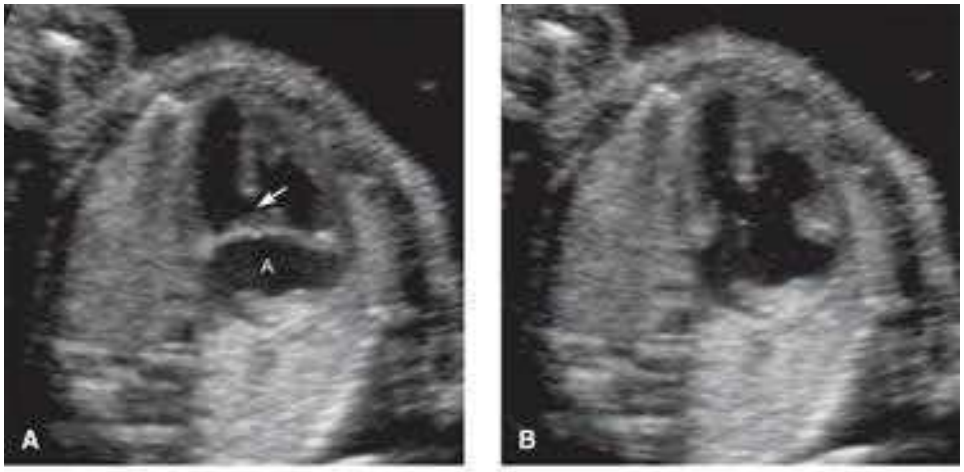
This is the most common congenital cardiac anomaly and is found in approximately 1 in 300 births (Cragan, 2009; Dolk, 2010). Even with adequate visualization, the prenatal detection rate of ventricular septal defect (VSD) is low. A defect may be appreciated in the membranous or muscular portion of the interventricular septum in the four-chamber view, and color Doppler demonstrates flow through the defect. Imaging of the left ventricular outflow tract may show discontinuity of the interventricular septum as it becomes the wall of the aorta (see Fig. 10-29). Fetal VSD is associated with other abnormalities and aneuploidy, and chromosomal microarray analysis should be offered. That said, the prognosis for an isolated defect is good. More than a third of prenatally diagnosed VSDs close in utero, and another third close in the first year of life (Axt-Fliedner, 2006; Paladini, 2002).

Endocardial Cushion Defect

This is also called an *atrioventricular (AV) septal defect* or *AV canal defect*. It has a prevalence of approximately 1 in 2500 births and is associated with trisomy 21 in more than half of cases (Christensen, 2013; Cragan, 2009; Dolk, 2010). The endocardial cushions are the crux of the heart, and defects jointly involve the atrial septum primum, interventricular septum, and medial leaflets of the mitral and tricuspid valves (Fig. 10-30). Approximately 6 percent of cases occur with heterotaxy syndromes, that is, those in which the heart and/or abdominal organs are on the incorrect side. Endocardial cushion defects associated with heterotaxy can have comorbid conduction system abnormalities resulting in third-degree AV block, which confers a poor prognosis (Chap. 16, Tachyarrhythmias).

FIGURE 10-30

Endocardial cushion defect. **A.** During ventricular systole, the lateral leaflets of the mitral and triscuspid valves come together in the midline. But the atrioventricular valve plane is abnormal, a common atrium (*A*) is observed, and there is a visible defect (*arrow*) in the interventricular septum. **B.** During diastolic filling, opening of the atrioventricular valves more clearly demonstrates the absence of their medial leaflets.

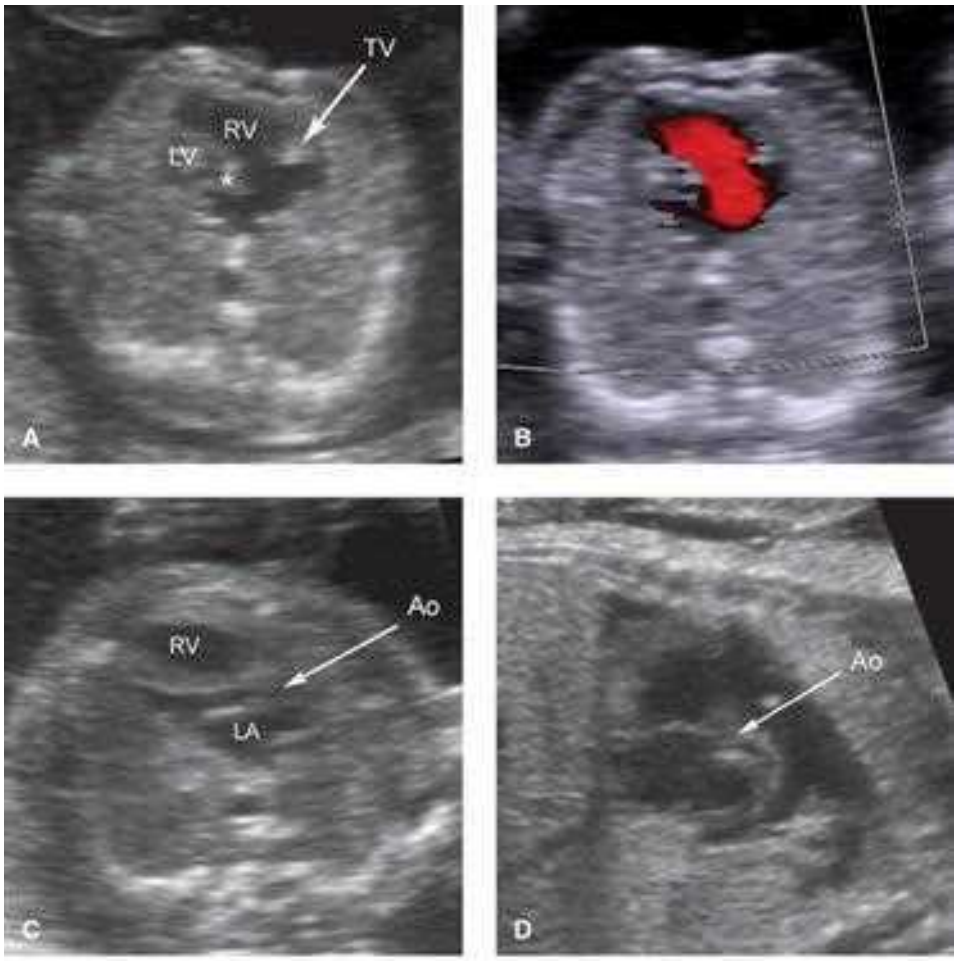


Hypoplastic Left Heart Syndrome

This anomaly is found in approximately 1 in 4000 births (Cragan, 2009; Dolk, 2010). Sonographically, the left side of the heart may appear “filled-in” or the left ventricle may be so small and attenuated that a ventricular chamber is difficult to appreciate (Fig. 10-31). There may be no visible left ventricular inflow or outflow, and reversal of flow may be documented in the aortic arch.

FIGURE 10-31

Hypoplastic left heart syndrome. **A.** In this 4-chamber view at 16 weeks, the left ventricle (*LV*) appears “filled in” and is significantly smaller than the right ventricle (*RV*). The tricuspid valve (*TV*) is open, whereas the mitral valve appears closed (*asterisk*). **B.** Color Doppler depicts flow from the right atrium to the right ventricle only, and left ventricular filling is not visible. **C.** The left ventricular outflow tract view demonstrates marked narrowing of the aorta (Ao). RV = right ventricle; LA = left atrium. **D.** The tiny circle (arrow) in this short axis view is the hypoplastic aortic root. (Reproduced with permission from Rafael Levy, RDMS.)



Although this anomaly was once considered a lethal prognosis, 70 percent of affected infants may now survive to adulthood (Feinstein, 2012). Postnatal treatment consists of a three-stage palliative repair or cardiac transplantation. Still, morbidity remains high, and developmental delays are common (Lloyd, 2017;

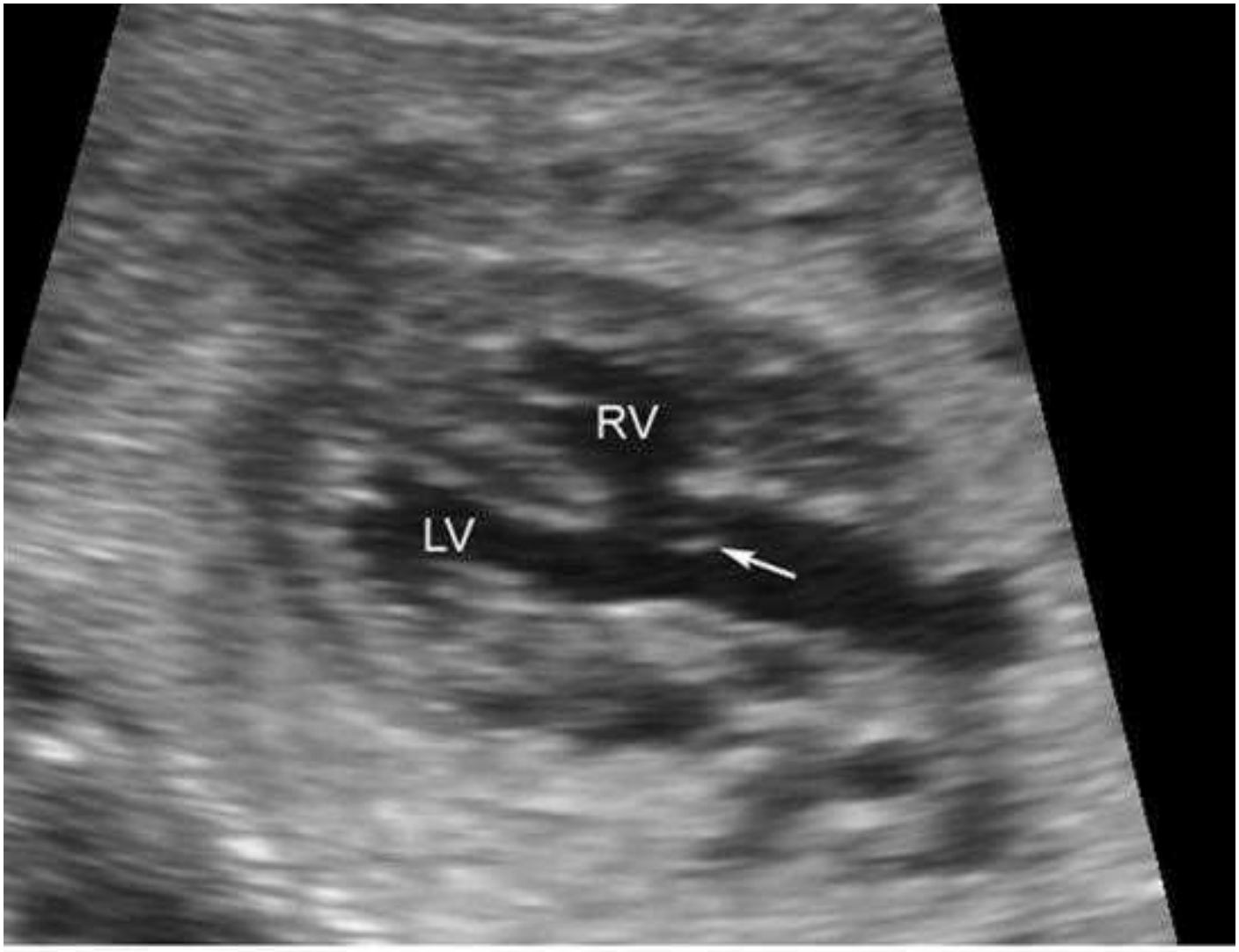
Paladini, 2017). This is a ductal-dependent lesion for which neonatal administration of prostaglandin therapy is essential. Fetal therapy for hypoplastic left heart is discussed in Chapter 16 (Radiofrequency Ablation).

Tetralogy of Fallot

This anomaly occurs in approximately 1 in 3000 births (Cragan, 2009; Dolk, 2010; Nelson, 2016). It includes a ventricular septal defect; an overriding aorta; a pulmonary valve abnormality, typically stenosis; and right ventricular hypertrophy (Fig. 10-32). The last does not present before birth. Due to the location of the ventricular septal defect, the four-chamber view may appear normal.

FIGURE 10-32

Tetralogy of Fallot. This image shows a ventricular septal defect with an overriding aorta in a fetus with tetralogy of Fallot. The arrow points to the aortic valve. The left ventricle (*LV*) and right ventricle (*RV*) are labeled.



Following postnatal repair, the 20-year survival rates exceed 95 percent (Knott-Craig, 1998). However, cases with *pulmonary atresia* have a more complicated course. There is also a variant in which the pulmonary valve is *absent.* These affected fetuses are at risk for hydrops and for tracheomalacia from compression of the trachea by an enlarged pulmonary artery.

Cardiac Rhabdomyoma

This is the most common cardiac tumor. Approximately 50 percent of cases are associated with tuberous sclerosis, an autosomal dominant disease with multiorgan system manifestations. Tuberous sclerosis is caused by mutations in the hamartin (*TSC1*) and tuberin (*TSC2*) genes.

Cardiac rhabdomyomas appear as well-circumscribed echogenic masses, usually within the ventricles or outflow tracts. They may be single or multiple; may grow in size during gestation; and occasionally, may lead to inflow or outflow obstruction. In cases without obstruction or large tumor size, the prognosis is relatively good from a cardiac standpoint, because the tumors tend to regress after the neonatal period. Because extracardiac findings of tuberous sclerosis may not be apparent with prenatal sonography, MR imaging may be considered to evaluate fetal CNS anatomy (Fetal Anatomical Evaluation).

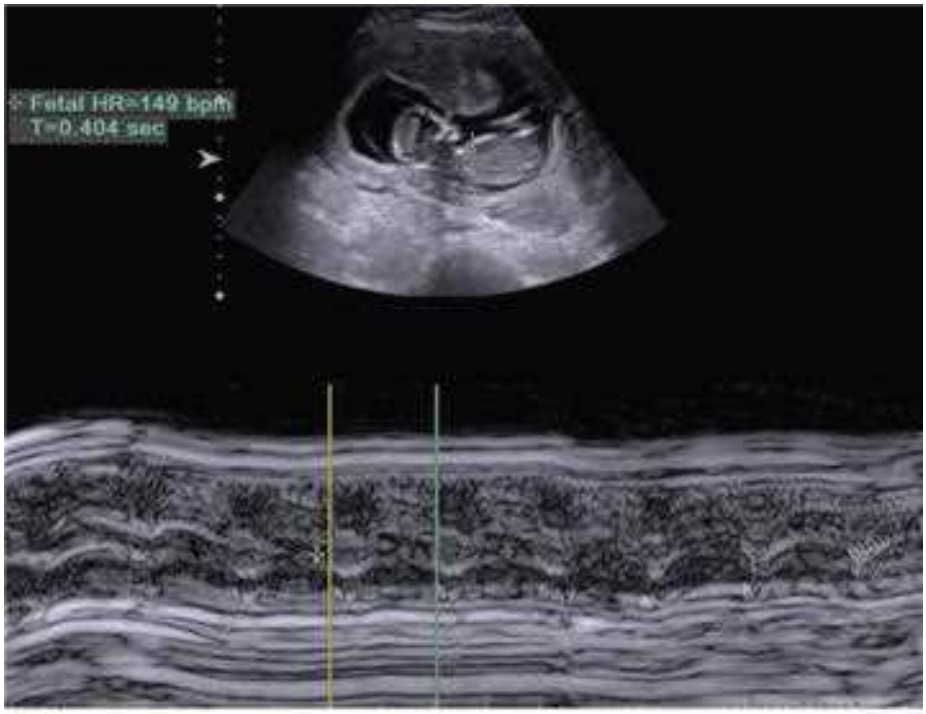
M-Mode

Motion-mode or M-mode imaging is a linear display of cardiac cycle events, with time on the x-axis and motion on the y-axis. It is often used to measure embryonic or fetal heart rate (Fig. 10-33). If an abnormality of heart rate or rhythm is identified, M-mode imaging permits separate evaluation of atrial and

ventricular waveforms. Thus, it is particularly useful for characterizing arrhythmias and their response to treatment (Chap. 16, Tachyarrhythmias). M-mode can also be used to assess ventricular function and atrial and ventricular outputs.

FIGURE 10-33

M-mode, or motion mode, is a linear display of the events of the cardiac cycle, with time on the x-axis and motion on the y-axis. M-mode is used commonly to measure the fetal heart rate, as in this 12-week fetus.

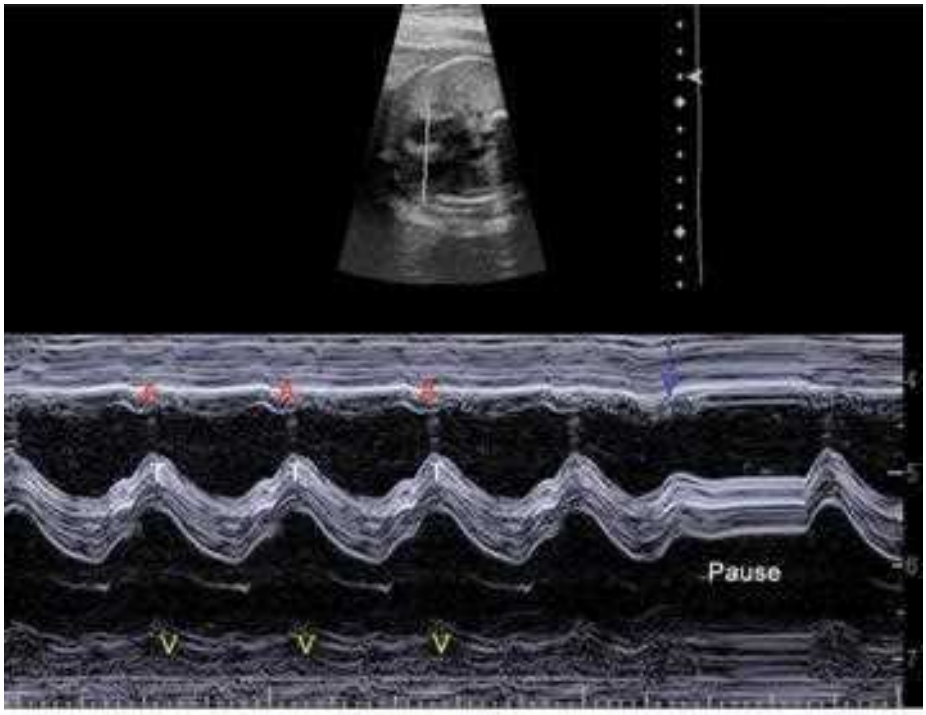


Premature Atrial Contractions

Also called atrial extrasystoles, these are the most common fetal arrhythmia and a frequent finding. They represent cardiac conduction system immaturity and typically resolve later in gestation or in the neonatal period. Premature atrial contractions (PACs) may be conducted and thus sound like an extra beat. However, they are more commonly blocked, and with handheld Doppler they sound like a dropped beat. As shown in Figure 10-34, the dropped beat may be demonstrated with M-mode evaluation as a compensatory pause that follows the premature contraction.

FIGURE 10-34

M-mode. In this image, there is normal concordance between atrial (*A*) and ventricular contractions (*V*). Movement of the tricuspid valve (*T*) is also shown. There is also a premature atrial contraction (*arrow*) and a subsequent early ventricular contraction, followed by a compensatory pause.

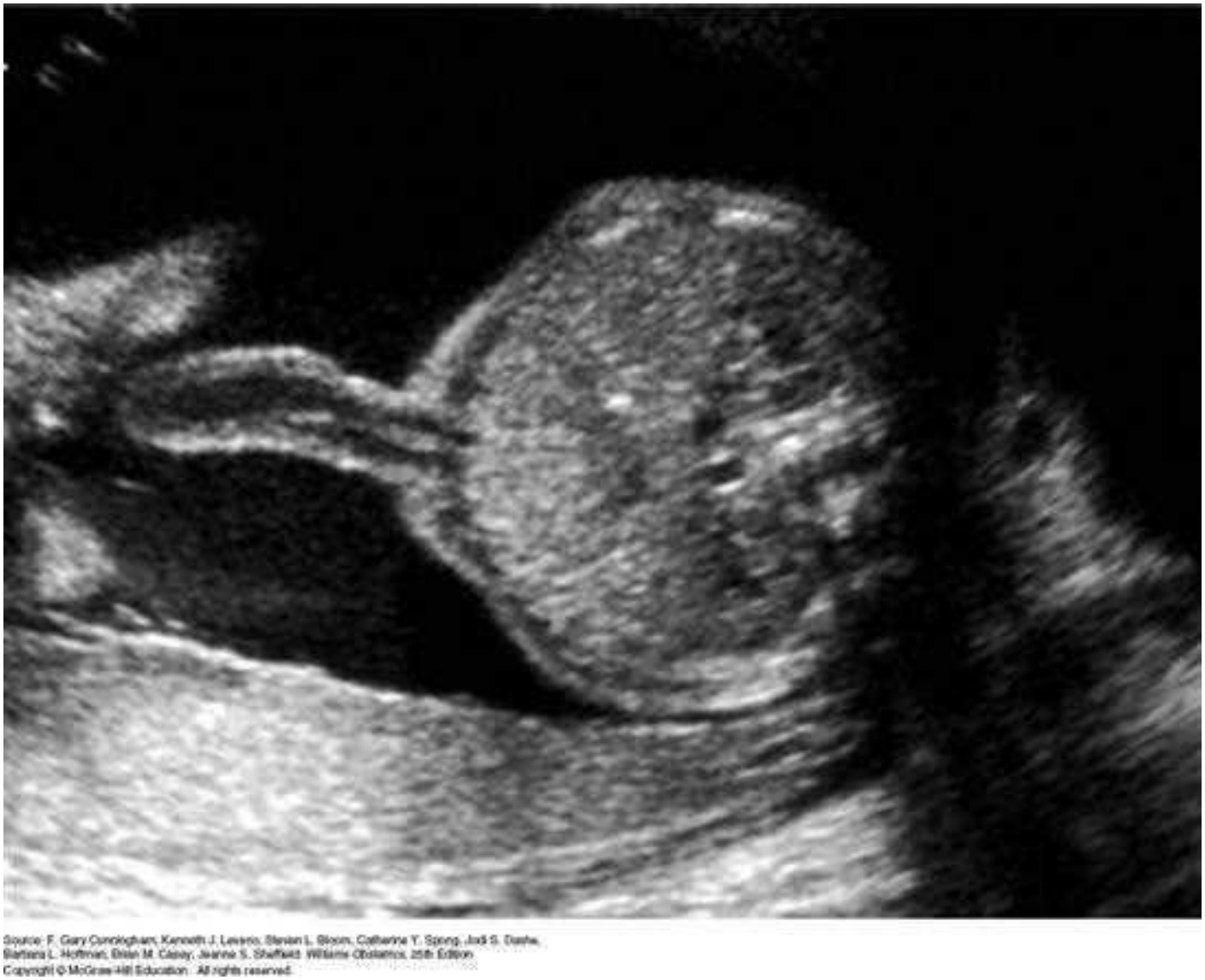


PACs sometimes occur with an atrial septal aneurysm but are not associated with major structural cardiac abnormalities. Older case reports describe an association with maternal caffeine consumption and with hydralazine (Lodeiro, 1989; Oei, 1989). In approximately 2 percent of cases, affected fetuses are later identified to have a *supraventricular tachycardia* (SVT) that requires urgent treatment (Copel, 2000). Accordingly, pregnancies with fetal PACs are often followed with fetal heart rate assessment as often as every 1 to 2 weeks until ectopy resolves. Treatment of fetal SVT and other arrhythmias is discussed in Chapter 16 (Tachyarrhythmias).

Abdominal Wall

The integrity of the abdominal wall is assessed at the level of the cord insertion during the standard examination (Fig. 10-35). Ventral wall defects include gastroschisis, omphalocele, and body stalk anomaly.

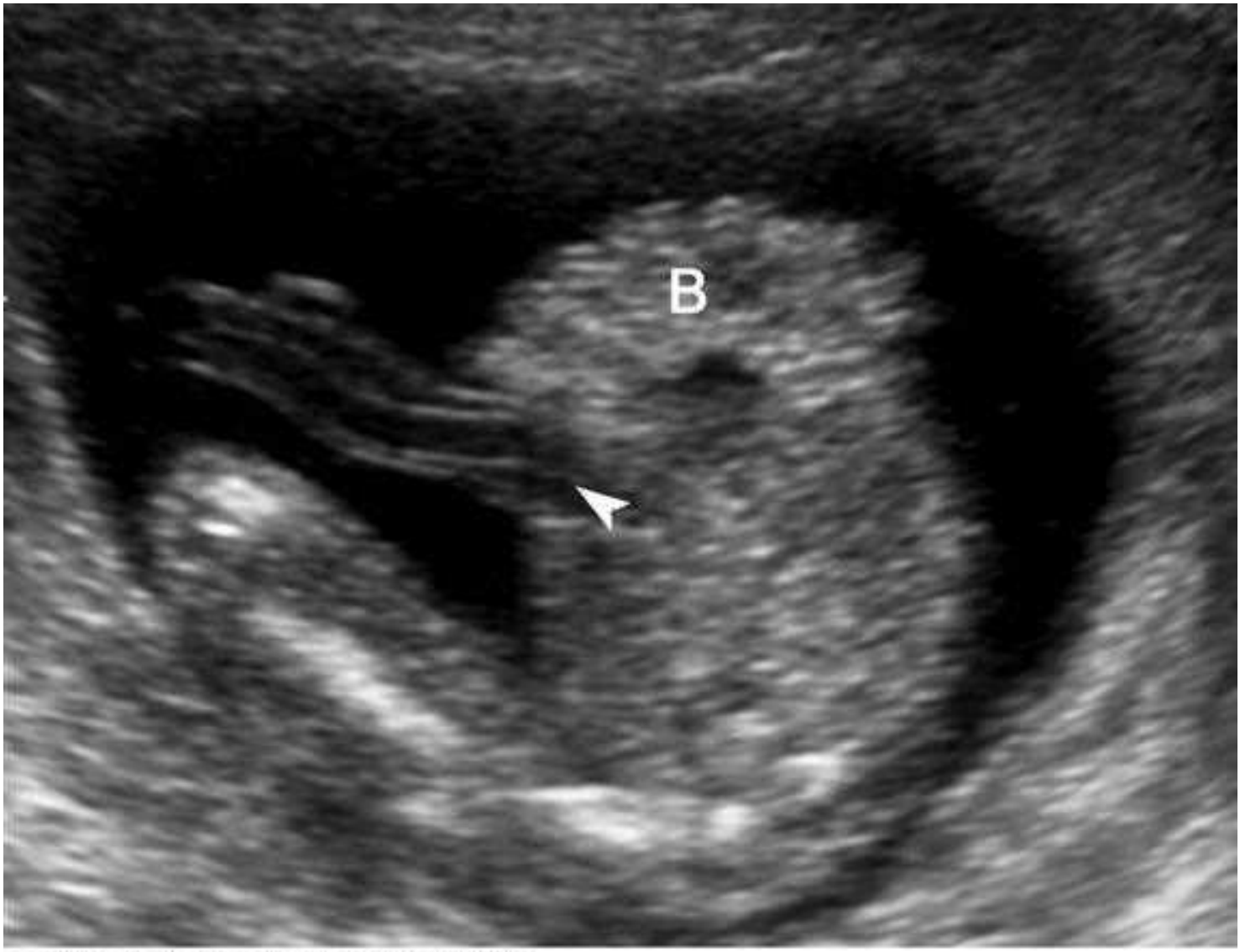
FIGURE 10-35
Normal ventral wall. Transverse view of the abdomen in a second-trimester fetus with an intact anterior abdominal wall and normal cord insertion.



Gastroschisis is a full-thickness abdominal wall defect located to the right of the umbilical cord insertion. Bowel herniates through the defect into the amnionic cavity (Fig. 10-36). The prevalence is approximately 1 in 2000 births (Jones, 2016; Nelson, 2015). Gastroschisis is the one major anomaly more common in fetuses of younger mothers, and the average maternal age is 20 years (Santiago-Muñoz, 2007). Coexisting bowel abnormalities such as *jejunal atresia* are found in approximately 15 percent of cases (Nelson, 2015; Overcash, 2014). Gastroschisis is not associated with aneuploidy, and the survival rate is 90 to 95 percent (Kitchanan, 2000; Nelson, 2015; Nembhard, 2001).

FIGURE 10-36

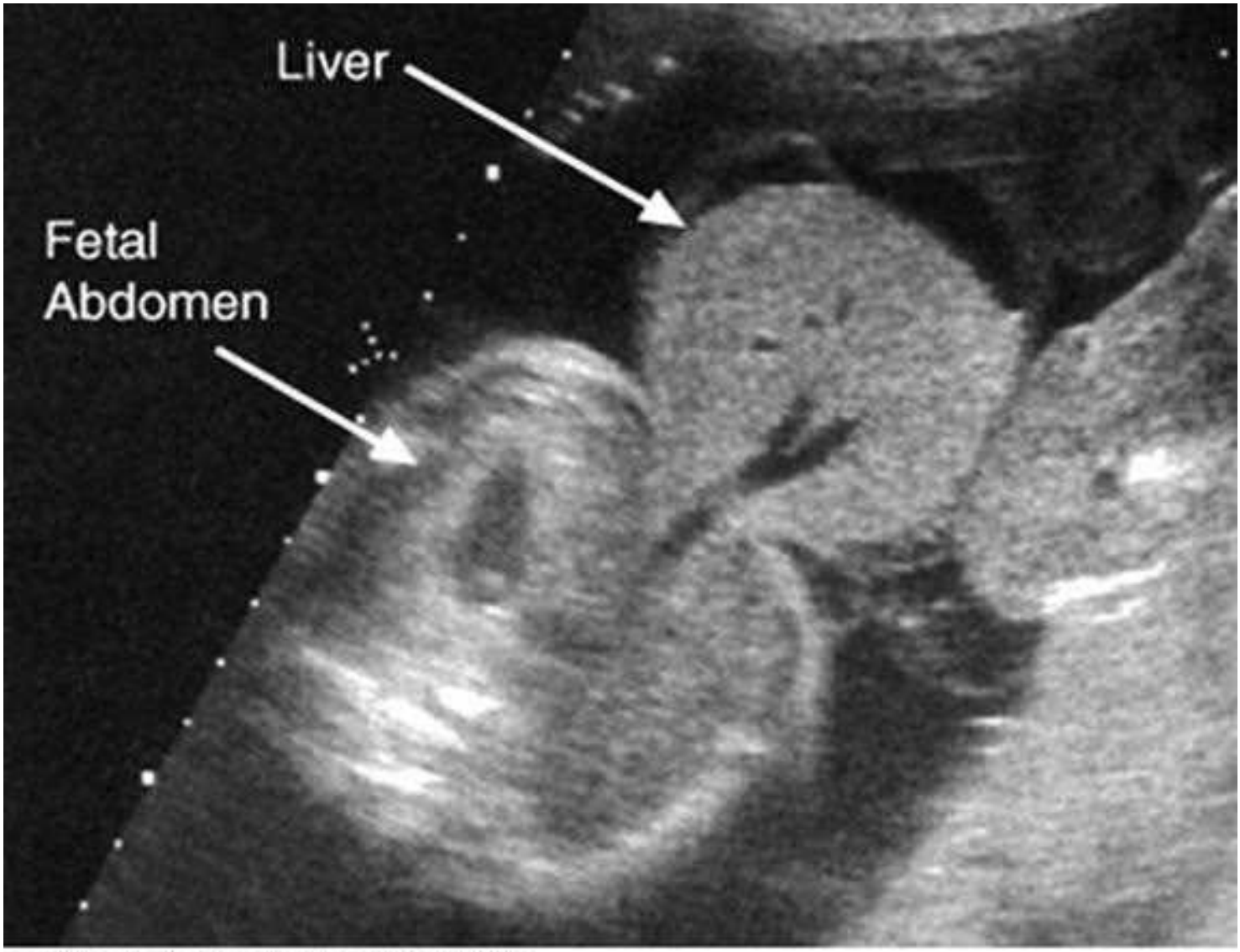
Gastroschisis. This 18-week fetus has a full-thickness ventral wall defect to the right of the cord insertion (*arrowhead*), through which multiple small bowel loops (*B*) have herniated into the amnionic cavity.



Fetal-growth restriction complicates gastroschisis in 15 to 40 percent of cases (Overcash, 2014; Santiago-Muñoz, 2007). Growth restriction does not appear to be associated with adverse outcomes such as longer hospitalization or higher mortality rate (Nelson, 2015; Overcash, 2014). However, earlier gestational age at delivery does pose a risk for adverse outcome with gastroschisis, and planned delivery at 36 to 37 weeks does not confer neonatal benefit (Al-Kaff, 2016; Overcash, 2014; South, 2013).

Omphalocele complicates 1 in 3000 to 5000 pregnancies (Canfield, 2006; Dolk, 2010). It forms when the lateral ectomesodermal folds fail to meet in the midline. This leaves the abdominal contents covered only by a two-layered sac of amnion and peritoneum into which the umbilical cord inserts (Fig. 10-37). More than half of cases are associated with other major anomalies or aneuploidy. Omphalocele also is a component of syndromes such as *Beckwith–Wiedemann, cloacal exstrophy,* and *pentalogy of Cantrell.* Smaller defects confer greater risk for aneuploidy (De Veciana, 1994). Chromosomal microarray analysis should be offered in all cases of omphalocele.

FIGURE 10-37
Omphalocele. Transverse view of the abdomen showing an omphalocele as a large abdominal wall defect with exteriorized liver covered by a thin membrane.



Body stalk anomaly, also known as *limb-body-wall complex* or *cyllosoma*, is a rare, lethal anomaly characterized by abnormal formation of the body wall. Typically, *no* abdominal wall is visible, and the abdominal organs extrude into the extraamnionic coelom. There is close approximation or fusion of the body to the placenta, and the umbilical cord is extremely short. Acute-angle scoliosis is another feature. Amnionic bands are often identified.

Gastrointestinal Tract

The stomach is visible in nearly all fetuses after 14 weeks' gestation. If the stomach is not seen during initial evaluation, the examination is repeated, and targeted sonography should be considered. Nonvisualization of the stomach may be secondary to impaired swallowing in the setting of oligohydramnios or to underlying causes such as esophageal atresia, a craniofacial anomaly, or a CNS or musculoskeletal abnormality. Fetuses with hydrops may also have impaired swallowing.

The bowel, liver, gallbladder, and spleen can be identified in many second- and third-trimester fetuses. Bowel appearance changes with fetal maturation. Occasionally, it may be bright or echogenic, which may indicate small amounts of swallowed intraamnionic blood, especially with comorbid MSAFP elevation. Bowel that appears as bright as fetal bone confers a slightly greater risk for underlying gastrointestinal malformations, for cystic fibrosis, for trisomy 21, and for congenital infection such as cytomegalovirus (Fig. 14-3).

Gastrointestinal Atresia

Bowel atresia is characterized by obstruction and proximal bowel dilation. In general, the more proximal the obstruction, the more likely it is to lead to hydramnios. At times, hydramnios from proximal small-bowel obstruction can be sufficiently severe to result in maternal respiratory compromise or preterm labor and may necessitate amnioreduction (Chap. 11, Oligohydramnios).

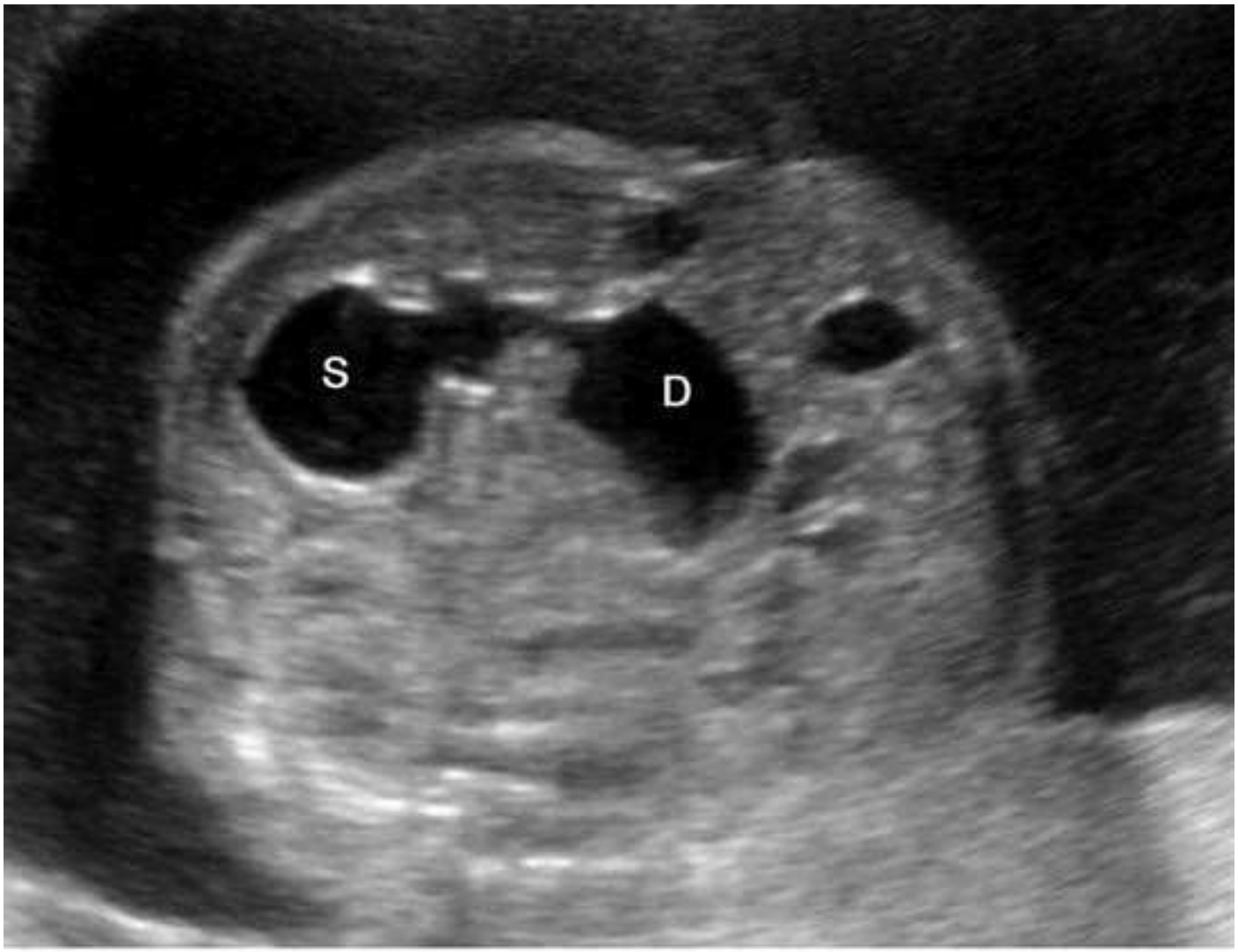
Esophageal atresia occurs in approximately 1 in 4000 births (Cragan, 2009; Pedersen, 2012). It may be suspected when the stomach cannot be visualized and hydramnios is present. That said, in up to 90 percent of cases, a concomitant *tracheoesophageal fistula* allows fluid to enter the stomach, such that prenatal detection is problematic. More than half have associated anomalies or genetic syndromes. Multiple malformations are present in 30 percent of cases, and aneuploidy such as trisomy 18 or 21, in 10 percent (Pedersen, 2012). Cardiac, urinary tract, and other gastrointestinal abnormalities are the most frequently

associated anomalies. Approximately 10 percent of cases of esophageal atresia occur as part of the VACTERL association, which is vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities (Pedersen, 2012).

Duodenal atresia is found in approximately 1 in 10,000 births (Best, 2012; Dolk, 2010). It is characterized by the sonographic *double-bubble sign,* which represents distention of the stomach and the first part of the duodenum (Fig. 10-38). This finding is usually not present before 22 to 24 weeks' gestation. Demonstrating continuity between the stomach and proximal duodenum confirms that the second "bubble" is the proximal duodenum. Approximately 30 percent of affected fetuses have an associated chromosomal abnormality or genetic syndrome, particularly trisomy 21. Of cases without a genetic abnormality, a third have associated anomalies, most commonly cardiac defects and other gastrointestinal abnormalities (Best, 2012). Obstructions in the more distal small bowel usually result in multiple dilated loops that may have enhanced peristaltic activity.

FIGURE 10-38

Duodenal atresia. The *double-bubble* sign represents distension of the stomach (*S*) and the first part of the duodenum (*D*), as seen on this axial abdominal image. Demonstrating continuity between the stomach and proximal duodenum confirms that the second "bubble" is the proximal duodenum.



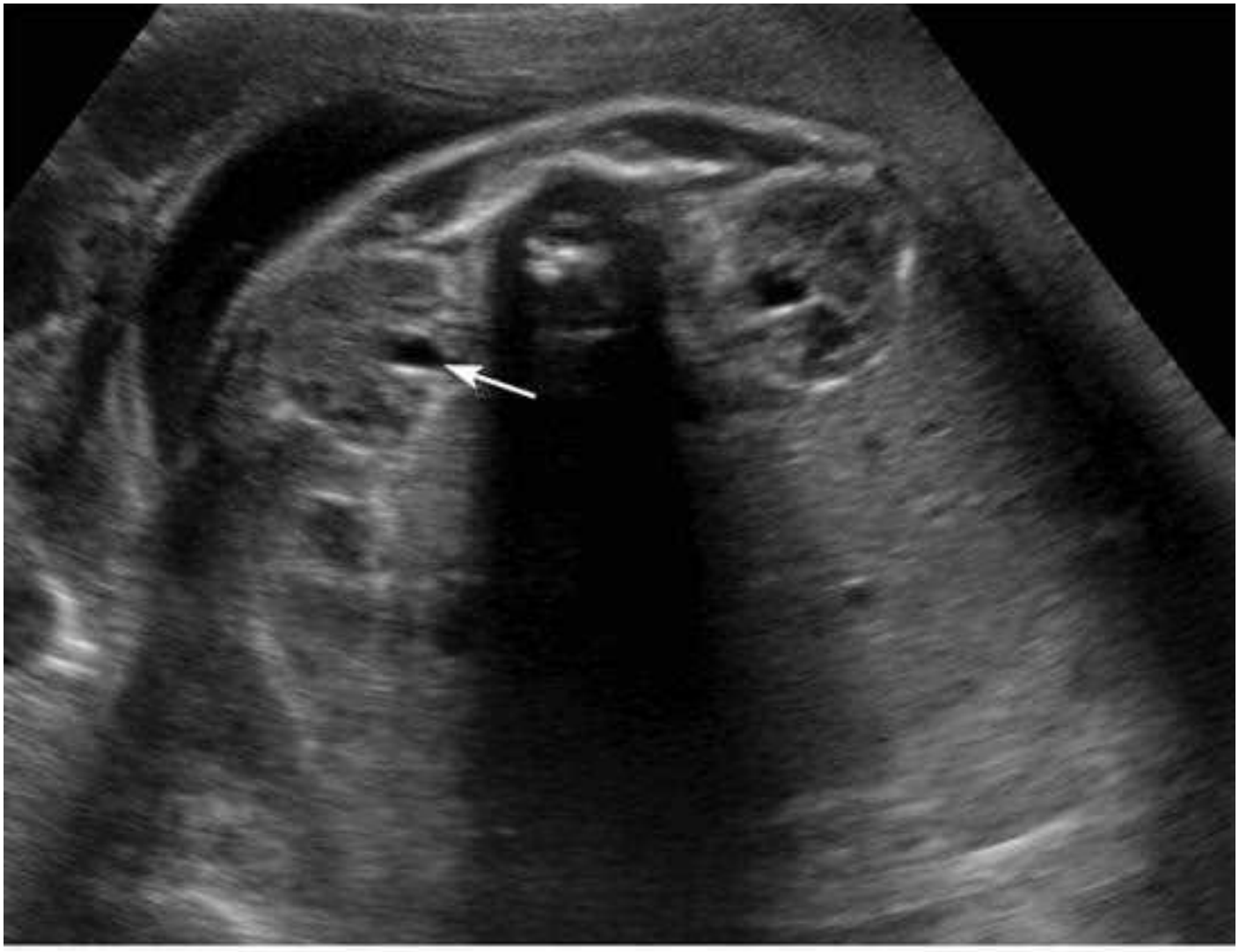
Large-bowel obstructions and anal atresia are less readily diagnosed by sonography, because hydramnios is not a typical feature and the bowel may not be significantly dilated. A transverse view through the pelvis may show an enlarged rectum as an anechoic structure between the bladder and the sacrum.

Kidneys and Urinary Tract

The fetal kidneys are visible adjacent to the spine, frequently in the first trimester and routinely by 18 weeks' gestation (Fig. 10-39). The length of the kidney approximates 20 mm at 20 weeks and grows by about 1.1 mm each week thereafter (Chitty, 2003). With advancing gestation, the kidneys become relatively less echogenic, and a rim of perinephric fat aids visualization of their margins.

FIGURE 10-39

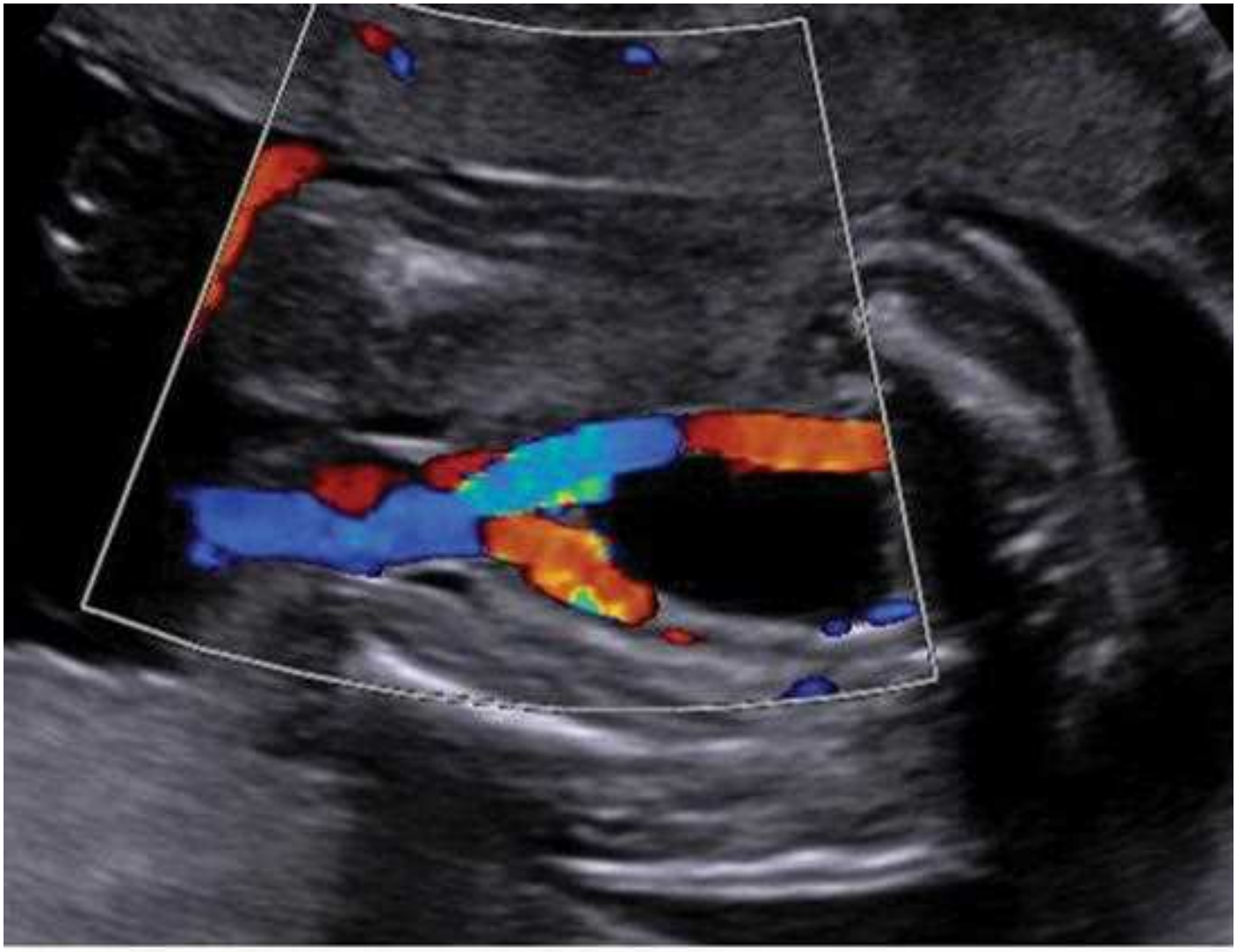
Normal fetal kidneys. The kidneys are visible adjacent to the fetal spine in this 29-week fetus. With advancing gestation, a rim of perinephric fat aids visualization of the kidney margins. A physiological amount of urine is visible in the renal pelves and is marked in one kidney by an arrow.



The fetal bladder is readily visible in the second trimester as a round, anechoic structure in the anterior midline of the pelvis. With application of Doppler, the bladder is outlined by the two superior vesical arteries as they become the umbilical arteries of the umbilical cord (Fig. 10-40 and Chap. 6, Umbilical Cord). The fetal ureters and urethra are not visible sonographically unless abnormally dilated.

FIGURE 10-40

Normal fetal bladder. The normal fetal bladder is readily visible as a round, fluid-filled structure in the anterior pelvis, outlined by the two superior vesical arteries as they become the umbilical arteries of the umbilical cord.



The placenta and membranes are the major sources of amnionic fluid early in pregnancy. However, after 18 weeks' gestation, most of the fluid is produced by the kidneys (Chap. 11, Normal Amnionic Fluid Volume). Fetal urine production rises from 5 mL/hr at 20 weeks to approximately 50 mL/hr at term (Rabinowitz, 1989). Normal amnionic fluid volume in the second half of pregnancy suggests urinary tract patency with at least one functioning kidney. But, unexplained oligohydramnios suggests a urinary tract defect or placental perfusion abnormality.

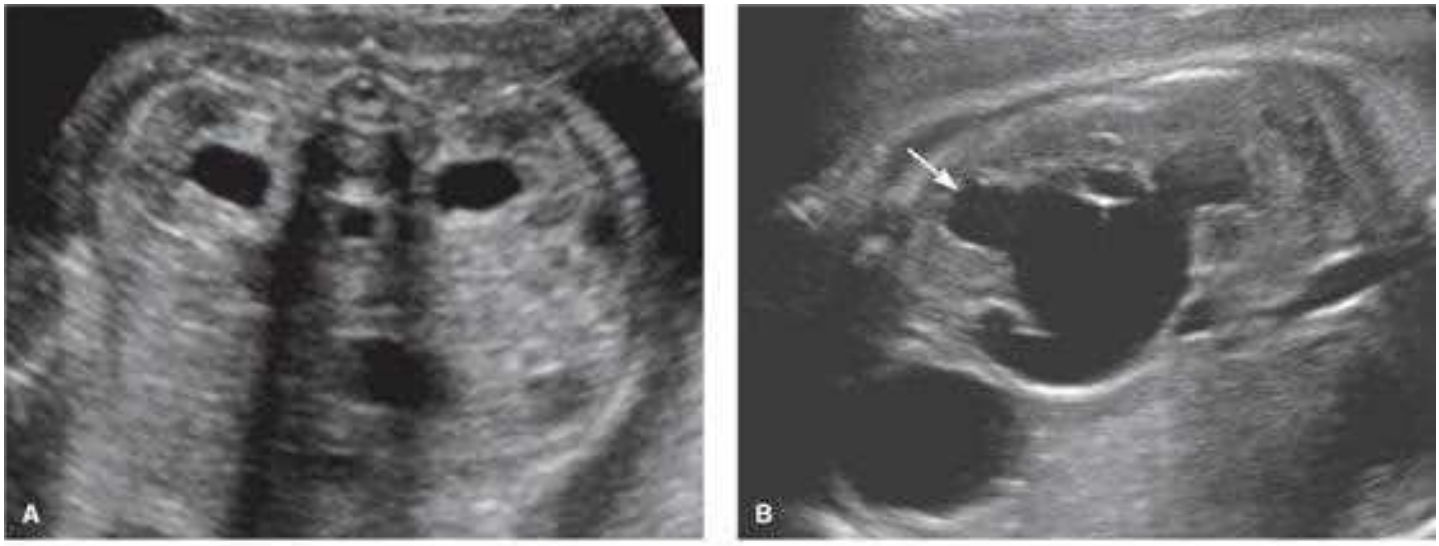
Renal Pelvis Dilatation

This finding is present in 1 to 5 percent of fetuses. It is also called urinary tract dilatation or hydronephrosis. In 40 to 90 percent of cases, it is transient or physiological and does not represent an underlying abnormality (Ismaili, 2003; Nguyen, 2010). In approximately a third of cases, a urinary tract abnormality is confirmed in the neonatal period. Of these, *ureteropelvic junction (UPJ) obstruction* and *vesicoureteral reflux (VUR)* are the most frequent.

The fetal renal pelvis is measured anterior to posterior in a transverse plane, and calipers are placed on the inner border of the fluid collection (Fig. 10-41). Although various thresholds have been defined, the pelvis is typically considered dilated if it exceeds 4 mm in the second trimester or 7 mm at approximately 32 weeks' gestation (Reddy, 2014). Typically, the second-trimester threshold is used to identify pregnancies that warrant subsequent third-trimester evaluation.

FIGURE 10-41

Renal pelvis dilatation. This common finding is identified in 1 to 5 percent of pregnancies. **A.** In this 34-week fetus with mild renal pelvis dilatation, the anterior-posterior diameter of the renal pelvis measured 7 mm in the transverse plane. **B.** Sagittal image of the kidney in a 32-week fetus with severe renal pelvis dilatation secondary to ureteropelvic junction obstruction. The arrow points to one of the rounded calyces.



The Society for Fetal Urology categorized renal pelvis dilatation based on a metaanalysis of more than 100,000 screened pregnancies (Table 10-10) (Lee, 2006; Nguyen, 2010). The degree of dilatation correlates with the likelihood of an underlying abnormality. Other suggestive findings of pathology include calyceal dilatation, cortical thinning, or dilatation elsewhere along the urinary tract. Mild pyelectasis in the second trimester is associated with a slightly greater risk for Down syndrome and is considered a soft marker for this (Fig. 14-3).

TABLE 10-10

Risk for Postnatal Urinary Abnormality According to Degree of Renal Pelvis Dilatation[a]

Dilatation	Second Trimester	Third Trimester	Postnatal Abnormality
Mild	4 to <7 mm	7 to <9 mm	12%
Moderate	7 to ≤10 mm	9 to ≤15 mm	45%
Severe	>10 mm	>15 mm	88%

[a]Society for Fetal Urology Classification.

Modified from Lee, 2006; Nguyen, 2010.

Ureteropelvic Junction Obstruction

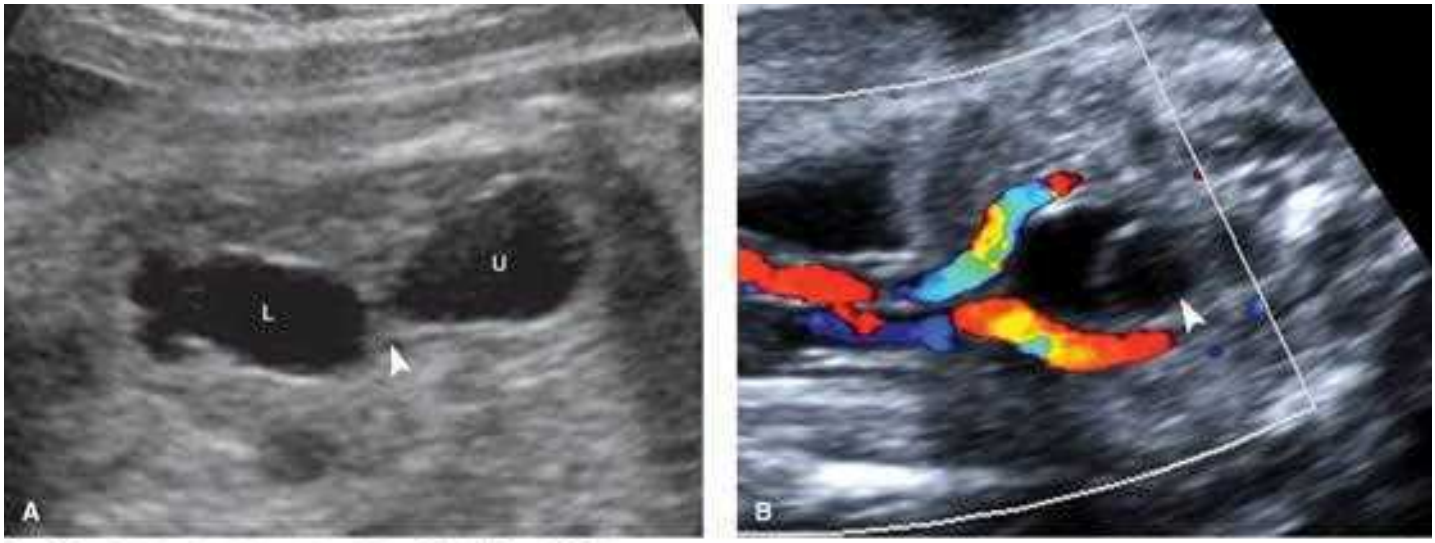
This condition is the most common abnormality associated with renal pelvis dilatation. The birth prevalence is 1 in 1000 to 2000, and males are affected three times more often than females (Williams, 2007; Woodward, 2002). Obstruction is generally functional rather than anatomical, and it is bilateral in up to a fourth of cases. The likelihood of ureteropelvic junction obstruction rises from 5 percent with mild renal pelvis dilatation to more than 50 percent with severe dilatation (Lee, 2006).

Duplicated Renal Collecting System

In this anatomical anomaly, the upper and lower poles of the kidney—called moieties—are each drained by a separate ureter (Fig. 10-42). Duplication is found in approximately 1 in 4000 pregnancies, is more common in females, and is bilateral in 15 to 20 percent of cases (James, 1998; Vergani, 1998; Whitten, 2001). Sonographically, an intervening tissue band separates two distinct renal pelves. Development of hydronephrosis or ureteral dilatation may occur due to abnormal implantation of one or both ureters within the bladder—a relationship that reflects the anatomical *Weigert-Meyer* rule. The upper pole ureter may develop obstruction from a ureterocele within the bladder, whereas the lower pole ureter has a shortened intravesical segment that predisposes to vesicoureteral reflux (see Fig. 10-42B). Thus, both moieties may become dilated from different etiologies, and both are at risk for loss of function.

FIGURE 10-42

Duplicated renal collecting system. The upper and lower moieties of the kidney are each drained by a separate ureter. **A.** Renal pelvis dilatation is visible in both the upper (*U*) and lower (*L*) pole moieties, which are separated by an intervening band of renal tissue (*arrowhead*). **B.** The bladder, encircled by the highlighted umbilical arteries, contains a ureterocele (*arrowhead*).

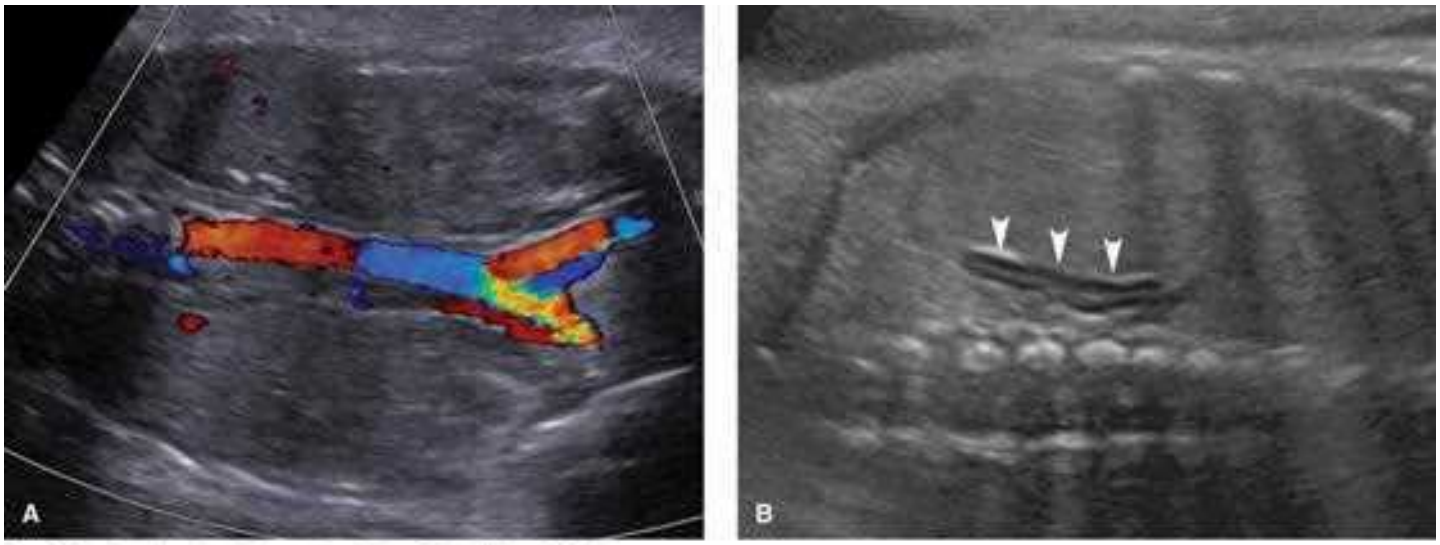


Renal Agenesis

The prevalence of bilateral renal agenesis is approximately 1 in 8000 births, whereas that of unilateral renal agenesis is 1 in 1000 births (Cragan, 2009; Dolk, 2010; Sheih, 1989; Wiesel, 2005). When a kidney is absent, color Doppler imaging of the descending aorta demonstrates absence of the ipsilateral renal artery (Fig. 10-43). In addition, the ipsilateral adrenal gland typically enlarges to fill the renal fossa, termed the *lying down adrenal sign* (Hoffman, 1992). As with other fetal anomalies, amniocentesis for chromosomal microarray analysis should be considered.

FIGURE 10-43

Renal agenesis. **A.** In this coronal image of the fetal abdomen, color Doppler shows the course of the abdominal aorta. The ultrasound beam is perpendicular to the aorta, demonstrating absence of the renal arteries bilaterally. **B.** This coronal image of a fetus with unilateral renal agenesis shows the adrenal gland (*arrowheads*) filling the renal fossa, termed the "lying-down" adrenal sign. The adrenal gland has a hypoechoic cortex and hyperechoic medulla.



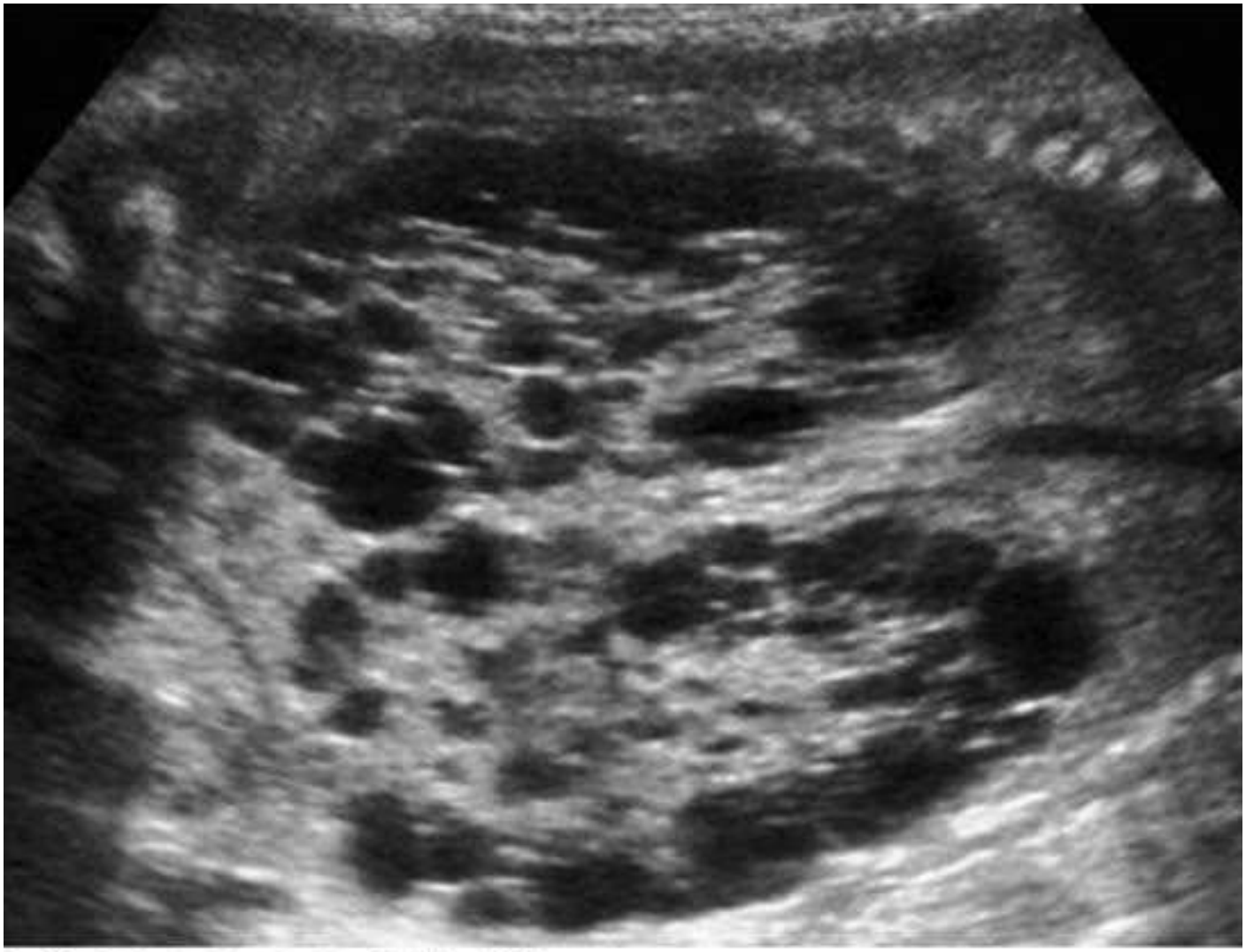
If renal agenesis is bilateral, no urine is produced, and the resulting anhydramnios leads to pulmonary hypoplasia, limb contractures, and a distinctively compressed face. When this combination results from renal agenesis, it is called *Potter syndrome,* after Dr. Edith Potter, who described it in 1946. When these abnormalities result from severely decreased amnionic fluid volume from another etiology, such as bilateral multicystic dysplastic kidney or autosomal recessive polycystic kidney disease, it is called *Potter sequence.* The prognosis for these abnormalities is extremely poor.

Multicystic Dysplastic Kidney

This severe form of renal dysplasia results in a nonfunctioning kidney. The nephrons and collecting ducts do not form normally, such that primitive ducts are surrounded by fibromuscular tissue, and the ureter is atretic (Hains, 2009). Sonographically, the kidney contains numerous smooth-walled cysts of varying size that do not communicate with the renal pelvis and are surrounded by echogenic cortex (Fig. 10-44).

FIGURE 10-44

Multicystic dysplastic kidneys. Coronal view of the fetal abdomen demonstrates markedly enlarged kidneys containing multiple cysts of varying sizes that do not communicate with a renal pelvis.



Unilateral multicystic dysplastic kidney (MCDK) has a prevalence of 1 in 4000 births. Contralateral renal abnormalities are present in 30 to 40 percent—most frequently vesicoureteral reflux or ureteropelvic junction obstruction (Schreuder, 2009). Nonrenal anomalies have been reported in 25 percent of cases, and cystic dysplasia may occur as a component of many genetic syndromes (Lazebnik, 1999; Schreuder, 2009). If MCDK is isolated and unilateral, the prognosis is generally good.

Bilateral MCDK is found in approximately 1 in 12,000 births. It is associated with severely decreased amnionic fluid volume starting early in gestation. This leads to Potter sequence and a poor prognosis (Lazebnik, 1999).

Polycystic Kidney Disease

Of the hereditary polycystic diseases, only the infantile form of *autosomal recessive polycystic kidney disease (ARPKD)* may be reliably diagnosed prenatally. ARPKD is a chronic, progressive disease of the kidneys and liver that results in cystic dilatation of the renal collecting ducts and in congenital hepatic fibrosis (Turkbey, 2009). The carrier frequency of a disease-causing mutation in the *PKHD1* gene approximates 1 in 70, and the disease prevalence is 1 in 20,000 (Zerres, 1998). The phenotypic variability of ARPKD ranges from lethal pulmonary hypoplasia at birth to presentation in late childhood or even adulthood with predominantly hepatic manifestations. Sonographically, infantile ARPKD displays abnormally large kidneys that fill and distend the fetal abdomen and have a solid, ground-glass texture. Severe oligohydramnios confers a poor prognosis.

Autosomal dominant polycystic kidney disease (ADPKD), which is far more common, usually does not manifest until adulthood (Chap. 53, Pregnancy Outcomes). Even so, some fetuses with ADPKD have mild renal enlargement and enhanced renal echogenicity in the setting of normal amnionic fluid volume. The differential diagnosis for these findings includes several genetic syndromes, aneuploidy, or normal variant.

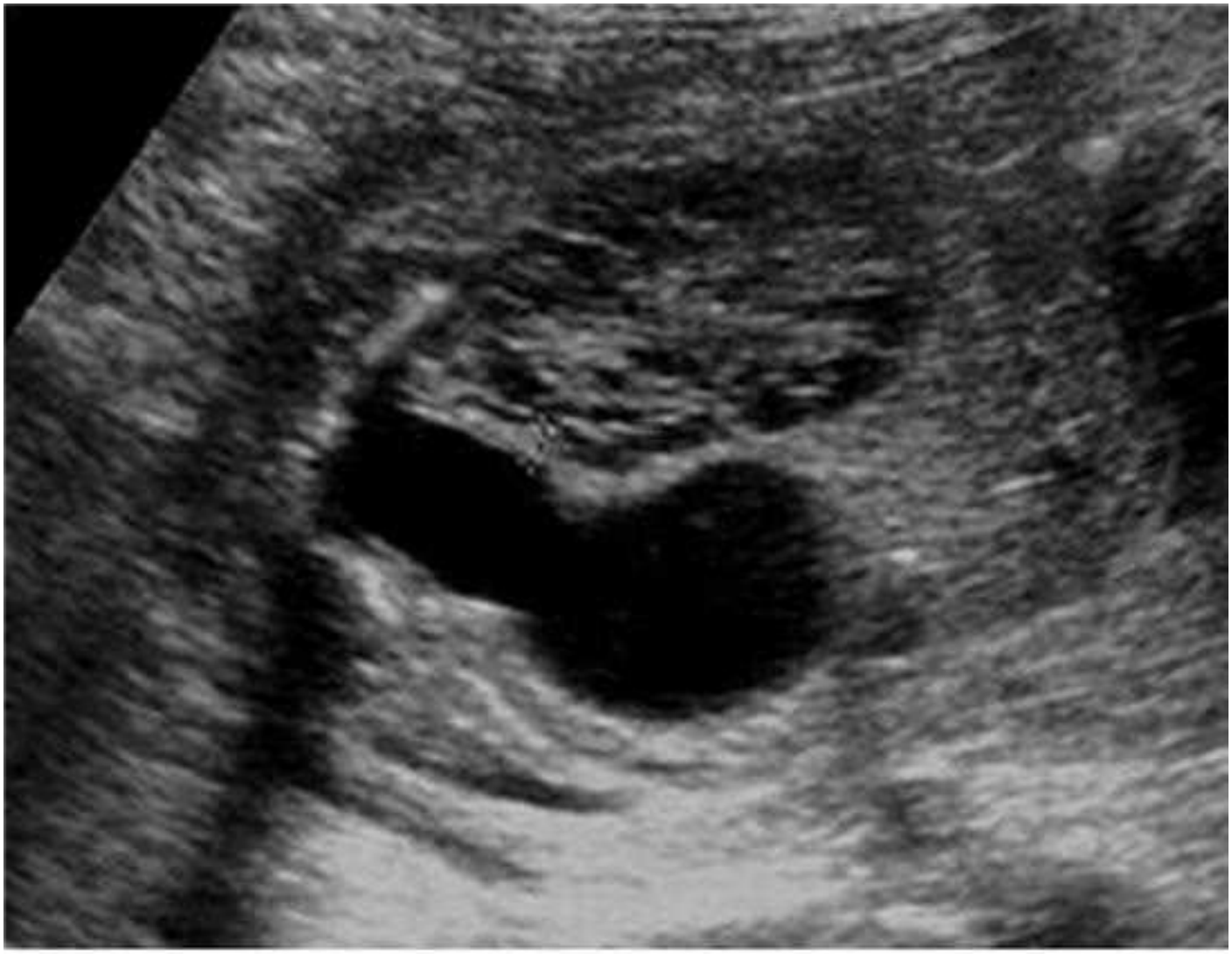
Bladder Outlet Obstruction

Distal obstruction of the urinary tract is more frequent in male fetuses, and the most common etiology is *posterior urethral valves*. Characteristically, the bladder and proximal urethra are dilated, termed the “keyhole” sign, and the bladder wall is thick (Fig. 10-45). Oligohydramnios, particularly before midpregnancy, portends a poor prognosis because of pulmonary hypoplasia. Unfortunately, the outcome may be poor even with normal amnionic fluid volume. Evaluation includes a careful search for associated anomalies, which may occur in 40 percent of cases, and for aneuploidy, which has been reported in 5 to 8 percent (Hayden, 1988; Hobbins, 1984; Mann, 2010). If neither are present, affected male fetuses with severe oligohydramnios who have fetal urinary electrolytes

suggesting a potentially favorable prognosis may be fetal therapy candidates. Evaluation and treatment of fetal bladder outlet obstruction is discussed in Chapter 16 (Urinary Shunts).

FIGURE 10-45

Posterior urethral valve. In this 19-week fetus with severe bladder outlet obstruction, the bladder is dilated and thick-walled, with dilatation of the proximal urethra that resembles a "keyhole." Adjacent to the bladder is an enlarged kidney with evidence of cystic dysplasia, conferring a poor prognosis.



Skeletal Abnormalities

The 2015 revision of the Nosology and Classification of Genetic Skeletal Disorders includes an impressive 436 skeletal anomalies in 42 groups, characterized by genetic abnormalities, phenotypic features, or radiographic criteria (Bonafe, 2015). The two types of skeletal dysplasias are *osteochondrodysplasias*—the generalized abnormal development of bone and/or cartilage, and *dysostoses*—which are abnormalities of individual bones, for example, *polydactyly.* In addition to these *malformations*, skeletal abnormalities include *deformations*, as with some cases of clubfoot, and *disruptions* such as limb-reduction defects.

Skeletal Dysplasias

The prevalence of skeletal dysplasias approximates 3 in 10,000 births. Two groups account for more than half of all cases: the *fibroblast growth factor 3 (FGFR3) chondrodysplasia* group and the *osteogenesis imperfecta* and decreased bone density group. Each occurs in 0.8 in 10,000 births (Stevenson, 2012).

Evaluation of a pregnancy with suspected skeletal dysplasia includes a survey of every long bone, as well as the hands and feet, skull size and shape, clavicles, scapulae, thorax, and spine. Reference tables are used to determine which long bones are affected and ascertain the degree of shortening (Appendix, Fetal Sonographic Measurements). Involvement of all long bones is termed *micromelia,* whereas predominant involvement of only the proximal, intermediate, or distal long bone segments is termed *rhizomelia, mesomelia,* and *acromelia*, respectively. The degree of ossification should be noted, as should presence of bowing or fractures. Each of these may provide clues to narrow the differential diagnosis and occasionally suggest a specific skeletal dysplasia. Many, if not most, skeletal dysplasias have a genetic component, and knowledge of specific mutations has advanced dramatically (Bonafe, 2015).

Although precise characterization may elude prenatal diagnosis, it is frequently possible to determine whether a skeletal dysplasia is lethal. Lethal dysplasias show profound long bone shortening, with measurements <5th percentile, and display femur length-to-abdominal circumference ratios below 16 percent (Nelson, 2014; Rahemtullah, 1997; Ramus, 1998). Generally, other sonographic abnormalities are evident. Pulmonary hypoplasia is suggested by a thoracic circumference <80 percent of the abdominal circumference value, by a thoracic circumference <2.5th percentile, and a cardiac circumference >50 percent of the thoracic circumference value (Appendix, Fetal Sonographic Measurements). Affected pregnancies also may develop hydramnios and/or hydrops (Nelson, 2014).

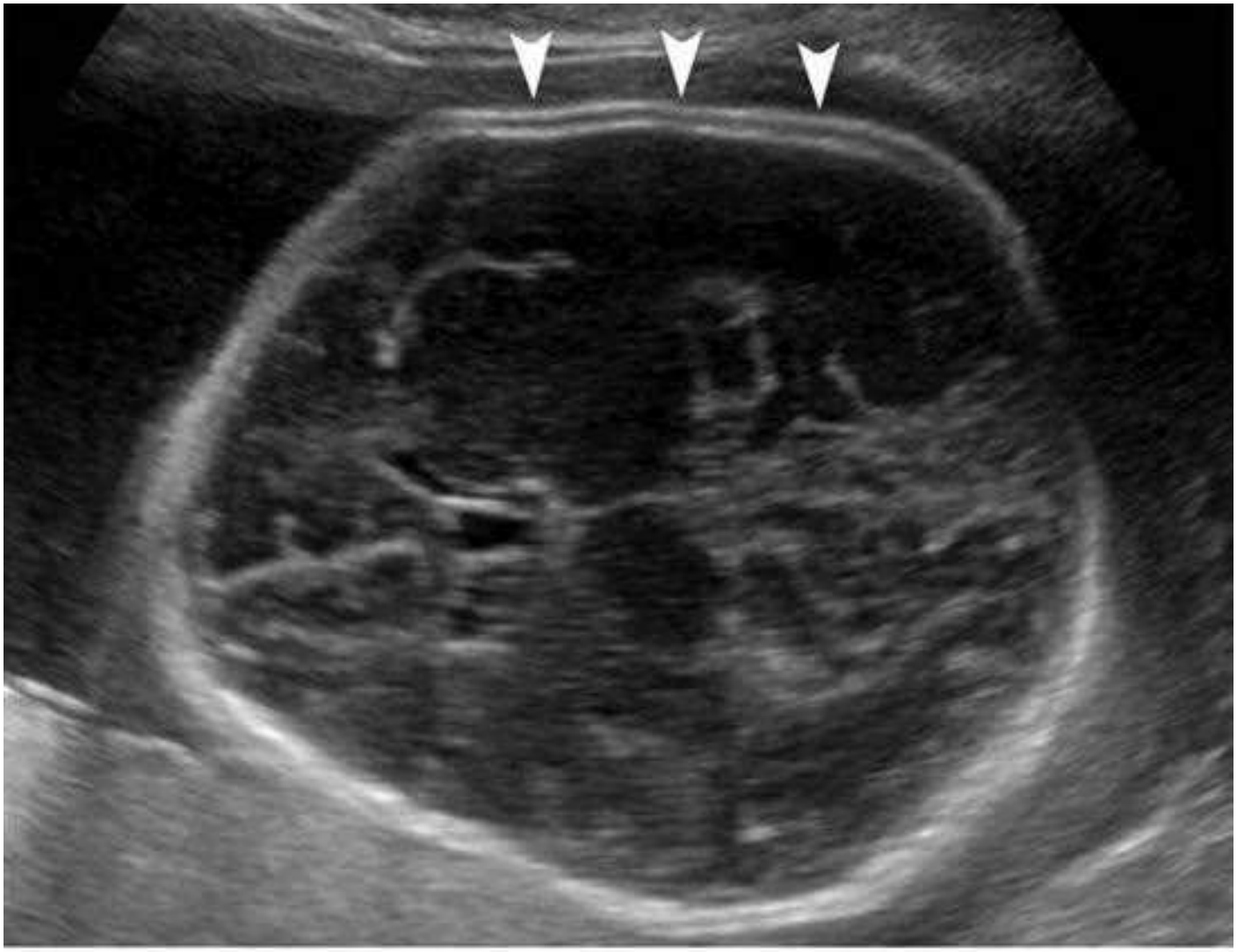
The FGFR3 chondrodysplasias include *achondroplasia* and *thanatophoric dysplasia.* Achondroplasia, also called *heterozygous achondroplasia*, is the most common nonlethal skeletal dysplasia. An impressive 98 percent of cases are due to a specific point mutation in the *FGFR3* gene. It has an autosomal dominant inheritance, and 80 percent of cases result from a new mutation. Achondroplasia is characterized by long bone shortening that is predominantly *rhizomelic*, an enlarged head with frontal bossing, depressed nasal bridge, exaggerated lumbar lordosis, and a trident configuration of the hands. Intelligence is typically normal. Sonographically, the femur and humerus measurements may not lie below the 5th percentile until the early third trimester. Thus, this condition is usually not diagnosed until late in pregnancy. In homozygotes, which represent 25 percent of the offspring of heterozygous parents, the condition is characterized by greater long bone shortening and is lethal.

The other major class of FGFR3 dysplasias, *thanatophoric dysplasia*, is the most common lethal skeletal disorder. It is characterized by severe micromelia, and affected fetuses—particularly those with type II—may develop a characteristic cloverleaf skull deformity (*Kleeblattschädel*) due to craniosynostosis. More than 99 percent of cases may be confirmed with genetic testing.

Osteogenesis imperfecta represents a group of skeletal dysplasias typified by hypomineralization. There are multiple types, and more than 90 percent of cases are characterized by a mutation in the *COL1A1* or *COL1A2* gene. Type IIa, also called the perinatal form, is lethal. It displays a profound lack of skull ossification, such that gentle pressure on the maternal abdomen from the ultrasound transducer results in visible skull deformation (Fig. 10-46). Other features include multiple in-utero fractures and ribs that appear “beaded.” Inheritance is autosomal dominant, such that all cases result from either new mutations or gonadal mosaicism (Chap. 13, Modes of Inheritance). Another skeletal dysplasia that results in severe hypomineralization is *hypophosphatasia*, which has an autosomal recessive inheritance.

FIGURE 10-46

Osteogenesis imperfecta. Type IIa, which is lethal, is characterized by such profound lack of skull ossification that gentle pressure on the maternal abdomen from the ultrasound transducer results in visible deformation (flattening) of the skull (*arrowheads*).

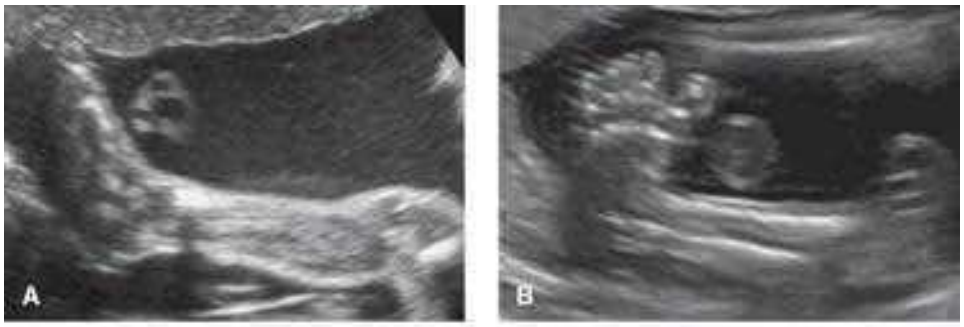


Clubfoot—Talipes Equinovarus

This disorder is notable for a deformed talus and shortened Achilles tendon. The affected foot is abnormally fixed and positioned with *equinus* (downward pointing), *varus* (inward rotation), and forefoot adduction. Most cases are considered malformations, with a multifactorial genetic component. However, an association with environmental factors and with early amniocentesis suggests that deformation also plays a role (Tredwell, 2001). Sonographically, the footprint is visible in the same plane as the tibia and fibula (Fig. 10-47).

FIGURE 10-47

Foot position. **A.** Normal fetal lower leg, demonstrating normal position of the foot. **B.** With talipes equinovarus, the foot "print" is visible in the same plane as the tibia and fibula.



The prevalence of clubfoot approximates 1 in 1000 births, and the male:female ratio is 2:1 (Carey, 2003; Pavone, 2012). Clubfoot is bilateral in approximately 50 percent of affected individuals, and associated anomalies are present in at least 50 percent of all cases (Mammen, 2004; Sharma, 2011). Frequently associated anomalies include neural-tube defects, arthrogryposis, and myotonic dystrophy and other genetic syndromes. In cases with associated anomalies, aneuploidy is

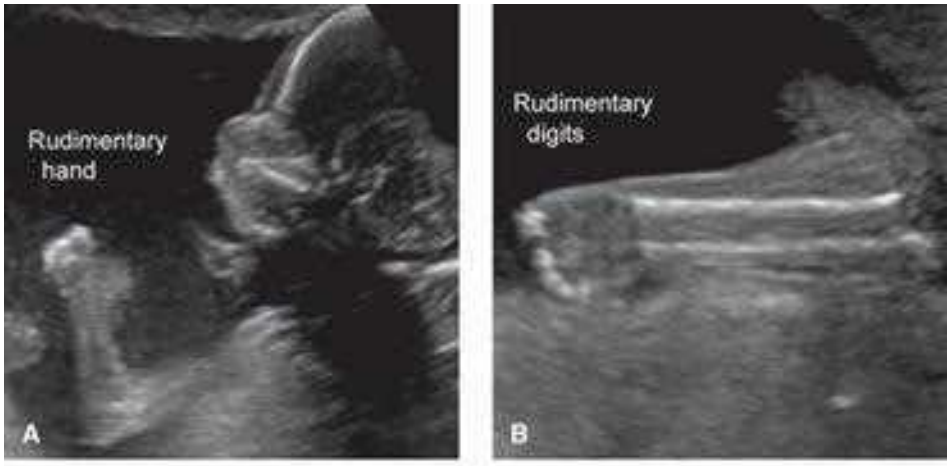
found in approximately 30 percent. In contrast, the rate is <4 percent when clubfoot appears isolated (Lauson, 2010; Sharma, 2011). Thus, a careful search for associated structural abnormalities is warranted, and chromosomal microarray analysis may be considered.

Limb-Reduction Defects

Documentation of the arms and legs is a component of the standard examination. The absence or hypoplasia of all or part of one or more extremities is a *limb-reduction defect*. The birth prevalence is 4 to 8 in 10,000 (Kucik, 2012; Stoll, 2010; Vasluian, 2013). Approximately half of these are isolated defects, up to one third occur as part of a recognized syndrome, and individuals in the remaining cases have other coexisting anomalies (Stoll, 2010; Vasluian, 2013). Upper extremities are affected more frequently than lower ones. Of categories, a terminal *transverse limb defect* lacks part or all of a distal limb to create a stump (Fig. 10-48). This is more common than a *longitudinal defect*, which is complete or partial absence of the long bone(s) on only one side of a given extremity.

FIGURE 10-48

Transverse limb-reduction defect. **A.** At 18 weeks' gestation, only a rudimentary hand was visible. **B.** By 24 weeks, the radius and ulna were normal in size and appearance, and small rudimentary digits were evident.



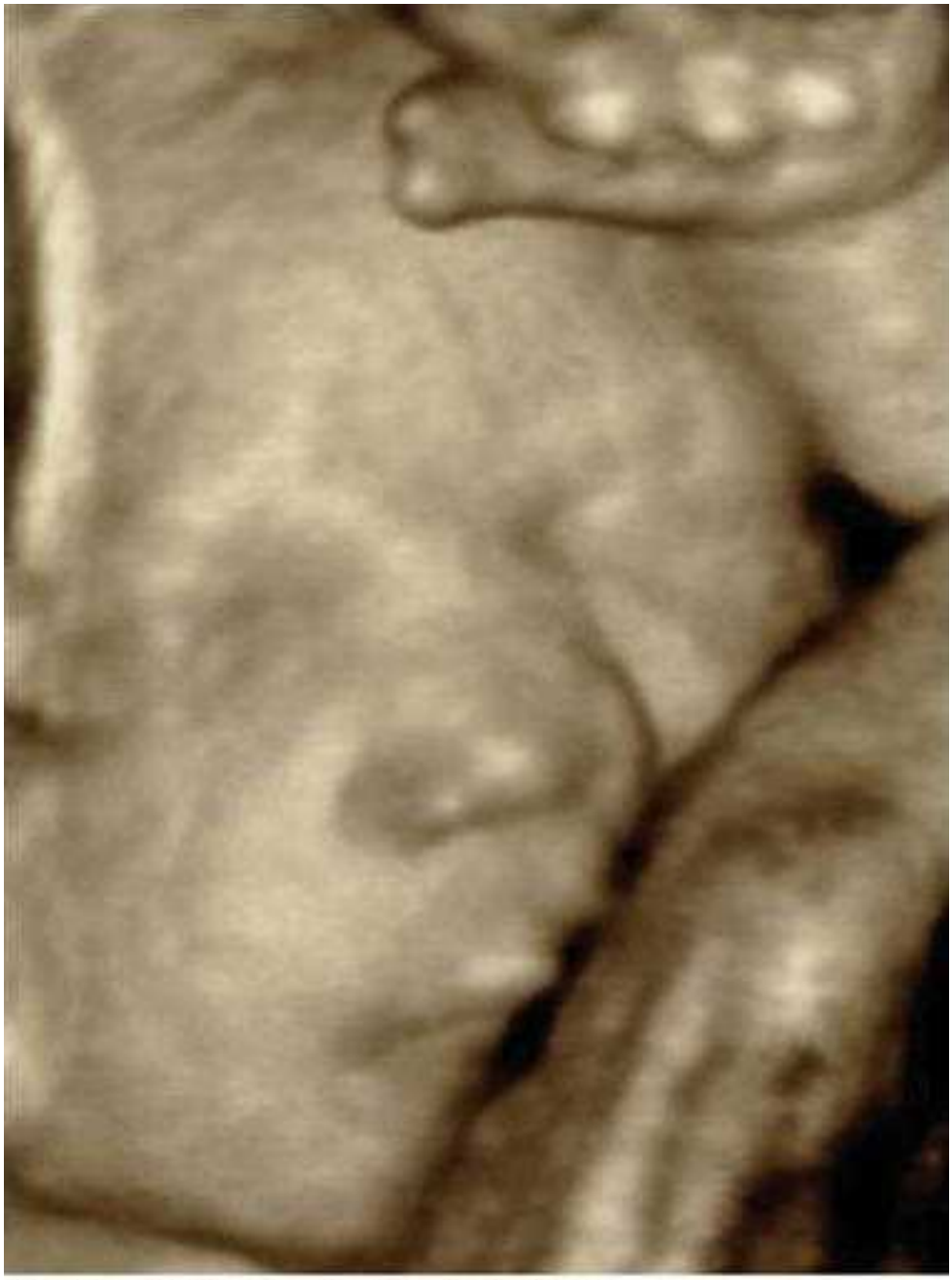
Absence of an entire extremity is termed *amelia. Phocomelia,* associated with thalidomide exposure, is an absence of one or more long bones with the hands or feet attached to the trunk (Chap. 12, Thalidomide and Lenalidomide). Limb-reduction defects are associated with numerous genetic syndromes, such as *Roberts syndrome*, an autosomal recessive condition characterized by *tetraphocomelia.* A *clubhand deformity*, usually from an absent radius, is associated with trisomy 18 and is also a component of the *thrombocytopenia-absent radius syndrome* (Fig. 13-5B). Limb-reduction defects may occur in the setting of a disruption such as amnionic-band sequence (Chap. 6, Amniochorion). They have also been associated with chorionic villus sampling when performed before 10 weeks' gestation (Fig. 14-6).

THREE- AND FOUR-DIMENSIONAL SONOGRAPHY

During the past two decades, three-dimensional (3-D) sonography has gone from a novelty to a standard feature of most modern ultrasound equipment (Fig. 10-49). 3-D sonography is not *routinely* used during a standard examination nor considered a required modality. However, it may be a component of specialized evaluations.

FIGURE 10-49

Fetal face. Surface rendered three-dimensional image of a normal fetal face and hand at 32 weeks.



Most 3-D scanning uses a special transducer developed for this purpose. After a region of interest is identified, a 3-D volume is acquired that can be rendered to display axial, sagittal, coronal, or oblique images. Sequential "slices" may be generated, similar to computed tomographic (CT) or MR images. Unlike two-dimensional (2-D) scanning, which appears to be in "real time," 3-D imaging is static and obtained by processing a volume of stored images. With *four-dimensional (4-D) sonography*, also known as real-time 3-D sonography, rapid reconstruction of the rendered images conveys the impression that the scanning is in real time.

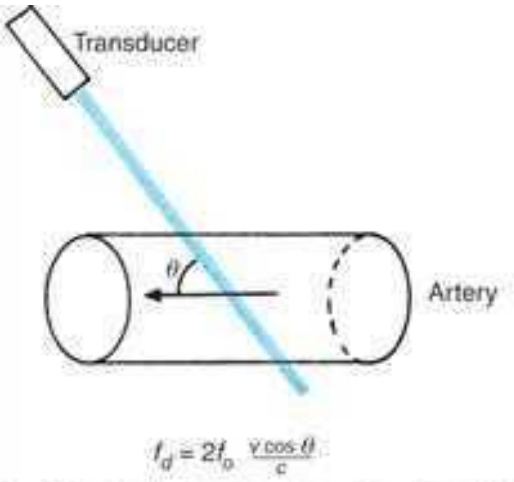
For 4-D imaging, one application known as *spatiotemporal image correlation—STIC* improves visualization of cardiac anatomy. During an automated sweep over the heart, the STIC application acquires a volume that includes thousands of 2D images captured at a rate as high as 150 frames per second (Devore, 2003). These individual images are obtained at different locations in the heart but at the same point in time. These views are subsequently arranged according to their spatial and temporal domains. This permits display of an ordered sequence of volume sets in a continuous cine loop (or video clip) of the cardiac cycle (Yeo, 2016). For example, after obtaining a volume sweep over the cardiac apex, an application such as Fetal Intelligent Navigation Echocardiography (FINE) can be applied to display videos of each of the different cardiac views shown in Fig. 10-28 (Garcia, 2016). It is hoped that such technology may eventually improve detection of fetal cardiac anomalies.

For selected anomalies, such as those of the face and skeleton, for tumors, and for some cases of neural-tube defects, 3-D sonography can add useful information (American College of Obstetricians and Gynecologists, 2016; Goncalves, 2005). That said, comparisons of 3-D and conventional 2-D sonography for the diagnosis of most congenital anomalies have not demonstrated better overall detection rates (Goncalves, 2006; Reddy, 2008). The American College of Obstetricians and Gynecologists (2016) concludes that proof of a clinical advantage of 3-D sonography for prenatal diagnosis is generally lacking.

DOPPLER

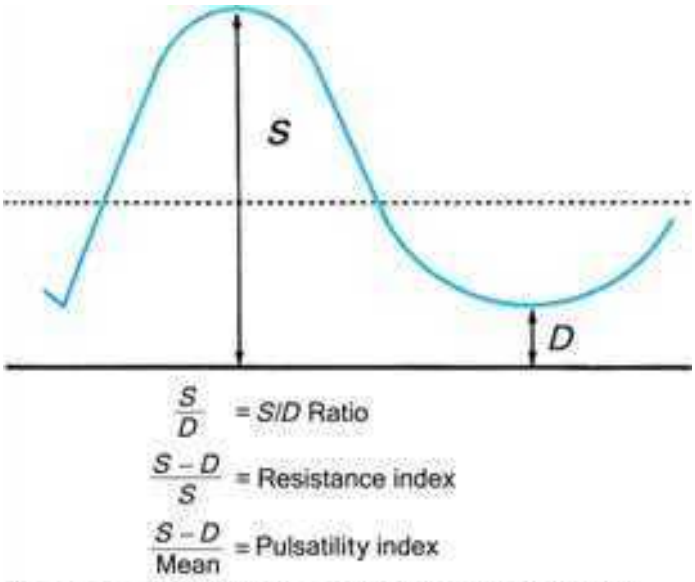
When sound waves strike a moving target, the frequency of the waves reflected back is shifted in proportion to the velocity and direction of that moving target—a phenomenon known as the *Doppler shift*. Because the magnitude and direction of the frequency shift depend on the relative motion of the moving target, Doppler can help evaluate flow within blood vessels. The Doppler equation is shown in Figure 10-50.

FIGURE 10-50
Doppler equation. Ultrasound emanating from the transducer with initial frequency f_0 strikes blood moving at velocity v. Reflected frequency f_d is dependent on angle θ between beam of sound and vessel.



An important component of the equation is the angle of insonation, abbreviated as theta (θ). This is the angle between the sound waves from the transducer and flow within the vessel. Measurement error becomes large when θ is not close to zero, in other words, when blood flow is not coming *directly* toward or away from the transducer. For this reason, ratios are often used to compare different waveform components, allowing cosine θ to cancel out of the equation. Figure 10-51 is a schematic of the Doppler waveform and describes the three ratios commonly used. The simplest is the *systolic-diastolic ratio (S/D ratio),* which compares the maximal (or peak) systolic flow with end-diastolic flow to evaluate downstream impedance to flow. Currently, two types of Doppler modalities are available for clinical use.

FIGURE 10-51
Doppler systolic–diastolic waveform indices of blood flow velocity. S represents the peak systolic flow or velocity, and D indicates the end-diastolic flow or velocity. The mean, which is the time-average mean velocity, is calculated from computer-digitized waveforms.



Continuous-wave Doppler equipment has two separate types of crystals—one transmits high-frequency sound waves, and another continuously captures signals. In M-mode imaging, continuous-wave Doppler is used to evaluate motion through time, however, it cannot image individual vessels.

Pulsed-wave Doppler uses only one crystal, which transmits the signal and then waits until the returning signal is received before transmitting another one. It allows precise targeting and visualization of the vessel of interest. Pulsed-wave Doppler can be configured to allow color-flow mapping—such that blood flowing

toward the transducer is displayed in red and that flowing away from the transducer appears in blue. Various combinations of pulsed-wave Doppler, color-flow Doppler, and real-time sonography are commercially available.

Umbilical Artery

Umbilical artery Doppler has been subjected to more rigorous assessment than any previous test of fetal health. The umbilical artery differs from other vessels in that it normally has forward flow throughout the cardiac cycle. Moreover, the amount of flow during diastole increases as gestation advances, and this reflects decreasing placental impedance. *As a result, the S/D ratio normally declines from approximately 4.0 at 20 weeks' gestation, to generally less than 3.0 after 30 weeks' and finally to 2.0 at term.* Because of downstream impedance to flow, *more* end-diastolic flow is observed at the placental cord insertion than at the fetal ventral wall. Thus, abnormalities such as absent or reversed end-diastolic flow will appear first at the fetal cord insertion site. The International Society of Ultrasound in Obstetrics and Gynecology recommends that umbilical artery Doppler measurements be made in a free loop of cord (Bhide, 2013). However, assessment close to the ventral wall insertion may optimize measurement reproducibility when flow is diminished (Berkley, 2012).

The waveform is considered abnormal if the S/D ratio is >95th percentile for gestational age. In extreme cases of growth restriction, end-diastolic flow can become absent or even reversed (Fig. 44-8). Such reversal of end-diastolic flow has been associated with greater than 70-percent obliteration of the small muscular arteries in placental tertiary stem villi (Kingdom, 1997; Morrow, 1989).

As described in Chapter 44 (Prevention), umbilical artery Doppler aids management of fetal-growth restriction and has been associated with improved outcome in these cases (American College of Obstetricians and Gynecologists, 2015). It is not recommended for complications other than growth restriction. Similarly, its use for growth-restriction screening is not advised (Berkley, 2012). Abnormal umbilical artery Doppler findings should prompt a complete fetal evaluation, if not already done, because abnormal measurements are associated with major fetal anomalies and aneuploidy (Wenstrom, 1991).

Ductus Arteriosus

Doppler evaluation of the ductus arteriosus has been used primarily to monitor fetuses exposed to indomethacin and other nonsteroidal antiinflammatory agents (NSAIDs). Indomethacin, which is used by some for tocolysis, may cause ductal constriction or closure, particularly when used in the third trimester (Huhta, 1987). The resulting increased pulmonary flow can cause reactive hypertrophy of the pulmonary arterioles and eventual development of pulmonary hypertension. In a review of 12 randomized controlled trials involving more than 200 exposed pregnancies, Koren and coworkers (2006) reported that NSAIDs raised the odds of ductal constriction 15-fold. When these agents are indicated, their duration is typically limited to less than 72 hours. And, women taking NSAIDs are closely monitored so that these can be discontinued if ductal constriction is identified. Fortunately, ductal constriction is often reversible after NSAID discontinuation.

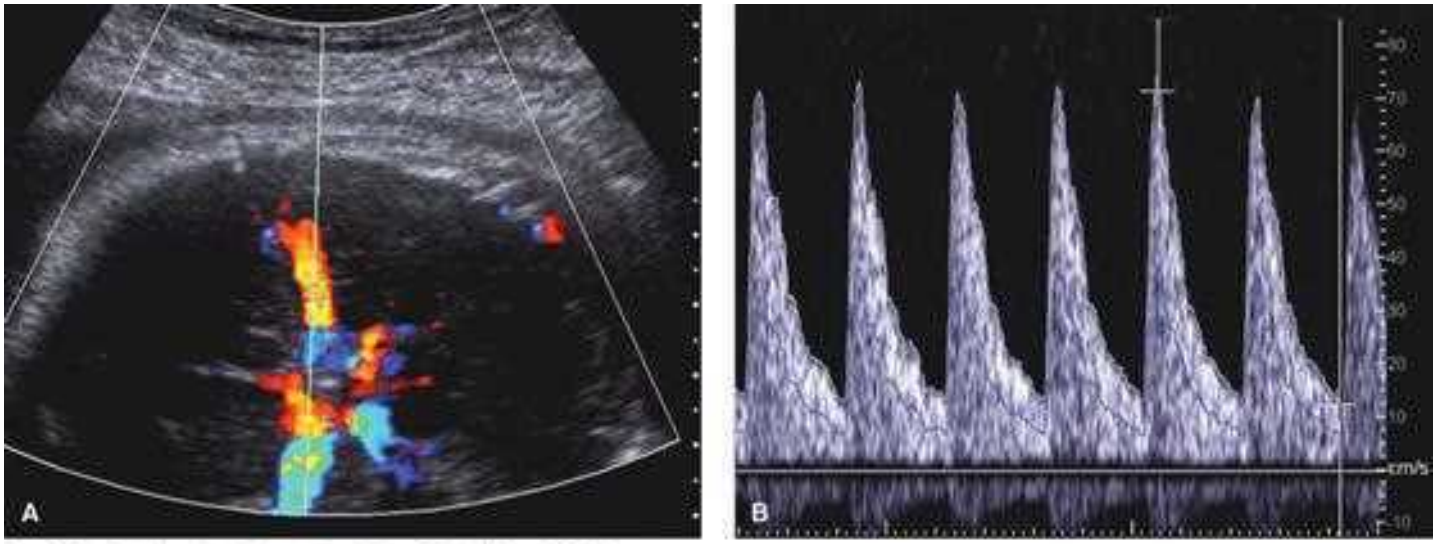
Uterine Artery

Uterine blood flow is estimated to rise from 50 mL/min early in gestation to 500 to 750 mL/min by term. The uterine artery Doppler waveform is characterized by high diastolic flow velocities and markedly turbulent flow. Greater resistance to flow and development of a *diastolic notch* are associated with later development of gestational hypertension, preeclampsia, and fetal-growth restriction. Zeeman and coworkers (2003) also found that women with chronic hypertension who had elevated uterine artery impedance at 16 to 20 weeks' gestation were at greater risk to develop superimposed preeclampsia. However, the technique, best testing interval, and defining criteria for this indication have not been standardized. As the predictive value of uterine artery Doppler testing is considered to be low, its use for screening or for clinical decision-making is not recommended in either high-risk or low-risk pregnancies (Sciscione, 2009).

Middle Cerebral Artery

Doppler interrogation of the middle cerebral artery (MCA) has been investigated and applied clinically for fetal anemia detection and fetal-growth restriction evaluation. Anatomically, the path of the MCA is such that flow often approaches the transducer "head-on," allowing for accurate determination of flow velocity (Fig. 10-52). The MCA is imaged in an axial view of the head at the base of the skull, ideally within 2 mm of the internal carotid artery origin. Velocity measurement is optimal when the insonating angle is close to zero, and no more than 30 degrees of angle correction should be used. In general, velocity assessment is not performed in other fetal vessels, because a larger insonating angle is needed and confers significant measurement error.

FIGURE 10-52
Middle cerebral artery (MCA) Doppler. **A.** Color Doppler of the circle of Willis, demonstrating the correct location to sample the MCA. **B.** The waveform demonstrates a peak systolic velocity exceeding 70 cm/sec in a 32-week fetus with severe fetal anemia secondary to Rh alloimmunization.



When fetal anemia is present, the *peak systolic velocity* is enhanced due to greater cardiac output and decreased blood viscosity (Segata, 2004). This has permitted the reliable, noninvasive detection of fetal anemia in cases of blood-group alloimmunization. Mari and colleagues (2000) demonstrated that an MCA peak systolic velocity threshold of 1.50 MoM could reliably identify fetuses with moderate or severe anemia. As discussed in Chapter 15 (Management of the Alloimmunized Pregnancy), MCA peak systolic velocity has replaced invasive testing with amniocentesis as the preferred test for fetal anemia detection (Society for Maternal-Fetal Medicine, 2015).

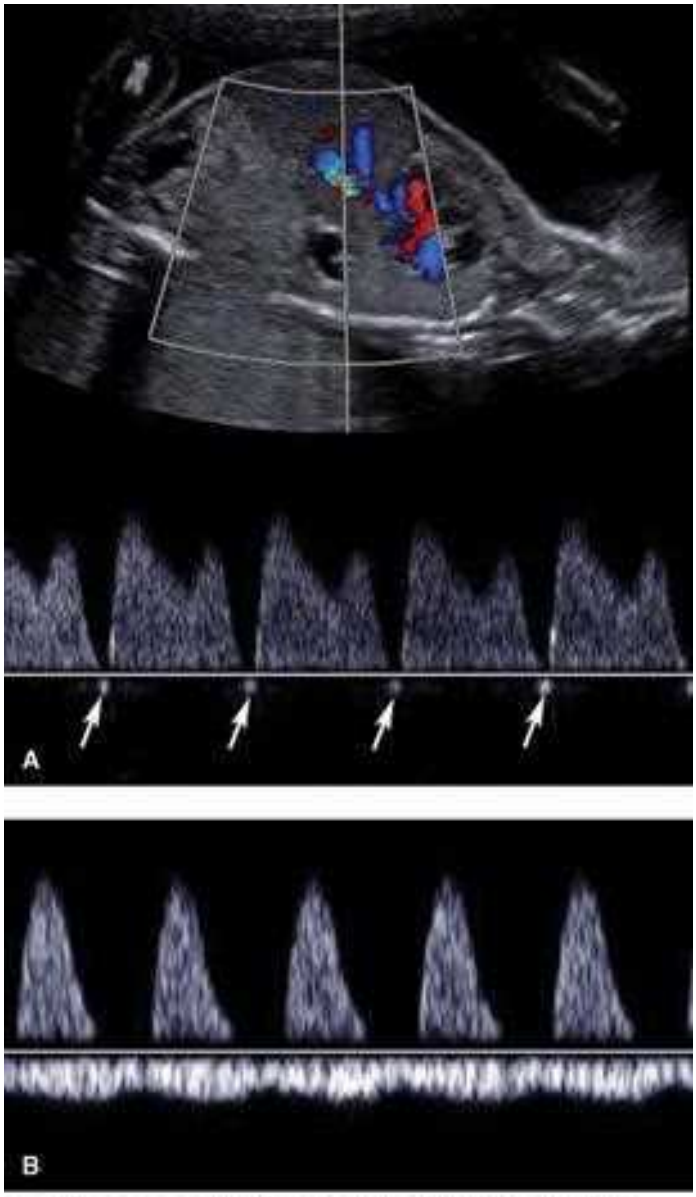
MCA Doppler has also been studied as an adjunct in evaluation of fetal-growth restriction. Fetal hypoxemia is believed to result in increased blood flow to the brain, heart, and adrenal glands, leading to greater end-diastolic flow in the MCA. This phenomenon, “brain-sparing,” is actually a misnomer, as it is not protective for the fetus but rather is associated with perinatal morbidity and mortality (Bahado-Singh, 1999; Cruz-Martinez, 2011). The utility of MCA Doppler to aid the timing of delivery is uncertain. It has *not* been evaluated in randomized trials or adopted as standard practice in the management of growth restriction (American College of Obstetricians and Gynecologists, 2015; Berkley, 2012).

Ductus Venosus

The ductus venosus is imaged as it branches from the umbilical vein at approximately the level of the diaphragm. Fetal position poses more of a challenge in imaging the ductus venosus than it does with either the umbilical artery or the middle cerebral artery. The waveform is biphasic and normally has forward flow throughout the cardiac cycle. The first peak reflects ventricular systole, and the second is ventricular diastolic filling. These are followed by a nadir during atrial contraction—termed the *a-wave*.

It is believed that Doppler findings in preterm fetuses with growth restriction show a progression in which umbilical artery Doppler abnormalities are followed by ones in the middle cerebral artery and then in the ductus venosus. However, manifestations of these abnormalities vary widely (Berkley, 2012). With severe fetal-growth restriction, cardiac dysfunction may lead to flow in the a-wave that is decreased, absent, and eventually reversed, along with pulsatile flow in the umbilical vein (Fig. 10-53).

FIGURE 10-53
Venous Doppler abnormalities. **A.** Reversal of a-wave flow in the ductus venosus. Arrows depict a-waves below the baseline. This finding may be identified with cardiac dysfunction in the setting of severe fetal-growth restriction. **B.** Pulsatile flow in the umbilical vein. The undulating umbilical venous waveform below the baseline indicates tricuspid regurgitation. Above the baseline is the umbilical artery waveform, in which there is no visible end-diastolic flow. Because the venous waveform is below the baseline in this image, it is not possible to determine whether the umbilical artery end-diastolic flow is reversed.



Ductus venosus abnormalities have potential to identify preterm growth-restricted fetuses that are at greatest risk for adverse outcomes (Baschat, 2003, 2004; Bilardo, 2004; Figueras, 2009). As noted by the Society for Maternal-Fetal Medicine, however, they have not been sufficiently evaluated in randomized trials (Berkley, 2012). In sum, Doppler assessment of vessels other than the umbilical artery has not been shown to improve perinatal outcome, and thus their role in clinical practice remains uncertain (American College of Obstetricians and Gynecologists, 2015).

MAGNETIC RESONANCE IMAGING

Image resolution with MR is often superior to that with sonography because it is not as hindered by bony interfaces, maternal obesity, oligohydramnios, or an engaged fetal head. Thus, it can serve as an adjunct to sonography in evaluating suspected fetal abnormalities. Examples include complex abnormalities of the fetal CNS, thorax, gastrointestinal system, genitourinary system, and musculoskeletal system. MR has also been used in the evaluation of maternal pelvic masses and placental invasion. MR imaging, however, is not portable, it is time-consuming, and its use is generally limited to referral centers with expertise in fetal imaging.

To guide clinical use, the American College of Radiology and Society for Pediatric Radiology (2015) have developed a practice guideline for fetal MR imaging. This document acknowledges primacy of sonography as the preferred screening modality. Moreover, it recommends that fetal MR imaging be used for problem solving to ideally contribute to prenatal diagnosis, counseling, treatment, and delivery planning. Specific indications for fetal MR imaging are listed in Table 10-11 and are discussed subsequently.

TABLE 10-11

Fetal Conditions for Which Magnetic Resonance Imaging May Be Indicated[a]

Brain and spine
Ventriculomegaly
Agenesis of the corpus callosum
Cavum septum pellucidum abnormalities
Holoprosencephaly
Posterior fossa abnormalities
Cerebral cortical malformation or migrational abnormalities
Cephalocele
Solid or cystic masses
Vascular malformations
Hydranencephaly
Infarctions
Hemorrhage
Monochorionic twin pregnancy complications
Neural-tube defects
Sacrococcygeal teratoma
Sacral agenesis (caudal regression)
Sirenomelia
Vertebral anomalies
Family history conferring a risk for brain anomaly
Skull, face, and neck
Venolymphatic malformations
Hemangiomas
Goiter
Teratomas
Facial clefts
Other abnormalities with potential airway obstruction
Thorax
Congenital cystic adenomatoid malformation
Extralobar pulmonary sequestration
Bronchogenic cyst or congenital lobar overinflation
Diaphragmatic hernia
Effusions
Mediastinal masses
Assessment for esophageal atresia
Evaluation of pulmonary hypoplasia secondary to diaphragmatic hernia, oligohydramnios, chest mass, or skeletal dysplasia
Abdomen, pelvis, and retroperitoneum
Abdominopelvic cystic mass evaluation
Tumor evaluation (sacrococcygeal teratoma, neuroblastoma, hemangioma, suprarenal or renal masses)
Complex genitourinary anomalies (bladder outlet obstruction syndromes, bladder exstrophy, cloacal exstrophy)
Assess renal anomalies with oligohydramnios
Diagnose bowel anomalies (anorectal malformations, complex obstructions)
Complications of monochorionic twins
Determine vascular anatomy prior to laser treatment
Assess morbidity after death of a monochorionic co-twin
Evaluate conjoined twins
Fetal surgery assessment
Fetal brain anatomy before and after surgical intervention
Anomalies for which fetal surgery is planned

[a]In some cases, magnetic resonance (MR) imaging is indicated only if the anomaly is suspected but cannot be adequately characterized sonographically, which is assessed on a case-by-case basis.

Data from American College of Radiology, 2015.

Safety

MR imaging uses no ionizing radiation, but theoretical concerns include the effects of fluctuating electromagnetic fields and high sound-intensity levels. The strength of the magnetic field is measured in *tesla (T),* and most imaging studies during pregnancy are performed using 1.5 T. A few preliminary studies advocate the use of 3 T for fetal imaging to potentially improve signal-to-noise ratios and thus image clarity (Victoria, 2016). For safety, all clinical examinations must adhere to the specific absorption rate, which is regulated by the Food and Drug Administration, and the ALARA principle should be followed. Thus, for routine clinical examinations, the lower field strength of 1.5 T is recommended (Prayer, 2017).

Human and tissue studies support the safety of fetal MR imaging. Repetitive exposure of human lung fibroblasts to a static 1.5-T magnetic field does not affect cellular proliferation (Wiskirchen, 1999). Fetal heart rate patterns have been evaluated before and during MR imaging, and no significant differences were observed (Vadeyar, 2000). Children exposed to MR as fetuses do not show a greater incidence of disease or disability when tested at age 9 months or 3 years (Baker, 1994; Clements, 2000).

Glover and associates (1995) attempted to mimic the sound level experienced by the fetal ear by having an adult volunteer swallow a microphone while the stomach was filled with a liter of fluid to represent the amnionic sac. Sound intensity was attenuated at least 30-dB from the body surface to the fluid-filled stomach and reduced the sound pressure from 120 dB to below 90 dB. This level is considerably less than the 135 dB experienced from vibroacoustic stimulation used in antepartum well-being assessments (Chap. 17, Acoustic Stimulation Tests). Cochlear function testing in infants exposed to 1.5-T MR imaging as fetuses showed no hearing impairment (Reeves, 2010).

The American College of Radiology (2013) concludes that based on available evidence, MR imaging has no documented deleterious effects on the developing fetus. Therefore, MR imaging can be performed in pregnancy if data are needed to care for the fetus or mother. Health-care providers who are pregnant may work in and around an MR unit, but it is recommended that they not remain in the MR scanner magnet room—known as Zone IV—while an examination is in progress.

Gadolinium-based MR contrast agents are gadolinium (Gd^{3+}) chelates. These contrast agents readily enter the fetal circulation and are excreted via fetal urination into amnionic fluid, where they may remain for an indeterminate period before being ingested and reabsorbed. The longer the gadolinium-chelate molecule remains in a protected space such as the amnionic sac, the greater the potential for dissociation of the toxic Gd^{3+} ion. Accordingly, gadolinium contrast should be avoided during pregnancy because of this potential for dissociation. Routine use of gadolinium is not recommended unless there are overwhelming potential benefits (American College of Radiology, 2013). In adults with renal disease, this contrast agent has been associated with development of nephrogenic systemic fibrosis, a potentially severe complication.

Technique

Before MR examination, all women complete a written safety questionnaire that includes information about metallic implants, pacemakers, or other metal- or iron-containing devices that may alter the study (American College of Radiology, 2013). Iron supplementation may cause artifact in the colon but does not usually affect the resolution of fetal images. In more than 4000 MR procedures performed at Parkland Hospital in pregnancy during the past 15 years, maternal anxiety secondary to claustrophobia and/or fear of MR equipment has developed in less than 1 percent of our patients. To reduce maternal anxiety in this small group, a single oral dose of diazepam, 5 to 10 mg, or lorazepam, 1 to 2 mg, may be given.

To begin an MR examination, women are placed in a supine or left lateral decubitus position. A torso coil is used in most circumstances to send and receive the radiofrequency pulses, but a body coil can be used alone to accommodate large maternal habitus. A series of three-plane localizers, or scout views, are obtained relative to the maternal coronal, sagittal, and axial planes. The gravid uterus is imaged in the maternal axial plane (7-mm slices, 0 gap) with a T2-weighted fast acquisition. Typically, these may be a single-shot fast spin echo sequence (SSFSE), half-Fourier acquisition single-shot turbo spin echo (HASTE), or rapid acquisition with relaxation enhancement (RARE), depending on the brand of machine. Next, a fast T1-weighted acquisition such as spoiled gradient echo (SPGR) is performed (7-mm thickness, 0 gap). These large-field-of-view acquisitions through the maternal abdomen and pelvis are particularly good for identifying fetal and maternal anatomy.

Orthogonal images of targeted fetal or maternal structures are then obtained. In these cases, 3- to 5-mm slice thickness, 0 gap T2-weighted acquisitions are performed in the coronal, sagittal, and axial planes. Depending on the anatomy and underlying suspected abnormality, T1-weighted images can be performed to evaluate for subacute hemorrhage, fat, or location of normal structures that appear bright on these sequences, such as liver and meconium in the colon (Brugger, 2006; Zaretsky, 2003b).

Short T1 inversion recovery (STIR) and frequency-selective fat-saturated T2-weighted images may provide differentiation in cases in which the water content of the abnormality is similar to that of the normal structure. An example is a thoracic mass compared with normal lung. Diffusion-weighted imaging may be employed to evaluate for restricted diffusion, which can be seen in ischemia, cellular tumors, or clotted blood (Brugger, 2006; Zaretsky, 2003b). Our series also includes an axial brain 3- to 5-mm T2-weighted sequence to obtain head biometry for gestational age estimation using the biparietal diameter and head circumference (Reichel, 2003).

Fetal Anatomical Evaluation

Whenever a fetal abnormality is identified, findings from the affected organ and other organ systems should be thoroughly characterized. Accordingly, a fetal anatomical survey is generally completed during each MR examination. In a recent prospective study, nearly 95 percent of the anatomical components recommended by the International Society of Ultrasound in Obstetrics and Gynecology were visible at 30 weeks' gestation (Millischer, 2013). The aorta and pulmonary artery were the most difficult to evaluate. Zaretsky and coworkers (2003a) similarly found that with the exclusion of cardiac structures, fetal anatomical evaluation was possible in 99 percent of cases.

Central Nervous System

For intracranial anomalies, very fast T2-weighted images produce excellent tissue contrast, and CSF-containing structures are hyperintense or bright. This allows exquisite detail of the posterior fossa, midline structures, and cerebral cortex. T1-weighted images are used to identify hemorrhage.

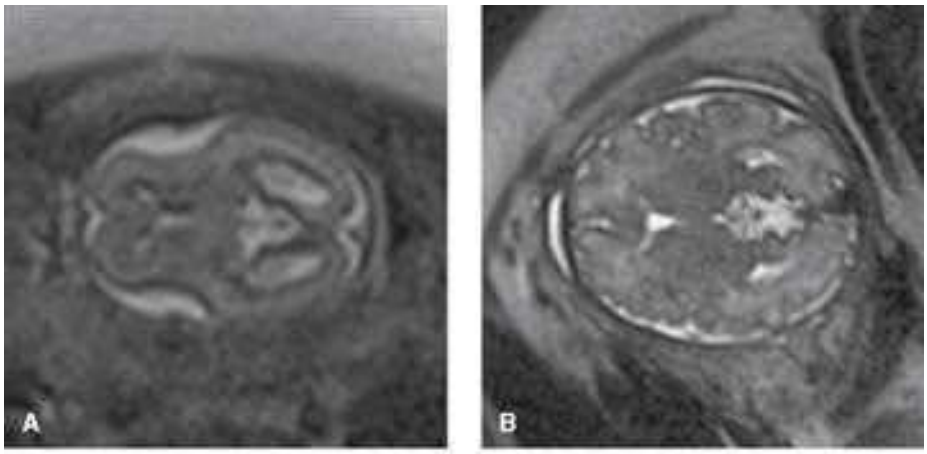
CNS biometry obtained with MR imaging is comparable with that obtained using sonography (Twickler, 2002). Nomograms have been published for multiple intracranial structures, including corpus callosum and cerebellar vermis lengths (Garel, 2004; Tilea, 2009).

MR imaging provides valuable added information for cerebral abnormalities suspected sonographically (Benacerraf, 2007; Li, 2012). In early studies, MR imaging changed the diagnosis in 40 to 50 percent of cases and affected management in 15 to 50 percent (Levine, 1999b; Simon, 2000; Twickler, 2003). Additional information is more likely to be gained when the examination is performed beyond 24 weeks' gestation. More recently, Griffiths and associates (2017) reported that MR evaluation of suspected fetal brain anomalies identified additional findings in nearly 50 percent and changed prognosis in 20 percent.

Fetuses with a cerebral abnormality may have a significant lag in cortical development. Levine and colleagues (1999a) demonstrated that MR imaging accurately portrays cerebral gyration and sulcation patterns (Fig. 10-54). Sonography permits limited evaluation of subtle migrational abnormalities, and MR imaging provides greater accuracy, particularly later in gestation.

FIGURE 10-54

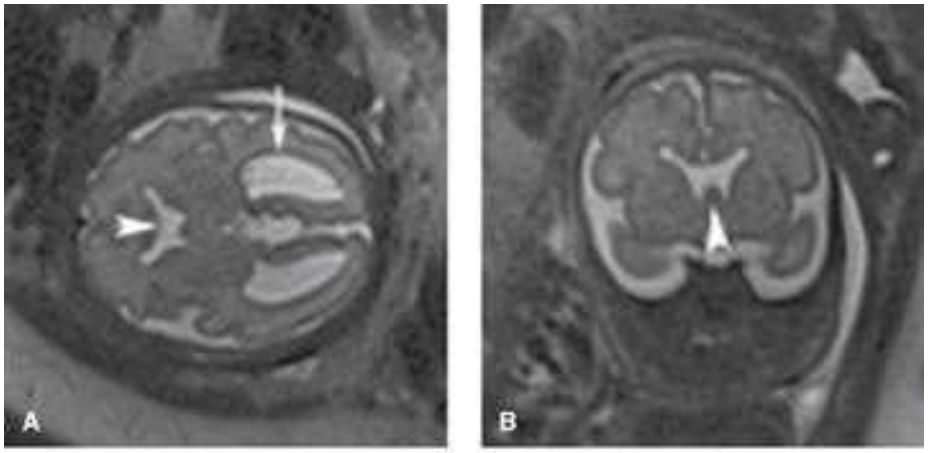
Axial images of the fetal brain at 23 weeks' gestation **(A)** and at 33 weeks **(B)** demonstrate the normal gyration and sulcation progression during fetal development. These images were obtained using a Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) sequence because it is relatively motion insensitive.



For ventriculomegaly, fetal MR imaging is selected to help identify associated underlying CNS dysmorphology (Ventriculomegaly). In cases of septo-optic dysplasia, MR imaging may confirm absence of the septum pellucidum and display hypoplastic optic tracts (Fig. 10-55). In other fetuses, MR imaging can also assist with identifying agenesis or dysgenesis of the corpus callosum and characterizing migrational abnormalities (Benacerraf, 2007; Li, 2012; Twickler, 2003).

FIGURE 10-55

Septo-optic dysplasia. Axial **(A)** and coronal **(B)** images at 30 weeks' gestation confirm absence of the cavum septum pellucidum (*arrowheads*) in both. There is also associated mild ventriculomegaly (*arrow*).

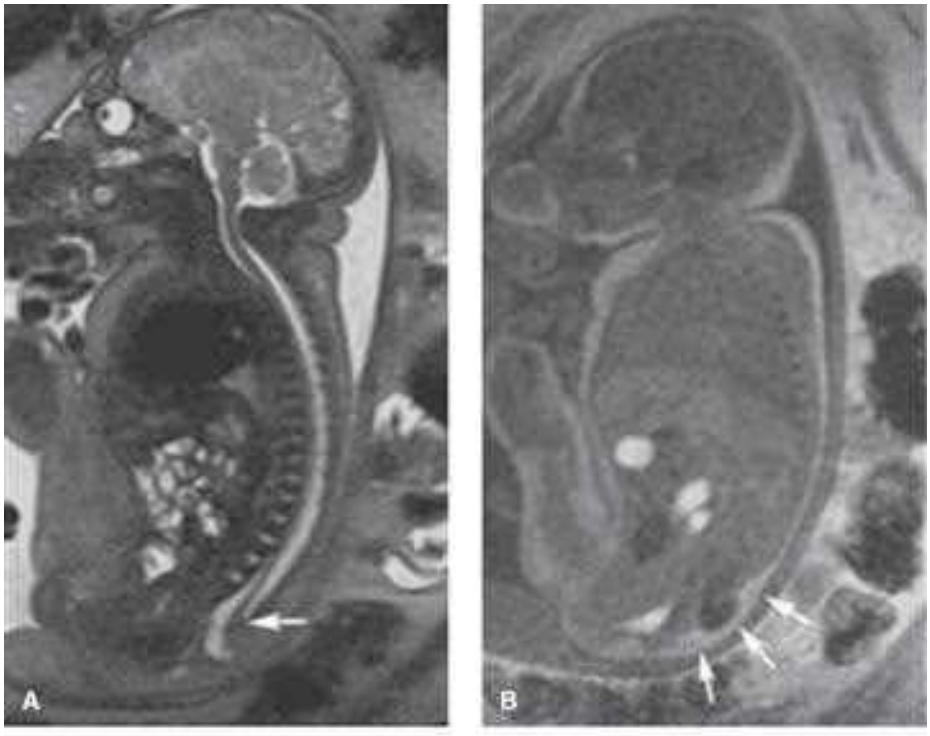


Another fetal MR imaging indication is evaluation of suspected intraventricular hemorrhage (IVH). Fetal IVH risk factors include atypical-appearing ventriculomegaly, neonatal alloimmune thrombocytopenia, and a monochorionic multifetal gestation complicated by demise of one fetus or by severe twin-twin transfusion syndrome (Hu, 2006). If hemorrhage is seen, MR imaging characteristics may indicate which structures are involved and approximately when bleeding occurred. In the setting of congenital fetal infections, MR imaging can delineate the variable degrees of neural parenchymal abnormality and subsequent maldevelopment (Soares de Oliveira-Szejnfeld, 2016).

Aside from cerebral structure, suspected spinal dysraphisms, including neural-tube defects, can also be further characterized for surgical planning. Figure 10-56 demonstrates a complex skin-covered dysraphism with associated tethering of the spinal cord. This terminal myelocystocele will benefit from early intervention following delivery.

FIGURE 10-56

Terminal myelocystocele, 36 weeks' gestation. **A.** In this sagittal T2-weighted image, the spinal cord is tethered, expanding into the terminal cyst (*arrow*). **B.** Seen in this T1-weighted image, the meningocele and terminal cyst are covered by subcutaneous fat (*arrows*) and skin.

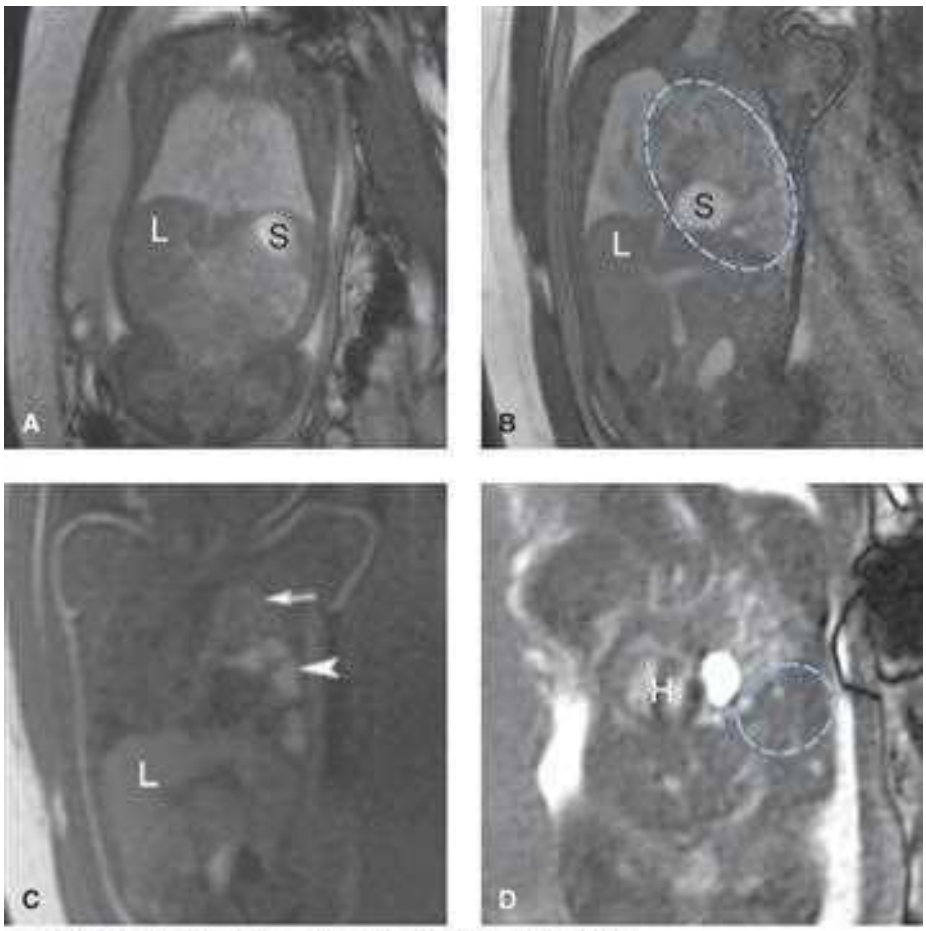


Thorax

Many thoracic abnormalities are readily seen with targeted sonography. MR imaging, however, may help delineate the location and size of space-occupying thoracic lesions and quantify remaining lung tissue volumes. MR imaging can aid in characterizing the type of congenital cystic adenomatoid malformation and in visualizing the blood supply of pulmonary sequestration (Heart). With congenital diaphragmatic hernia, MR imaging can help verify and quantify the abdominal organs within the thorax. This includes the volume of herniated liver and compressed lung tissue volumes (Fig. 10-57) (Debus, 2013; Lee, 2011; Mehollin-Ray, 2012). Also in fetuses with diaphragmatic hernia, MR imaging can assist in identifying other organ-system abnormalities, which may greatly affect fetal prognosis (Kul, 2012). MR imaging similarly is used for chest evaluation in skeletal dysplasia and to measure lung volumes in pregnancies with prolonged oligohydramnios secondary to renal disease or ruptured membranes (Messerschmidt, 2011; Zaretsky, 2005).

FIGURE 10-57

A. Coronal image of normal lungs on a balanced sequence at 29 weeks' gestation. The liver (*L*) and stomach (*S*) lie below the diaphragm. **B.** Left-sided congenital diaphragmatic hernia (CDH) (*dotted ellipse*) seen on balanced sequence at 33 weeks. **C.** The T1-weighted sequence confirms the subdiaphragmatic position of the liver and better delineates the small bowel (*arrow*) and meconium-containing colon (*arrowhead*) that have herniated into the chest. **D.** Another image of a left-sided CDH at 22 weeks demonstrates no normal lung, the heart (*H*) displaced into the right chest, and an elevated liver (*dotted ellipse*).



Abdomen

When sonographic viewing of fetal abdominal abnormalities is limited by oligohydramnios or maternal obesity, MR imaging may add value (Caire, 2003). Hawkins and coworkers (2008) found that lack of signal in a contracted fetal bladder on T2-weighted sequences was associated with lethal renal abnormalities (Fig. 10-58). Differences in signal characteristics between meconium in the fetal colon and urine in the bladder may permit definition of cystic abdominal abnormalities (Farhataziz, 2005). Given the predictable pattern of meconium accumulation within the gastrointestinal tract and high signal intensity on T1-weighted sequences, MR imaging is a complementary tool in diagnosing gastrointestinal abnormalities and complex cloacal malformations (Furey, 2016). Peritoneal calcifications related to meconium peritonitis are more readily apparent sonographically, whereas pseudocysts and resultant abnormalities of meconium migration are better delineated with MR imaging.

FIGURE 10-58

A. Sagittal short T1 inversion recovery (STIR) image through a fetus with posterior urethral valve at 23 weeks' gestation. Notice the characteristic dilation of the posterior urethra (*arrowhead*). **B.** At 31 weeks, a coronal image shows progression of severe hydronephrosis, cystic changes in the parenchyma, hydroureter, and anhydramnios. The lungs (*L*) show a decreased signal and are small. **C.** An axial balanced sequence shows a distended bladder (*B*) with thickened wall (*arrows*).

Adjunct to Fetal Therapy

As indications for fetal therapy have grown, MR imaging is used preoperatively to outline abnormalities. At some centers, before laser ablation of placental anastomoses for twin-twin transfusion syndrome, MR imaging is performed to assess the fetal brain for IVH or periventricular leukomalacia (Chap. 45, Twin-Twin Transfusion Syndrome) (Hu, 2006; Kline-Fath, 2007). Because of its precision in visualizing brain and spine findings in cases of myelomeningocele, it is often used preoperatively. For sacrococcygeal teratomas, if fetal surgery is considered, MR imaging may identify tumor extension into the fetal pelvis (Avni, 2002; Neubert, 2004; Perrone, 2017). With a fetal neck mass for which an EXIT is considered, MR imaging may help delineate the lesion extent and its effect on the oral cavity, hypopharynx, and trachea (Hirose, 2003; Lazar, 2012; Ogamo, 2005; Shiraishi, 2000). Finally, MR imaging can also calculate a jaw index when an EXIT procedure may be needed for severe micrognathia (MacArthur, 2012; Morris, 2009). Fetal therapy is discussed in Chapter 16 (Ex-Utero Intrapartum Treatment).

Placenta

The clinical importance of identifying women with placenta accreta is discussed in Chapter 41 (Morbidly Adherent Placenta). Sonography is generally used to identify placental invasion into the myometrium, however, MR evaluation is an adjunct for indeterminate cases. Findings concerning for invasion include dark intraplacental bands on T2-weighted images, focal bulging, and placental heterogeneity (Leyendecker, 2012). When used in a complementary role, MR imaging sensitivity is high for detection of placental invasion, although the depth of invasion is difficult to predict. Clinical risk factors and sonographic findings should be taken into account when interpreting MR placental images.

Emerging Concepts

Of these, MR diffusion tensor imaging and tractography may allow further understanding of neural development and more precise definition of abnormality and pathology (Kasprian, 2008; Mitter, 2015). Automatic and semiautomated extraction of quantitative data from MR imaging volumetric acquisitions of fetal brain and placenta may enable subanalyses of massive datasets not previously possible with laborious manual segmentation (Tourbier, 2017; Wang, 2016). Using multiparametric MR of the placenta in vivo will expand our understanding of function and pathology without risk to mother or fetus. Last, although echocardiography will always be paramount in fetal heart assessment, MR imaging may contribute to volumetric cardiac analysis and will further evaluation of the aorta, which is often difficult to completely examine sonographically (Lloyd, 2017).

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CHAPTER 11: Amnionic Fluid

It is generally agreed that amniotic fluid represents in great part a transudation from the maternal vessels, but many authorities consider that a portion of it is derived from urinary secretion of the foetus.

—J. Whitridge Williams (1903)

INTRODUCTION

At the time Williams wrote this, the fetal kidney was thought by many to be nonfunctional. Since that time, however, much has been learned of this complex multifunctional *liquor amnii*. Amnionic fluid serves several roles during pregnancy. Fetal breathing of amnionic fluid is essential for normal lung growth, and fetal swallowing permits gastrointestinal (GI) tract development. Amnionic fluid also creates a physical space for fetal movement, which is necessary for neuromusculoskeletal maturation. It further guards against umbilical cord compression and protects the fetus from trauma. Amnionic fluid even has bacteriostatic properties. Abnormalities of volume may result from fetal or placental pathology—indicating a problem with fluid production or its circulation. These volume extremes may be associated with increased risks for adverse pregnancy outcome.

NORMAL AMNIONIC FLUID VOLUME

Amnionic fluid volume increases from approximately 30 mL at 10 weeks to 200 mL by 16 weeks and reaches 800 mL by the mid-third trimester (Brace, 1989; Magann, 1997). The fluid is approximately 98-percent water. A full-term fetus contains roughly 2800 mL of water and the placenta another 400 mL, such that the term uterus holds nearly 4 liters of water (Modena, 2004). Abnormally decreased fluid volume is termed *oligohydramnios,* whereas abnormally increased fluid volume is termed *hydramnios* or *polyhydramnios.*

Physiology

Early in pregnancy, the amnionic cavity is filled with fluid that is similar in composition to extracellular fluid. During the first half of pregnancy, transfer of water and other small molecules takes place across the amnion—*transmembranous flow;* across the fetal vessels on placental surface—*intramembranous flow*; and *transcutaneous flow*—across fetal skin. Fetal urine production begins between 8 and 11 weeks' gestation, but it does not become a major component of amnionic fluid until the second trimester, which explains why fetuses with lethal renal abnormalities may not manifest severe oligohydramnios until after 18 weeks. Water transport across the fetal skin continues until keratinization occurs at 22 to 25 weeks. This explains why extremely preterm neonates can experience significant fluid loss across their skin.

With advancing gestation, four pathways play a major role in amnionic fluid volume regulation (Table 11-1). First, fetal urination is the primary source of amnionic fluid in the second half of pregnancy. By term, fetal urine production may exceed 1 liter per day, and the entire amnionic fluid volume is recirculated on a daily basis. Fetal urine osmolality is similar to that of amnionic fluid and significantly hypotonic to that of maternal and fetal plasma. Specifically, the osmolality of maternal and fetal plasma approximates 280 mOsm/mL, whereas that of amnionic fluid is about 260 mOsm/L. The hypotonicity of amnionic fluid accounts for significant *intramembranous* fluid transfer across and into fetal vessels on the placental surface. This transfer reaches 400 mL per day and is a second regulator of fluid volume (Mann, 1996). In the setting of maternal dehydration, the resultant increase in maternal osmolality favors fluid transfer from the fetus to the mother, and then from the amnionic fluid compartment into the fetus (Moore, 2010).

TABLE 11-1

Amnionic Fluid Volume Regulation in Late Pregnancy

Pathway	Effect on Volume	Approximate Daily Volume (mL)
Fetal urination	Production	1000
Fetal swallowing	Resorption	750
Fetal lung fluid secretion	Production	350
Intramembranous flow across fetal vessels on the placental surface	Resorption	400
Transmembranous flow across amnionic membrane	Resorption	Minimal

Data from Magann, 2011; Modena, 2004; Moore, 2010.

An important third source of amnionic fluid regulation is the respiratory tract. Approximately 350 mL of lung fluid is produced daily late in gestation, and half of this is immediately swallowed. Last, fetal swallowing is the primary mechanism for amnionic fluid resorption and averages 500 to 1000 mL per day (Mann, 1996). Impaired swallowing, secondary to either a central nervous system abnormality or GI tract obstruction, can result in an impressive degree of hydramnios. The remaining pathways are transmembranous and transcutaneous flow, which together account for a far smaller proportion of fluid transport in the second half of pregnancy.

Measurement

From a practical standpoint, the actual volume of amnionic fluid is rarely measured outside of the research setting. That said, direct measurement and dye-dilution methods of fluid quantification have contributed to our understanding of normal physiology. These measurements have further been used to validate sonographic fluid assessment techniques. Dye dilution involves injecting a small quantity of a dye such as aminohippurate into the amnionic cavity under sonographic guidance and then sampling the amnionic fluid to determine the dye concentration and hence to calculate the volume.

Brace and Wolf (1989) reviewed 12 studies done through the 1960s in which amnionic fluid volume was assessed using these measurement techniques. Although fluid volume increased across gestation, they found that the mean value did not change significantly between 22 and 39 weeks—it was approximately 750 mL. There was considerable variation at each week of gestation, especially in the mid-third trimester, when the 5th percentile was 300 mL and the 95th percentile nearly 2000 mL. In contrast, Magann and colleagues (1997), using dye-dilution measurements, found that amnionic fluid volume rose with advancing gestation. Specifically, the average fluid volume was approximately 400 mL between 22 and 30 weeks, doubling thereafter to a mean of 800 mL. The volume remained at this level until 40 weeks and then declined by approximately 8 percent per week. The two reports differed in the regression methodology employed, and despite different conclusions, both identified a wide normal range, particularly in the third trimester. This normal variation is similarly observed sonographically.

Sonographic Assessment

Amnionic fluid volume evaluation is a component of every standard sonogram performed in the second or third trimester (Chap. 10, Amnionic Fluid Volume). It may be measured using either of two semi-quantitative techniques, the single deepest pocket of fluid or the amnionic fluid index (AFI), which was described by Phelan and associates (1987). Both measurements are reproducible and, in the setting of a fluid abnormality, can be followed serially over time to assess trends and to aid communication among providers. For these reasons, semiquantitative assessment of amnionic fluid is preferred to qualitative or subjective estimation (American College of Obstetricians and Gynecologists, 2016). Using either technique, a fluid pocket must be at least 1 cm in width to be considered adequate. Fetal parts or loops of umbilical cord may be visible in the pocket, but they are not included in the measurement. Color Doppler is generally used to verify that umbilical cord is not within the measurement.

Single Deepest Pocket

This is also called the largest or *maximal vertical pocket* of amnionic fluid. The ultrasound transducer is held perpendicular to the floor and parallel to the long axis of the woman. Then, while scanning in the sagittal plane, the largest vertical pocket of fluid is identified and measured. *The single deepest pocket measurement is considered normal if above 2 cm and less than 8 cm, with values below and above this range indicating oligohydramnios and hydramnios, respectively.* These thresholds are based on data from Chamberlain and associates (1984) and correspond to the 3rd and 97th percentiles. When evaluating twin pregnancies and other multifetal gestations, a single deepest pocket of amnionic fluid is assessed in each gestational sac, again using a normal range of more than 2 cm to less than 8 cm (Hernandez, 2012; Society for Maternal-Fetal Medicine, 2013). The fetal biophysical profile

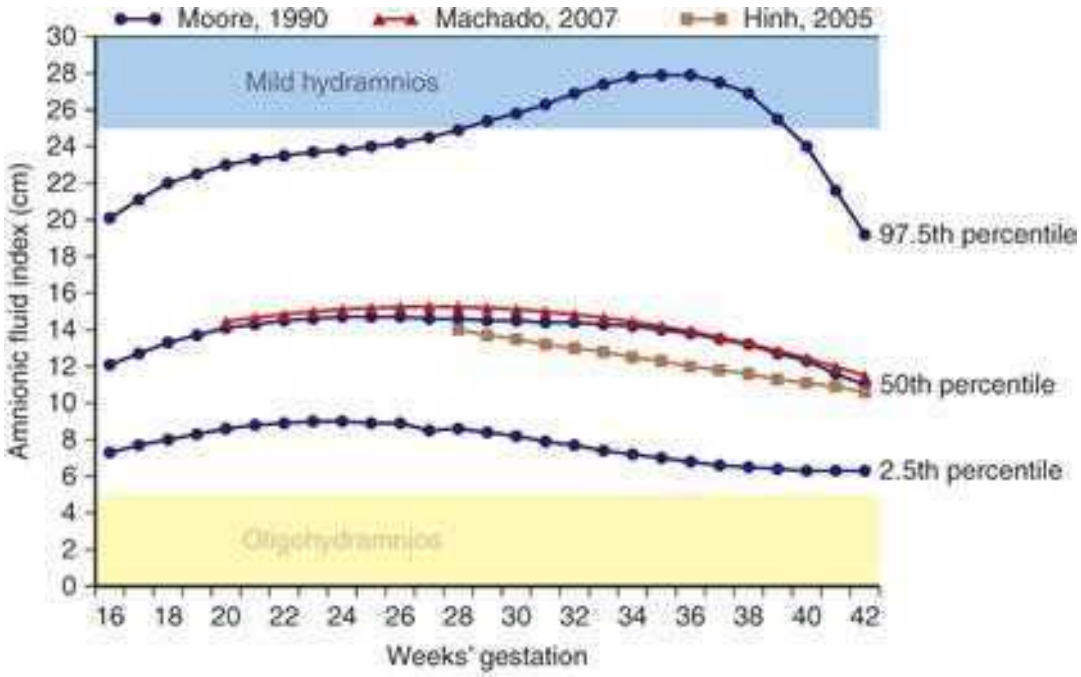
similarly uses a single deepest vertical pocket threshold of more than 2 cm to indicate normal amnionic fluid volume. This is discussed further in Chapter 17 (Acoustic Stimulation Tests).

Amnionic Fluid Index

As with the single deepest fluid pocket measurement, the ultrasound transducer is held perpendicular to the floor and parallel to the long axis of the woman. The uterus is divided into four equal quadrants—the right and left upper and lower quadrants, respectively. The AFI is the sum of the single deepest pocket from each quadrant. The intraobserver variability of the AFI approximates 1 cm, and the interobserver variability is about 2 cm. Variations are larger when fluid volumes are above the normal range (Moore, 1990; Rutherford, 1987). A useful guideline is that the AFI approximates three times the single deepest pocket of fluid (Hill, 2003).

Determination of whether the AFI is normal may be based on either a static numerical threshold or a gestational age-specific percentile reference range. The AFI is generally considered normal if greater than 5 cm and below 24 or 25 cm. Values outside these ranges indicate oligohydramnios and hydramnios, respectively. The upper threshold of 24 cm is used in consensus documents (American College of Obstetricians and Gynecologists, 2016; Reddy, 2014). The 25-cm threshold is often applied in research studies (Khan, 2017; Luo, 2017; Pri-Paz, 2012). Moore and Cayle (1990) have provided normal curves for AFI values based on a cross-sectional evaluation of nearly 800 uncomplicated pregnancies. The mean AFI was found to be between 12 and 15 cm from 16 weeks until 40 weeks' gestation. Other investigators have published nomograms with similar mean values (Hinh, 2005; Machado, 2007). Figure 11-1 depicts these AFI nomogram reference values in relation to commonly used thresholds for hydramnios and oligohydramnios.

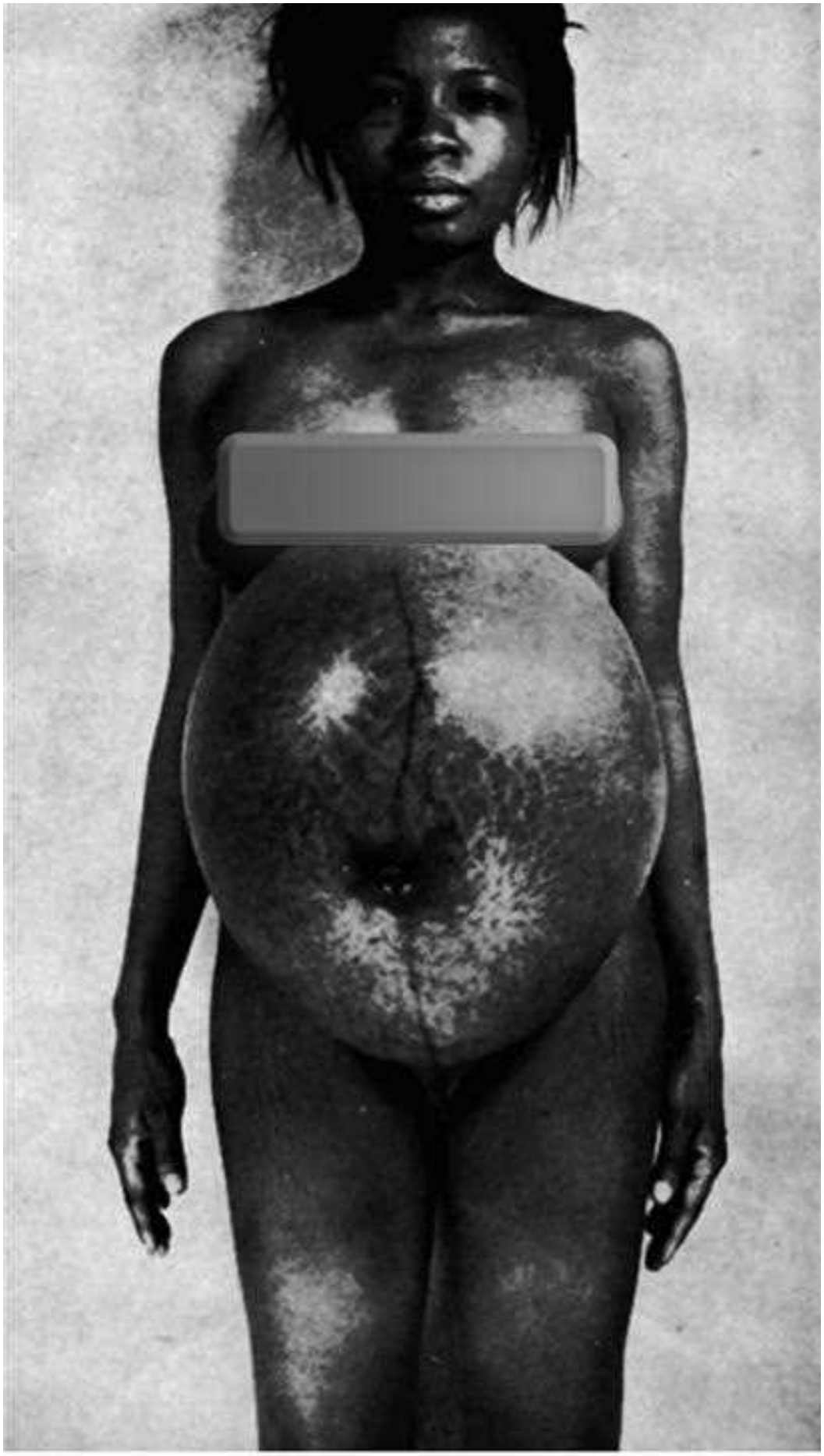
FIGURE 11-1
Amnionic fluid index (AFI) according to gestational-age-specific and threshold values. The blue curves represent the 2.5th, 50th, and 97.5th AFI percentile values, based on the nomogram by Moore (1990). Red and tan curves represent 50th percentile values for AFI from Machado (2007) and from Hinh and Ladinsky (2005), respectively. The light blue and yellow shaded bars indicate threshold values used to define hydramnios and oligohydramnios, respectively.



HYDRAMNIOS

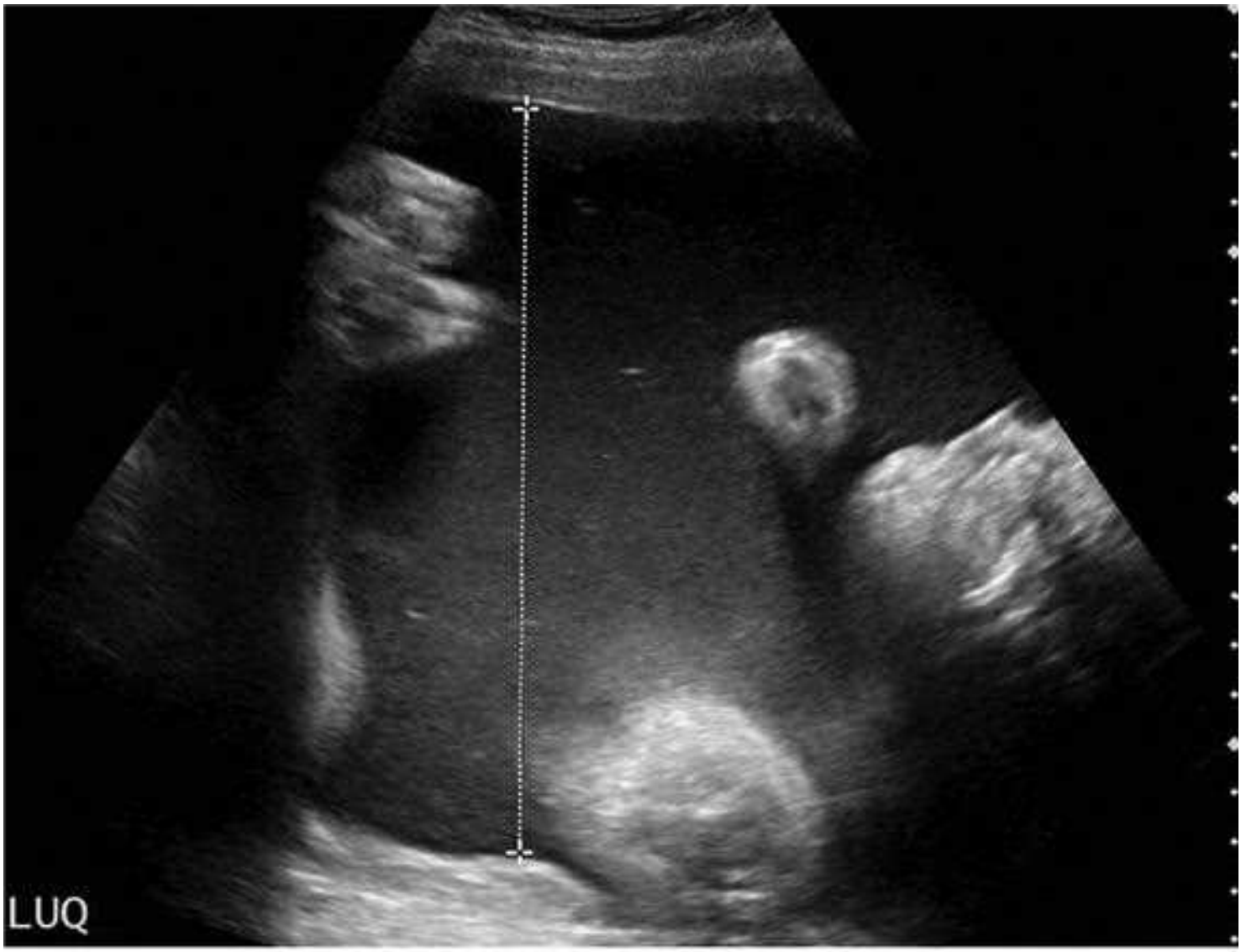
This is an abnormally increased amnionic fluid volume, and it complicates 1 to 2 percent of singleton pregnancies (Dashe, 2002; Khan, 2017; Pri-Paz, 2012). It is more frequently noted in multifetal gestations (Hernandez, 2012). Hydramnios may be suspected if the uterine size exceeds that expected for gestational age. The uterus may feel tense, and palpating fetal small parts or auscultating fetal heart tones may be difficult. An extreme example is shown in Figure 11-2.

FIGURE 11-2
Severe hydramnios—5500 mL of amnionic fluid was measured at delivery.



Hydramnios may be further categorized according to degree. Such categorization is primarily used in research studies to stratify risks. Several groups have termed hydramnios as *mild* if the AFI is 25 to 29.9 cm; *moderate,* if 30 to 34.9 cm; and *severe,* if 35 cm or more (Lazebnik, 1999; Luo, 2016; Odibo, 2016; Pri-Paz, 2012). Mild hydramnios is the most common, comprising approximately two thirds of cases; moderate hydramnios accounts for about 20 percent; and severe hydramnios for approximately 15 percent. Using the single deepest pocket of amnionic fluid, mild hydramnios is defined as 8 to 9.9 cm, moderate as 10 to 11.9 cm, and severe hydramnios as 12 cm or more (Fig. 11-3). In general, severe hydramnios is far more likely to have an underlying etiology and to have consequences for the pregnancy than mild hydramnios, which is frequently idiopathic and benign.

FIGURE 11-3
Sonogram of severe hydramnios at 35 weeks in a pregnancy complicated by fetal aqueductal stenosis. This pocket of amnionic fluid measures >15 cm, and the amnionic fluid index measured nearly 50 cm.



Etiology

Underlying causes of hydramnios include fetal anomalies—either structural abnormalities or genetic syndromes—in approximately 15 percent, and diabetes in 15 to 20 percent (Table 11-2). Congenital infection, red blood cell alloimmunization, and placental chorioangioma are less frequent etiologies. Infections that may present with hydramnios include cytomegalovirus, toxoplasmosis, syphilis, and parvovirus. Hydramnios is often a component of *hydrops fetalis*, and several of the above causes—selected anomalies, infections, and alloimmunization—may result in a hydropic fetus and placenta. The underlying pathophysiology in such cases is complex but is frequently related to a high cardiac-output state. Severe fetal anemia is a classic example. Because the etiologies of hydramnios are so varied, hydramnios treatment also differs and is tailored in most cases to the underlying cause.

TABLE 11-2

Hydramnios: Prevalence and Associated Etiologies—Values in Percent

	Golan (1993) n = 149	Many (1995) n = 275	Biggio (1999) n = 370	Dashe (2002) n = 672	Pri-Paz (2012) n = 655
Prevalence	1	1	1	1	2
Amnionic fluid index					
Mild 25–29.9 cm	—	72	—	66	64
Moderate 30–34.9 cm		20		22	21
Severe >35 cm		8		12	15
Etiology					
Idiopathic	65	69	72	82	52
Fetal anomaly[a]	19	15[a]	8	11[a]	38[a]
Diabetes	15	18	20	7	18

[a]A significant correlation was identified between severity of hydramnios and likelihood of an anomalous infant.

Congenital Anomalies

Selected anomalies and the likely mechanism by which they cause hydramnios are shown in Table 11-3. Many of these abnormalities are depicted and discussed in Chapter 10. Because of this association, targeted sonography is indicated whenever hydramnios is identified. If a fetal abnormality is encountered concurrent with hydramnios, amniocentesis with chromosomal microarray analysis should be offered, because the aneuploidy risk is significantly elevated (Dashe, 2002; Pri-Paz, 2012).

TABLE 11-3

Selected Anomalies and Mechanism for Hydramnios

Mechanism	Anomaly Examples
Impaired swallowing (CNS)	Anencephaly
	Hydranencephaly
	Holoprosencephaly
Impaired swallowing (craniofacial)	Cleft lip/palate
	Micrognathia
Tracheal compression or obstruction	Neck venolymphatic abnormality
	CHAOS[a]
Thoracic etiology (mediastinal shift)	Diaphragmatic hernia[a]
	Cystic adenomatoid malformation[a]
	Pulmonary sequestration[a]
High-output cardiac state	Ebstein anomaly[a]
	Tetralogy of Fallot with absent pulmonary valve[a]
	Thyrotoxicosis[a]
Functional cardiac etiology	Cardiomyopathy, myocarditis[a]
Cardiac arrhythmia	Tachyarrhythmia[a]: atrial flutter, atrial fibrillation, supraventricular tachycardia
	Bradyarrhythmia[a]: heart block
GI obstruction	Esophageal atresia
	Duodenal atresia
Renal-Urinary	Ureteropelvic junction obstruction (“paradoxical hydramnios”)
	Baarter syndrome
Neurological or muscular etiology	Arthrogryposis, akinesia sequence
	Myotonic dystrophy
Neoplastic etiology	Sacrococcygeal teratoma[a]
	Mesoblastic nephroma[a]
	Placental chorioangioma[a]

[a]Poses risk for hydrops.

CHAOS = congenital high-airway obstruction sequence; GI = gastrointestinal.

Importantly, the degree of hydramnios correlates with the likelihood of an anomalous infant (Lazebnik, 1999; Pri-Paz, 2012). At Parkland Hospital, the prevalence of an anomalous neonate was approximately 8 percent with mild hydramnios, 12 percent with moderate hydramnios, and more than 30 percent with severe hydramnios (Dashe, 2002). Even if no abnormality was detected with targeted sonography, the likelihood of a major anomaly identified at birth was 1 to 2 percent if hydramnios was mild or moderate and 10 percent if hydramnios was severe. The overall reported risk that an underlying anomaly will be discovered after delivery has ranged from 9 percent in the neonatal period to 28 percent among infants followed to 1 year of age (Abele, 2012; Dorleijn, 2009). The anomaly risk is particularly high with hydramnios coexistent with fetal-growth restriction (Lazebnik, 1999).

Although amnionic fluid volume abnormalities are associated with fetal malformations, the converse is not usually the case. In the Spanish Collaborative Study of Congenital Malformations that included more than 27,000 anomalous infants, only 4 percent of pregnancies were complicated by hydramnios, and another 3 percent with oligohydramnios (Martinez-Frias, 1999).

Diabetes Mellitus

The amnionic fluid glucose concentration is higher in diabetic women than in those without diabetes, and the AFI may correlate with the amnionic fluid glucose concentration (Dashe, 2000; Spellacy, 1973; Weiss, 1985). Such findings support the hypothesis that maternal hyperglycemia causes fetal hyperglycemia, with resulting fetal osmotic diuresis into the amnionic fluid compartment. That said, rescreening for gestational diabetes in pregnancies with hydramnios does not appear to be beneficial, provided that the second-trimester glucose tolerance test result was normal (Frank Wolf, 2017).

Multifetal Gestation

Hydramnios is generally defined in multifetal gestations as a single deepest amnionic fluid pocket measuring 8 cm or more. It may be further characterized as moderate if the single deepest pocket is at least 10 cm and severe if this pocket is at least 12 cm. In a review of nearly 2000 twin gestations, Hernandez and colleagues (2012) identified hydramnios in 18 percent of both monochorionic and dichorionic pregnancies. As in singletons, severe hydramnios was more strongly associated with fetal abnormalities. In monochorionic gestations, hydramnios of one sac and oligohydramnios of the other are diagnostic criteria for twin-twin transfusion syndrome (TTTS), discussed in Chapter 45 (Twin-Twin Transfusion Syndrome). Isolated hydramnios of one sac also may precede the development of this syndrome (Chon, 2014). In the absence of TTTS, hydramnios does not generally raise pregnancy risks in nonanomalous twins (Hernandez, 2012).

Idiopathic Hydramnios

This accounts for up to 70 percent of cases of hydramnios and is thus identified in as many as 1 percent of pregnancies (Panting-Kemp, 1999; Pri-Paz, 2012; Wiegand, 2016). Idiopathic hydramnios is rarely identified during midtrimester sonography and is often an incidental finding later in gestation. The gestational age at sonographic detection usually lies between 32 and 35 weeks (Abele, 2012; Odibo, 2016; Wiegand, 2016). Although it is a diagnosis of exclusion, an underlying fetal abnormality may subsequently become apparent with advancing gestation, particularly if the degree of hydramnios becomes severe. In the absence of an etiology, idiopathic hydramnios is mild in approximately 80 percent of cases, and resolution is reported in more than a third of affected pregnancies (Odibo, 2016; Wiegand, 2016). Mild, idiopathic hydramnios is most commonly a benign finding, and associated pregnancy outcomes are usually good.

Complications

Unless hydramnios is severe or develops rapidly, maternal symptoms are infrequent. With chronic hydramnios, fluid accumulates gradually, and a woman may tolerate excessive abdominal distention with relatively little discomfort. Acute hydramnios, however, tends to develop earlier in pregnancy. It may result in preterm labor before 28 weeks or in symptoms that become so debilitating as to necessitate intervention.

Symptoms may arise from pressure exerted within the overdistended uterus and upon adjacent organs. When distention is excessive, such as that shown in Figure 11-2, the mother may suffer dyspnea and orthopnea to such a degree that she may be able to breathe comfortably only when upright. Edema may develop as a consequence of major venous system compression by the enlarged uterus, and it tends to be most pronounced in the lower extremities, vulva, and abdominal wall. Rarely, oliguria may result from ureteral obstruction by the enlarged uterus (Chap. 53, Lower Genital Tract Lesions). Maternal complications such as these are typically associated with severe hydramnios from an underlying etiology.

Maternal complications associated with hydramnios include placental abruption, uterine dysfunction during labor, and postpartum hemorrhage. Placental abruption is fortunately infrequent. It may result from the rapid decompression of an overdistended uterus that follows fetal-membrane rupture or therapeutic amnioreduction. With prematurely ruptured membranes, a placental abruption occasionally occurs days or weeks after amniorrhexis. Uterine dysfunction consequent to overdistention may lead to postpartum atony and, in turn, postpartum hemorrhage.

Pregnancy Outcomes

Some outcomes more common with hydramnios include birthweight >4000 g, cesarean delivery, and importantly, perinatal mortality. Pregnancies with idiopathic hydramnios are associated with birthweights exceeding 4000 g in nearly 25 percent of cases, and the likelihood appears to be greater if the hydramnios is moderate or severe (Luo, 2016; Odibo, 2016; Wiegand, 2016). A rationale for this association is that larger fetuses have higher urine output, by virtue of their increased volume of distribution, and fetal urine is the largest contributor to amnionic fluid volume. Cesarean delivery rates are also higher in pregnancies with idiopathic hydramnios, with reported rates of 35 to 55 percent (Dorleijn, 2009; Khan, 2017; Odibo, 2016).

An unresolved question is whether hydramnios alone raises the risk for perinatal mortality. Some studies have found no increase in stillbirth or neonatal death rates with idiopathic hydramnios, whereas others show a greater risk (Khan, 2017; Pilliod, 2015; Wiegand, 2016). Using birth certificate data from the state of California, Pilliod and coworkers (2015) identified hydramnios in 0.4 percent of singleton, nonanomalous pregnancies, and affected pregnancies had significantly greater stillbirth rates. At 37 weeks, the stillbirth risk was sevenfold higher in pregnancies with hydramnios. By 40 weeks, this risk was more than tenfold higher-66 per 10,000 births compared with 6 per 10,000 without hydramnios.

Risks appear to be compounded when a growth-restricted fetus is identified with hydramnios (Erez, 2005). The combination also has a recognized association with trisomy 18. When an underlying cause is identified, degree of hydramnios has been associated with likelihood of preterm delivery, small-for-gestational age newborn, and perinatal mortality (Pri-Paz, 2012). However, *idiopathic* hydramnios is generally not associated with preterm birth (Magann, 2010; Many, 1995; Panting-Kemp, 1999).

Management

As previously noted, treatment is directed to the underlying cause. Occasionally, severe hydramnios may result in early preterm labor or the development of maternal respiratory compromise. In such cases, large-volume amniocentesis—termed *amnioreduction*—may be needed. The technique is similar to that for genetic amniocentesis, described in Chapter 14 (Technique). One difference is that it is generally done with a larger needle, 18- or 20-gauge, and uses either an evacuated container bottle or a larger syringe. Approximately 1000 to 2000 mL of fluid is slowly withdrawn over 20 to 30 minutes, depending on the severity of hydramnios and gestational age. The goal is to restore amnionic fluid volume to the upper normal range. Hydramnios severe enough to necessitate amnioreduction almost invariably has an underlying cause, and subsequent amnioreduction procedures may be required as often as weekly or even semiweekly.

In a review of 138 singleton pregnancies requiring amnioreduction for hydramnios, a fetal GI malformation was identified in 20 percent, a chromosomal abnormality or genetic condition in almost 30 percent, and a neurological abnormality in 8 percent (Dickinson, 2014). In only 20 percent of cases was the hydramnios idiopathic. The initial amnioreduction procedure in this series was performed at 31 weeks' gestation, and the median gestational age at delivery was 36 weeks. Complications within 48 hours of amnioreduction included delivery in 4 percent and ruptured membranes in 1 percent. There was no instance of chorioamnionitis, placental abruption, or bradycardia requiring delivery (Dickinson, 2014).

OLIGOHYDRAMNIOS

This is an abnormally decreased amount of amnionic fluid. Oligohydramnios complicates approximately 1 to 2 percent of pregnancies (Casey, 2000; Petrozella, 2011). When no measurable pocket of amnionic fluid is identified, the term *anhydramnios* may be used. Unlike hydramnios, which is often mild and often confers a benign prognosis in the absence of an underlying etiology, oligohydramnios is always a cause for concern, as discussed in Pregnancy Outcomes.

The sonographic diagnosis of oligohydramnios is usually based on an AFI less than 5 cm or a single deepest pocket of amnionic fluid below 2 cm (American College of Obstetricians and Gynecologists, 2016). Using the Moore nomogram, an AFI threshold of 5 cm is below the 2.5th percentile throughout the second and third trimesters (see Fig. 11-1). Either criterion is considered acceptable. However, use of AFI rather than single deepest pocket will identify more pregnancies as having oligohydramnios, without evidence of improvement in pregnancy outcomes (Kehl, 2016; Nabhan, 2010). When evaluating multifetal pregnancies for TTTS, a single deepest pocket below 2 cm is used to define oligohydramnios (Society for Maternal-Fetal Medicine, 2013).

Etiology

Pregnancies complicated by oligohydramnios include those in which the amnionic fluid volume has been severely diminished since the early second trimester and those in which the fluid volume was normal until near-term or even full-term. The prognosis depends heavily on the underlying cause and thus varies. Whenever oligohydramnios is diagnosed, it becomes an important consideration in clinical management.

Early-Onset Oligohydramnios

When amnionic fluid volume is abnormally decreased from the early second trimester, it may reflect a fetal abnormality that precludes normal urination, or it may represent a placental abnormality sufficiently severe to impair perfusion. In either circumstance, the prognosis is poor. Ruptured membranes should be excluded, and targeted sonography is performed to assess for fetal and placental abnormalities.

Oligohydramnios after Midpregnancy

When amnionic fluid volume becomes abnormally decreased in the late second or in the third trimester, it is very often associated with fetal-growth restriction, with a placental abnormality, or with a maternal complication such as preeclampsia or vascular disease (Table 11-4). The underlying cause in such cases is frequently uteroplacental insufficiency, which can impair fetal growth and reduce fetal urine output. Exposure to selected medications has also been linked with oligohydramnios as discussed subsequently. Investigation of third-trimester oligohydramnios generally includes evaluation for ruptured membranes and sonography to assess fetal growth. Umbilical artery Doppler studies are recommended if growth restriction is identified (Chap. 10, Doppler). Oligohydramnios is commonly encountered in late-term and *postterm pregnancies* (Chap. 43, Placental Dysfunction). Magann and coworkers (1997) found that amnionic fluid volume decreased by approximately 8 percent per week beyond 40 weeks.

TABLE 11-4

Pregnancy Outcomes in Women Diagnosed with Oligohydramnios between 24 and 34 Weeks' Gestation

Factor	AFI ≤5 cm (n = 166)	AFI 8 to 24 cm (n = 28,185)	*p* Value
Major malformation	42 (25)	634 (2)	<.001
Stillbirth	8 (5)	133 (<1)	<.001
Gestational age at delivery[a]	35.1 ± 3.3	39.2 ± 2.0	<.001
Preterm birth, spontaneous[a]	49 (42)	1698 (6)	<.001
Preterm birth, indicated[a]	23 (20)	405 (2)	<.001
Cesarean delivery for nonreassuring fetal status[a]	10 (9)	1083 (4)	<.001
Birthweight <10th percentile[a]	61 (53)	3388 (12)	<.001
<3rd percentile[a]	43 (37)	1130 (4)	<.001
Neonatal death[a]	1 (1)	24 (<1)	<.001[b]

Data expressed as No. (%) and mean ± standard deviation.

[a]Anomalous infants excluded.

[b]This difference was no longer significant after adjustment for gestational age at delivery.

Data from Petrozella, 2011.

Congenital Anomalies

By approximately 18 weeks, the fetal kidneys are the main contributor to amnionic fluid volume. Selected renal abnormalities that lead to absent fetal urine production include bilateral *renal agenesis*, bilateral *multicystic dysplastic kidney*, unilateral renal agenesis with contralateral multicystic dysplastic kidney, and the infantile form of *autosomal recessive polycystic kidney disease*. Urinary abnormalities may also result in oligohydramnios because of fetal *bladder outlet obstruction*. Examples of this are *posterior urethral valves*, *urethral atresia* or *stenosis*, or the *megacystis microcolon intestinal hypoperistalsis syndrome*. Complex fetal genitourinary abnormalities such as *persistent cloaca* and *sirenomelia* similarly may result in a lack of amnionic fluid. Many of these renal and urinary abnormalities are discussed and depicted in Chapter 10 (Renal Pelvis Dilatation). If no amnionic fluid is visible beyond the mid-second trimester due to a genitourinary etiology, the prognosis is extremely poor unless fetal therapy is an option. Fetuses with bladder-outlet obstruction may be candidates for vesicoamnionic shunt placement (Chap. 16, Urinary Shunts).

Medication

Oligohydramnios has been associated with exposure to drugs that block the renin-angiotensin system. These include angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, and nonsteroidal antiinflammatory drugs (NSAIDs). When taken in the second or third trimester, ACE inhibitors and angiotensin-receptor blockers may create fetal hypotension, renal hypoperfusion, and renal ischemia, with subsequent anuric renal failure (Bullo, 2012; Guron, 2000). Fetal skull bone hypoplasia and limb contractures have also been described (Schaefer, 2003). NSAIDs can be associated with

fetal ductus arteriosus constriction and with lower fetal urine production. In neonates, their use may result in acute and chronic renal insufficiency (Fanos, 2011). These agents are discussed in Chapter 12 (Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs).

Pregnancy Outcomes

Oligohydramnios is associated with adverse pregnancy outcomes. Casey and colleagues (2000) found that an AFI ≤5 cm complicated 2 percent of pregnancies undergoing sonography at Parkland Hospital after 34 weeks' gestation. Fetal malformation rates were elevated in those with oligohydramnios. Even in their absence, rates of stillbirth, growth restriction, nonreassuring heart rate pattern, and meconium aspiration syndrome were higher than in nonaffected pregnancies. Petrozella and associates (2011) similarly reported that an AFI ≤5 cm identified between 24 and 34 weeks was associated with increased risks for stillbirth, spontaneous or medically indicated preterm birth, heart rate pattern abnormalities, and growth restriction (see Table 11-4). In one metaanalysis comprising more than 10,000 pregnancies, women with oligohydramnios had a twofold greater risk for cesarean delivery for fetal distress and a fivefold higher risk for an Apgar score <7 at 5 minutes compared with pregnancies with a normal AFI (Chauhan, 1999).

As discussed, evidence suggests that if oligohydramnios is defined as an AFI ≤5 cm rather than a single deepest pocket ≤2 cm, more pregnancies will be classified as such. One review of trials encompassing more than 3200 high-risk and low-risk pregnancies compared outcomes according to which definition was used (Nabhan, 2008). Rates of cesarean delivery, neonatal intensive care unit admission, umbilical artery pH <7.1, or Apgar score <7 at 5 minutes did not differ between groups. Using AFI criteria, however, twice as many pregnancies were diagnosed with oligohydramnios. In this group, there was a doubling of the labor induction rate and a 50-percent increase in the cesarean delivery rate for fetal distress. Kehl and colleagues (2016) performed a prospective trial with more than 1000 term pregnancies in which women with oligohydramnios, defined either by an AFI <5 cm or a single deepest pocket <2 cm, were randomized to labor induction or expectant care. Significantly more pregnancies were diagnosed with oligohydramnios using the AFI criterion—10 percent compared with just 2 percent—when single deepest pocket was used. This led to a higher rate of labor induction in the AFI group, but no difference in neonatal outcomes.

Pulmonary Hypoplasia

When diminished amnionic fluid is first identified before the mid-second trimester, particularly before 20 to 22 weeks, pulmonary hypoplasia is a significant concern. The underlying etiology is a major factor in the prognosis for such pregnancies. Severe oligohydramnios secondary to a renal abnormality generally has a lethal prognosis. If a placental hematoma or chronic abruption is severe enough to result in oligohydramnios—the *chronic abruption-oligohydramnios sequence (CAOS)*—it commonly also causes growth restriction (Chap. 41, Frequency). The prognosis for this constellation is similarly poor. Oligohydramnios that results from membrane rupture in the second trimester is reviewed in Chapter 42 (Considerations with Expectant Management).

Management

Initially, an evaluation for fetal anomalies and growth is essential. In a pregnancy complicated by oligohydramnios and fetal-growth restriction, close fetal surveillance is important because of associated morbidity and mortality (Chap. 44, Management). Oligohydramnios detected before 36 weeks' gestation in the presence of normal fetal anatomy and growth is generally managed expectantly in conjunction with enhanced fetal surveillance. However, evidence of fetal or maternal compromise will override potential complications from preterm delivery. Antepartum management of oligohydramnios may include maternal hydration. In a recent review of 16 trials of pregnancies with apparent isolated oligohydramnios, oral or intravenous hydration was associated with significant improvement in the AFI. However, it was not clear whether this translated into better pregnancy outcomes (Gizzo, 2015).

Amnioinfusion, discussed in Chapter 24 (Management Options), may be used intrapartum to help resolve variable fetal heart rate decelerations. It is not considered treatment for oligohydramnios per se, although the decelerations are presumed secondary to umbilical cord compression resulting from lack of amnionic fluid. Amnioinfusion is not the standard of care for other etiologies of oligohydramnios and is not generally recommended.

"Borderline" Oligohydramnios

The term *borderline AFI* or *borderline oligohydramnios* is somewhat controversial. It usually refers to an AFI between 5 and 8 cm (Magann, 2011; Petrozella, 2011). Through the mid-third trimester, an AFI value of 8 cm is below the 5th percentile on the Moore nomogram (see Fig. 11-1). Petrozella and colleagues (2011) found that pregnancies between 24 and 34 weeks with an AFI between 5 and 8 cm were not more likely than those with an AFI above 8 cm to be complicated by maternal hypertension, stillbirth, or neonatal death. That said, higher rates of preterm delivery, cesarean delivery for a nonreassuring fetal heart rate pattern, and fetal-growth restriction were found. Wood and colleagues (2014) similarly reported a higher rate of fetal-growth restriction in pregnancies with borderline AFI. Thus, results evaluating pregnancy outcomes with borderline AFI have been mixed. Magann and associates (2011) concluded that evidence is insufficient to support fetal testing or delivery in this setting.

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CHAPTER 12: Teratology, Teratogens, and Fetotoxic Agents

All infectious diseases have a tendency to bring about death of the child and its subsequent expulsion from the uterus. The fatal result is usually due to the transmission of toxins, and occasionally the specific micro-organisms from the mother to the child. Poisoning with phosphorus, lead, illuminating gas, and other substances may lead to similar results.

—J. Whitridge Williams (1903)

INTRODUCTION

Other than referring to fetal deformities that might impede vaginal delivery, little is written in the first edition of this book regarding teratogens and fetal malformations. This is despite the fact that birth defects are common, and 2 to 3 percent of all newborns have a major congenital abnormality detectable at birth (Cragan, 2009; Dolk, 2010). There are undoubtedly medications that pose significant risk to the developing embryo or fetus (Table 12-1). However, 80 percent of birth defects do not have an obvious etiology, and of those with an identified cause, nearly 95 percent of cases have chromosomal or genetic origins (Feldkamp, 2017). The Food and Drug Administration (FDA) (2005) estimates that less than 1 percent of all birth defects are caused by medications. Their remarkably small contribution to congenital abnormalities is shown in Figure 12-1.

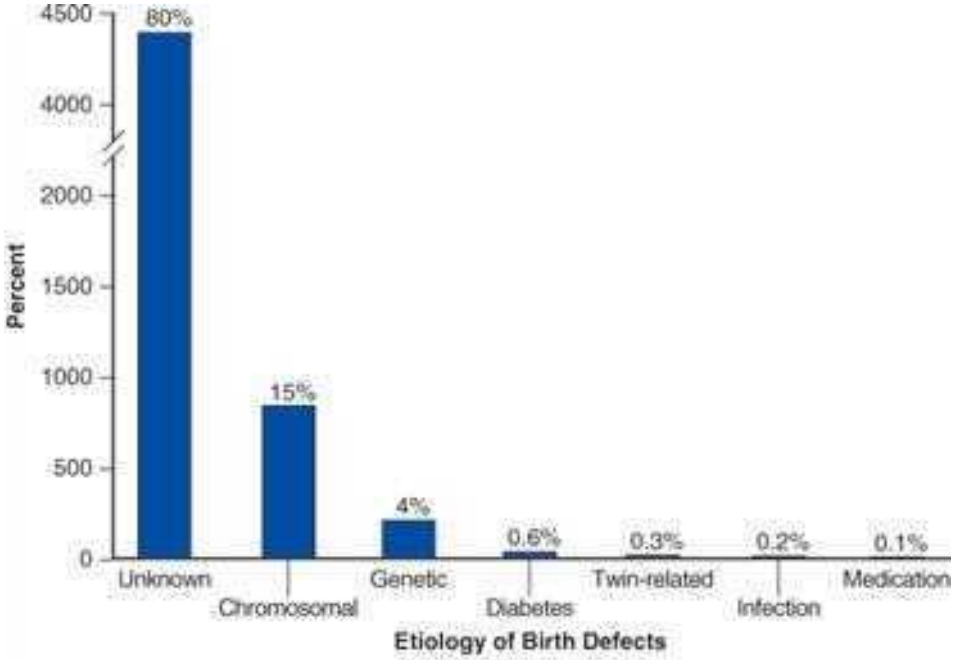
TABLE 12-1

Selected Teratogens and Fetotoxic Agents

Acitretin	
Alcohol	Lithium
Ambrisentan	Macitentan
Angiotensin-converting enzyme inhibitors	Methimazole
Angiotensin-receptor blockers	Mercury
Androgens	Methotrexate
Bexarotene	Misoprostol
Bosentan	Mycophenolate
Carbamazepine	Paroxetine
Chloramphenicol	Phenobarbital
Cocaine	Phenytoin
Corticosteroids	Radioactive iodine
Cyclophosphamide	Ribavirin
Danazol	Tamoxifen
Diethylstilbestrol (DES)	Tetracycline
Efavirenz	Thalidomide
Fluconazole	Tobacco
Isotretinoin	Toluene
Lamotrigine	Topiramate
Lead	Trastuzumab
Leflunomide	Tretinoin
Lenalidomide	Valproic acid
	Warfarin

FIGURE 12-1

Etiology of birth defects. Known and unknown causes of 5504 birth defects from a population-based review of 270,878 births.



That said, significant concern surrounds medication use in pregnancy. This is because so many pregnant women are prescribed medications and because safety data are often lacking. Investigators from the National Birth Defects Prevention Study found that women take an average of two to three medications per pregnancy and that 70 percent use medication in the first trimester (Mitchell, 2011). And, in one review of medications approved by the FDA between 2000 and 2010, the Teratogen Information System (TERIS) advisory board deemed the pregnancy risk "undetermined" for more than 95 percent of these agents (Adam, 2011).

TERATOLOGY

The study of birth defects and their etiology is termed teratology, derived from the Greek *teratos,* meaning monster. A *teratogen* may be defined as any agent that acts during embryonic or fetal development to produce a permanent alteration of form or function. Thus, a teratogen may be a medication or other chemical substance, a physical or environmental factor such as heat or radiation, a maternal metabolite as in diabetes or phenylketonuria, or an infection such as cytomegalovirus. Even obesity is considered a teratogen (Stothard, 2009; Waller, 2007).

Strictly defined, a teratogen causes only structural abnormalities. A *hadegen*—after the god Hades—is an agent that interferes with organ maturation and function, and a *trophogen* alters growth. Substances in the latter two groups typically affect development in the fetal period or after birth, when exposures are often more difficult to document. In most circumstances, the term teratogen is used to refer to all three types of agents.

Criteria for Determining Teratogenicity

The guidelines shown in Table 12-2 were proposed by Shepard (1994) as a framework for discussion and have proven useful for more than 25 years. Although each individual criterion is not required to establish teratogenicity, the following tenets must be considered (Shepard, 2002a):

TABLE 12-2

Criteria for Determining Teratogenicity

Essential Criteria: 1. Careful delineation of clinical cases, particularly if there is a specific defect or syndrome 2. Proof that exposure occurred at critical time during development (see Fig. 12-2) 3. Consistent findings by at least two epidemiological studies with: a. exclusion of bias, b. adjustment for confounding variables, c. adequate sample size (power), d. prospective ascertainment if possible, and e. relative risk (RR) of 3.0 or greater, some recommend RR of 6.0 or greater ***or*** For a rare environmental exposure associated with a rare defect, at least three reported cases. This is easiest if defect is severe
Ancillary Criteria: 4. The association is biologically plausible 5. Teratogenicity in experimental animals is important but not essential 6. The agent acts in an unaltered form in an experimental model

Data from from Shepard 1994, 2002a.

The defect has been completely characterized. This is preferably done by a geneticist or dysmorphologist because various genetic and environmental factors may produce similar anomalies. It is easiest to prove causation when a rare exposure produces a rare defect, when at least three cases with the same exposure have been identified, and when the defect is severe.

The agent must cross the placenta. Although almost all drugs cross the placenta, transport must be of sufficient quantity to directly influence embryonic or fetal development or to alter maternal or placental metabolism to exert an indirect effect. Placental transfer depends on maternal metabolism; on specific characteristics of the drug, such as protein binding and storage, molecular size, electrical charge, and lipid solubility; and on placental metabolism, such as by the cytochrome P_{450} enzyme system. In early pregnancy, the placenta also has a relatively thick membrane that slows diffusion.

Exposure must occur during a critical developmental period.

The *preimplantation period* is the 2 weeks between fertilization and implantation and is known as the “all or none” period. As the zygote undergoes cleavage, an insult damaging a large number of cells typically causes embryonic death. However, if only a few cells are injured, compensation may be possible and allow normal development (Clayton-Smith, 1996). From animal data, insults that appreciably diminish the cell number in the inner cell mass may produce a dose-dependent diminution in body length or size (Iahnaccone, 1987).

The *embryonic period* extends from the second through the eighth week postconception. It encompasses organogenesis and is thus the most crucial period with regard to structural malformations. Critical developmental periods for each organ system are illustrated in Figure 12-2.

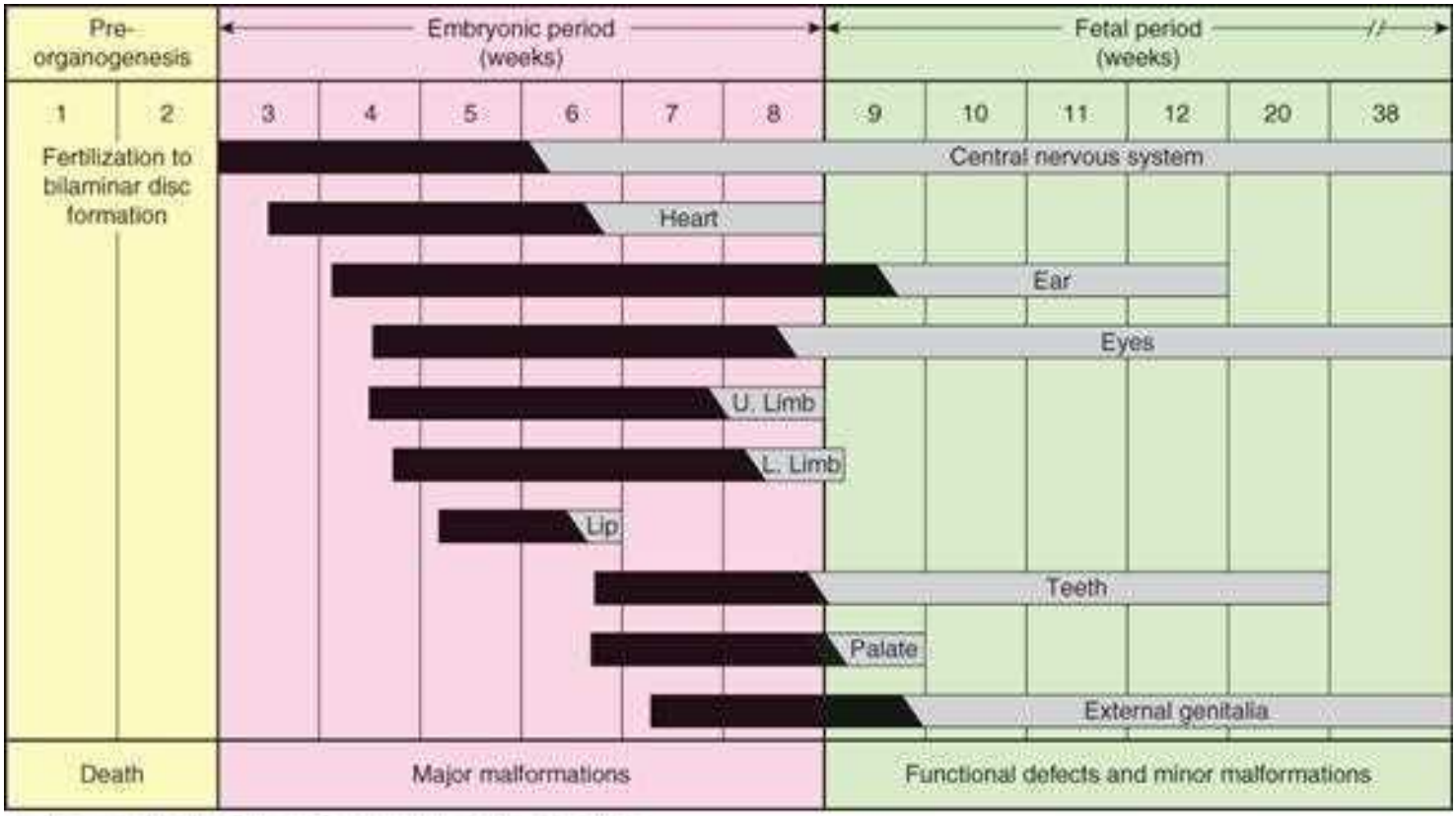
The *fetal period*, which is beyond 8 weeks postconception, is characterized by continued maturation and functional development. During this time, certain organs remain vulnerable.

A biologically plausible association is supportive. Because birth defects and medication exposures are both common, they may be temporally but not causally related.

Epidemiological findings must be consistent. Because initial evaluation of teratogen exposure is often retrospective, it may be hampered by recall bias, inadequate reporting, and incomplete assessment of the exposed population. Potential confounding factors include varying dosages, concomitant drug therapy, and comorbid maternal disease(s). Familial and environmental variables can also influence development of birth defects. Thus, an important criterion for teratogenicity is that two or more high-quality epidemiological studies report similar findings. Finally, a relative risk of *3.0 or greater* is generally considered necessary to support the hypothesis, whereas a lesser risk is interpreted with caution (Khoury, 1992).

The suspected teratogen causes a defect in animal studies. This criterion is not obligatory. In fact, the Teratology Society (2005) states that establishment of causation in teratology-related litigation requires human data.

FIGURE 12-2
Timing of organogenesis during the embryonic period. (Reproduced with permission from Salder TW: Langman’s Medical Embryology, 6th ed. Baltimore, Williams & Wilkins; 1990.)



Failure to employ these tenets and criteria has contributed to erroneous conclusions regarding the safety of some widely used drugs. The poster child for this is the medicolegal fiasco surrounding Bendectin. This antiemetic was a combination of doxylamine and pyridoxine, with or without dicyclomine, and was safe and effective for nausea and vomiting in early pregnancy. More than 30 million women used this drug worldwide, and the 3-percent congenital anomaly rate among exposed fetuses was not different from the background rate (McKeigue, 1994). Despite considerable evidence that this combination of an antihistamine and a B-vitamin is not teratogenic, Bendectin was the target of numerous lawsuits, and the financial burden of defending these forced its withdrawal from the marketplace. As a consequence, hospitalizations for hyperemesis doubled (Koren, 1998). Ironically, the combination of doxylamine and pyridoxine was subsequently remarketed under the brand name Diclegis and was approved by the FDA in 2013.

Studies in Pregnant Women

The study of medication safety—or teratogenicity—in pregnant women is fraught with complications. First, animal studies are considered necessary but insufficient. For example, thalidomide is harmless in several animal species but resulted in phocomelia in thousands of children born across Europe in the late 1950s and early 1960s. Second, medications are rarely approved by the FDA for a pregnancy-related indication. Instead, pregnant women are considered a special population and summarily excluded from medication trials. Last, drug concentration and thus embryo-fetal exposure are affected by pregnancy physiology. These include changes in volume of distribution, cardiac output, gastrointestinal absorption, hepatic metabolism, and renal clearance. In the absence of research trials, counseling is based on case reports or series, case-control studies, cohort studies, and pregnancy registry data.

Case Reports and Series

Many, if not most, major teratogens were first described by clinicians who observed a rare defect occurring after a rare exposure. This has been termed the “astute clinician model” (Carey, 2009). Congenital rubella syndrome was identified in this way by Gregg (1941), an Australian ophthalmologist whose observations challenged the view that the uterine environment was impervious to noxious agents. Other teratogens identified through case series include thalidomide and alcohol (Jones, 1973; Lenz, 1962). Shepard (2002a) recommended that establishment of teratogenicity in this way requires proven exposure at a critical time in development and probably at least three such cases, each carefully delineated. Unfortunately, teratogens are less likely to be identified if the exposure is uncommon, if the defects are relatively nonspecific, or if abnormalities develop in only a small proportion of exposed fetuses. A major limitation of case series is their lack of a control group.

Case-Control Studies

These studies begin with groups of affected infants (cases) and unaffected controls and are structured to allow retrospective assessment of prenatal exposure to particular substances. Case-control studies are an efficient way to study rare outcomes (Alwan, 2015). These permit investigators to evaluate associations and generate useful hypotheses. However, case-control studies have inherent potential for *recall bias.* Namely, parents of an affected infant are often more likely to recall exposure than those whose child is not ill. Confounding by indication is another concern, that is, the indication for the medication

may be the cause of the birth defect. And importantly, birth defect registries have statistical power to detect small differences that may not be clinically meaningful. Grimes and Schulz (2012) have cautioned that unless odds ratios in case-control studies are above three- to fourfold, the observed associations may not be correct.

The National Birth Defects Prevention Study

An excellent example of a population-based case-control study is the National Birth Defects Prevention Study (NBDPS). Funded by Congress and coordinated by the National Center on Birth Defects and Developmental Disabilities, the NBDPS took place between 1997 and 2013 across ten states with active birth defects surveillance programs. Clinical geneticists reviewed each potential case, and standardized telephone interviews were conducted with mothers whose pregnancies were affected or unaffected to obtain information regarding medication exposure and risk factors (Mitchell, 2011; Reefhuis, 2015). Live births, stillbirths, and terminated pregnancies were included and totaled approximately 32,000 cases and nearly 12,000 controls.

The NBDPS has yielded more than 200 scientific manuscripts. It identified novel—although often small—associations between individual birth defects and the following classes of medications: antibiotics, antidepressants, antiemetics, antihypertensives, asthma medications, nonsteroidal antiinflammatory drugs (NSAIDs), and opioids (Ailes, 2016; Broussard, 2011; Fisher, 2017; Hernandez, 2012; Lin, 2012; Munsie, 2011). The NBDPS also found associations between birth defects and exposures such as secondhand smoke, pesticides, and nitrogen oxide, which is a marker of traffic-related air pollution (Hoyt, 2016; Rocheleau, 2015; Stingone, 2017).

The NBDPS did have limitations related to study design. First, interviews were conducted 6 weeks to 2 years following delivery, which raised the likelihood of recall bias. For example, 25 percent of women could not remember which antibiotic they had taken (Ailes, 2016). Another weakness was that only two thirds of women agreed to participate, and there were differences in ethnicity and socioeconomic status between cases and controls. These factors potentially led to selection bias (Reefhuis, 2015). In addition, medical records were not reviewed to verify dosage, and this precluded assessment of dose-response relationships. And a major limitation was that because the NBDPS included only a small number of cases of each birth defect and analyzed them for multiple maternal exposures, it was not possible to adjust for multiple comparisons. As a result, some of the associations observed were likely due to chance (Alwan, 2015). For example, the study of antibiotics and birth defects included 43 comparisons and identified four significant associations, but chance alone predicted that two associations would be identified (Ailes, 2016). Last, the low absolute risk of an abnormality complicates counseling and prenatal management. In many instances, the risk identified by the NBDPS was as low as 1 case per 1000 exposed pregnancies.

Cohort Studies

These studies begin with cohorts of pregnant women who are exposed or unexposed to a particular medication. The percentage of infants or children affected with birth defects is examined in each cohort. Because individual birth defects are rare, cohort studies require a *very* large sample size. Medicaid datasets and private insurance claims databases are commonly used for cohort studies of teratogenicity in the United States (Ehrenstein, 2010). Inability to adjust for confounding variables—such as the indication for which the medication was needed—may be an important limitation of this study design.

Pregnancy Registries

Potentially harmful agents may be monitored by clinicians who prospectively enroll exposed pregnancies in a registry. The FDA (2017b) maintains an active list on their webpage titled Pregnancy Registries. As of 2017, this included registries for 100 individual medications and for medication groups used to treat asthma, autoimmune disease, cancer, epilepsy, human immunodeficiency virus (HIV) infection, and transplant rejection. Similar to case series, exposure registries are hampered by lack of a control group. The prevalence of an abnormality identified through a registry requires knowledge of the baseline prevalence of that anomaly in the population. Investigators typically use a birth defect registry to assess population prevalence. One example is the Metropolitan Atlanta Congenital Defects Program, which is an active surveillance program established in 1967 for fetuses and infants with birth defects.

COUNSELING FOR MEDICATION EXPOSURE

Questions regarding medication and illicit drug use should be part of routine preconceptional and prenatal care. Misinformation is common. Individuals tend to underestimate the background risk for birth defects in the general population and exaggerate potential risks associated with medication exposure. In a recent population-based study of more than 270,000 births from Utah that included 5500 fetuses and infants with major birth defects, only 4 cases were attributed to medication exposure (see Fig. 12-1) (Feldkamp, 2017). And yet, Koren and colleagues (1989) reported that a fourth of women exposed to nonteratogenic drugs thought they had a 25-percent risk for fetal anomalies. Misinformation may be amplified by inaccurate reports in the lay press. Knowledgeable counseling may allay anxiety considerably and may even avert pregnancy termination.

Several sources are available to assist providers with accurate and updated risk information. PubMed is a free tool from the National Center for Biomedical Information that aids rapid search of published research. Online databases, such as Reprotox, TERIS, and Shepard's Online Catalog of Teratogenic Agents, offer reviews of medication risks. They summarize human and animal studies of teratogenicity and fetotoxicity, address the quality of the available evidence, and provide magnitude of risk. Lactmed, a database from the National Library of Medicine, specifically deals with medication use by breastfeeding women. Its entries on specific medications describe levels in breast milk and potential effects on the infant. Finally, with recent changes to the FDA labeling requirements, discussed next, the manufacturer's prescribing information has become increasingly helpful.

The Food and Drug Administration: Letters and Labels

In 1979, the FDA developed a letter classification system in an effort to provide therapeutic guidance for prescribing medications in pregnancy. Five categories—A, B, C, D, and X—were intended to summarize available evidence from human or animal studies of embryonic–fetal risk. These letters also conveyed benefits of the given medication balanced against its potential risks. The system, shown in Table 12-3, was intended to simplify risk–benefit data.

TABLE 12-3

Food and Drug Administration Letter Categories for Drugs and Medications (1979–2015)[a]

Category A:	Studies in pregnant women have not shown an increased risk for fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy, and the possibility of fetal harm appears remote.
Category B:	Animal reproduction studies have been performed and have revealed no evidence of impaired fertility or harm to the fetus.
	or
	Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy, and there is no evidence of a risk in later trimesters.
Category C:	Animal reproduction studies have shown that this medication is teratogenic (or embryocidal or has other adverse effect), and there are no adequate and well-controlled studies in pregnant women.
	or
	There are no animal reproduction studies and no adequate and well-controlled studies in humans.
Category D:	This medication can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if a woman becomes pregnant while taking this medication, she should be apprised of the potential hazard to the fetus.
Category X:	This medication is contraindicated in women who are or may become pregnant. It may cause fetal harm.

[a]Medications approved after June 2015 are not assigned a letter category, whereas older medications will have letter categories phased out after this date.

Unfortunately, information regarding medication risk was very often incomplete and led to an overreliance on the definition of the letter category alone. However, a higher letter grade did not necessarily mean greater risk, and drugs in the same category often had very different risks. Very few medications—fewer than 1 percent—had demonstrated safety in human pregnancy (category A), and most had no safety data in human or animal studies (category C). Another difficulty was that the classification system did not address inadvertent exposure, a common reason for counseling. Ultimately, it is the responsibility of the clinician to interpret letter category information in the context of medication dosage and route, timing of exposure during pregnancy, other medications used, and underlying medical condition(s).

To address these deficiencies, new labeling requirements were created and went into effect in 2015. Updates to older medications will be phased in over time (Food and Drug Administration, 2014). With the new requirements, the FDA letter categories have been (or will be) removed from all prescription drug and biological product labeling. The format for providing information includes a summary of risks, clinical considerations, and available data. The pregnancy subsection has registry information, if available, as well as labor and delivery information. For each medication, a lactation subsection—formerly called "nursing mothers"—is included. There is also a section to address potential risks in females and males with reproductive potential.

Presenting Risk Information

In addition to potential embryonic and fetal risks from drug exposure, counseling should discuss the risks and/or genetic implications of the underlying condition for which the drug is given. Risks associated with not treating the condition are also described. Even the manner in which information is presented affects perception. For example, women given negative information—such as a 2-percent chance of a malformed newborn—are more likely to perceive an exaggerated risk than women given positive information—such as a 98-percent chance of an unaffected infant (Jasper, 2001). Instead of citing a higher odds ratio, it may be helpful to provide the *absolute risk* for a particular defect or the *attributable risk*, which is the difference between prevalence in exposed and unexposed individuals (Conover, 2011). The association between oral corticosteroid medications and cleft lip sounds far more concerning when presented as a tripling or 200-percent increase in risk than when described as an increase from 1 per 1000 to 3 per 1000 or as a 99.7-percent likelihood of no cleft development following exposure.

With a few notable exceptions, most commonly prescribed drugs and medications can be used with relative safety during pregnancy. Many drugs discussed in this chapter are *low-risk teratogens*, which are medications that produce defects in fewer than 10 per 1000 maternal exposures (Shepard, 2002a). Because risks conferred by low-risk teratogens are so close to the population background rate of fetal anomalies, they may not be a major factor in deciding whether to discontinue treatment for an important condition (Shepard, 2002b). *Remember that all women have an approximate 3-percent chance of having a newborn with a birth defect.* Although exposure to a confirmed teratogen may elevate this risk, the magnitude of the increase is usually only 1 or 2 percent or at most, doubled or tripled. The concept of risk versus benefit is often central to counseling. Some untreated diseases pose a more serious threat to both mother and fetus than medication exposure risks.

KNOWN AND SUSPECTED TERATOGENS

Considering the thousands of compounds available, relatively few medications and other substances are considered to be major human teratogens. The most common examples are listed in Table 12-1. With few exceptions, in every clinical situation potentially requiring therapy with a known teratogen, alternative drugs can be given with relative safety. Realizing limitations in available evidence, pregnant women should be advised to take any medication only when it is clearly needed. In general, targeted sonography is indicated if there has been exposure to any major teratogen during the embryonic period.

Alcohol

Ethanol is a potent and prevalent teratogen. It is considered the leading cause of preventable developmental disabilities worldwide (Hoyme, 2016). In the United States, 8 percent of pregnant women report drinking alcohol and between 1 and 2 percent admit to binge drinking (Centers for Disease Control and Prevention, 2012).

The fetal effects of alcohol abuse have been recognized since the 1800s. Lemoine (1968) and Jones (1973) and their coworkers are credited with describing the spectrum of alcohol-related fetal defects known as *fetal alcohol syndrome* (Table 12-4). For every child with the syndrome, many more are born with neurobehavioral deficits from alcohol exposure (American College of Obstetricians and Gynecologists, 2013). *Fetal alcohol spectrum disorder* is an umbrella term that includes five conditions attributed to prenatal alcohol damage: (1) fetal alcohol syndrome, (2) partial fetal alcohol syndrome, (3) alcohol-related birth defects, (4) alcohol-related neurodevelopmental disorder, and (5) neurobehavioral disorder associated with prenatal alcohol exposure (Williams, 2015). The birth prevalence of fetal alcohol syndrome is estimated to be as high as 1 percent in the United States (Centers for Disease Control, 2012; Guerri, 2009). But, studies of school children have identified fetal alcohol spectrum disorder in 2 to 5 percent (May, 2009, 2014).

TABLE 12-4

Criteria for Prenatal Alcohol Exposure, Fetal Alcohol Syndrome, and Alcohol-Related Birth Defects

Documented Prenatal Alcohol Exposure—one or more required

1. ≥6 drinks per week for ≥2 weeks
2. ≥3 drinks per occasion for ≥2 occasions
3. Risk identified with a validated screening questionnaire
4. Laboratory testing indicating alcohol intoxication or positive alcohol-exposure biomarker
5. Documentation of an alcohol-related legal or social problem

Fetal Alcohol Syndrome Diagnostic Criteria—all required

1. Dysmorphic facial features (≥2 required)
    a. Short palpebral fissures
    b. Thin vermilion border of the upper lip
    c. Smooth philtrum
2. Prenatal and/or postnatal growth impairment, ≤10th percentile
3. Abnormal brain growth, morphogenesis, or physiology (≥1 required)
    a. Head circumference ≤10th percentile
    b. Structural brain abnormalities
    c. Recurrent nonfebrile seizures
4. Neurobehavioral impairment (defined as >1.5 SD below mean)
    a. Child <3 years: developmental delay
    b. Child ≥3 years: global cognitive impairment, or cognitive deficit in at least 1 neurobehavioral domain, or behavioral deficit in at least 1 domain

Alcohol-Related Birth Defects

Cardiac: atrial or ventricular septal defect, aberrant great vessels, conotruncal heart defects

Skeletal: radioulnar synostosis, vertebral segmentation defects, joint contractures, scoliosis

Renal: aplastic or hypoplastic kidneys, dysplastic kidneys, horseshoe kidney, ureteral duplication

Eyes: strabismus, ptosis, retinal vascular abnormalities, optic nerve hypoplasia

Ears: conductive or neurosensory hearing loss

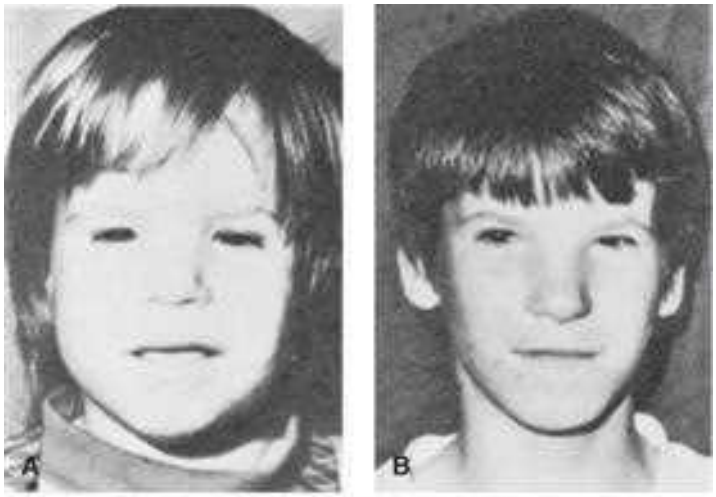
Data from Hoyme, 2016.

Criteria and Characteristics

Fetal alcohol syndrome has specific criteria (see Table 12-4). These include central nervous system (CNS) abnormalities, pre- or postnatal growth impairment, and a characteristic pattern of minor facial abnormalities (Fig. 12-3). Similar criteria have been established for the other conditions that make up fetal alcohol spectrum disorder (Hoyme, 2016). Prenatal alcohol exposure criteria are also available to assist with assessment.

FIGURE 12-3

Fetal alcohol syndrome. **A.** At 2½ years. **B.** At 12 years. Note persistence of short palpebral fissures, epicanthal folds, flat midface, hypoplastic philtrum, and thin upper vermilion border. (Reproduced with permission from Streissguth AP, Clarren, SK, Jones KL. Natural history of fetal alcohol syndrome: a 10-year follow-up of eleven patients, Lancet. 1985 Jul 13;2(8446):85–91.)



Alcohol-related birth defects include cardiac and renal anomalies, orthopedic problems, and abnormalities of the eyes and ears (see Table 12-4). An association has further been reported between periconceptional alcohol use and omphalocele and gastroschisis (Richardson, 2011). There are no established sonographic criteria for prenatal diagnosis of fetal alcohol syndrome. That said, in some cases, major abnormalities or growth restriction may be suggestive (Paintner, 2012).

Dose Effect

Fetal vulnerability to alcohol is modified by genetic components, nutritional status, environmental factors, coexisting maternal disease, and maternal age (Abel, 1995). The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics have stressed that *no* amount of alcohol can be considered safe in pregnancy (Williams, 2015). Binge drinking, however, is believed to pose particularly high risk for alcohol-related birth defects and has also been linked to a higher risk for stillbirth (Centers for Disease Control, 2012; Maier, 2001; Strandberg-Larsen, 2008).

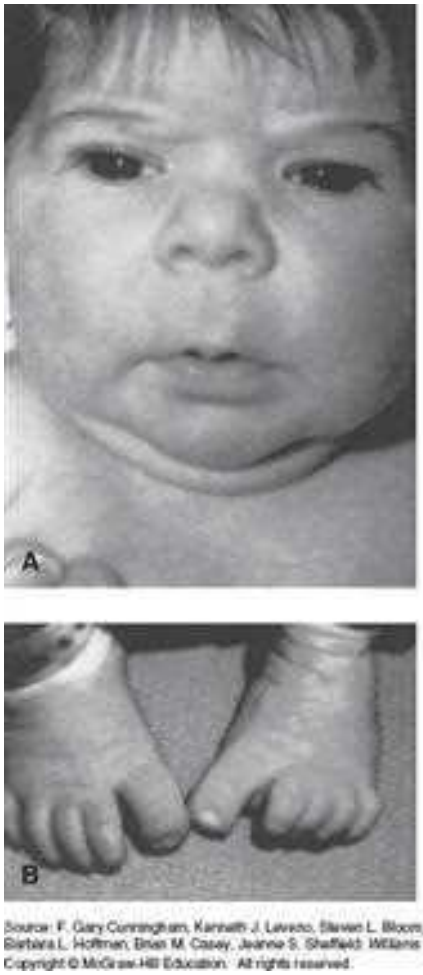
Antiepileptic Medications

Traditionally, women with epilepsy requiring treatment with medication were informed that their risk for fetal malformations was increased. More recent data suggest that the risk may not be as great as once thought, particularly for newer agents. The most frequently reported anomalies are orofacial clefts, cardiac malformations, and neural-tube defects.

Of agents in current use, valproic acid confers the greatest risk (Vajda, 2014). The North American Antiepileptic Drug (NAAED) Pregnancy Registry reported that major malformations developed in 9 percent of fetuses with first-trimester valproate exposure. This included a 4-percent risk for neural-tube defects (Hernandez-Diaz, 2012). School-aged children with in utero exposure to valproic acid have poorer cognitive development—including significantly lower intelligence quotient (IQ) scores—than children exposed to other antiepileptic drugs (Bromley, 2014; Meador, 2009).

Regarding other specific anticonvulsants, one recent metaanalysis identified higher malformation rates among exposed children compared with rates among children born to women with untreated epilepsy. Rates were twofold higher among children exposed to carbamazepine or phenytoin, threefold higher among those exposed to phenobarbital, and fourfold higher among those exposed to topiramate as monotherapy (Weston, 2016). The risk for fetal malformations is approximately doubled if multiple agents are required (Vajda, 2016). Several older anticonvulsants also produce a constellation of malformations similar to the fetal hydantoin syndrome, which is described in Figure 12-4.

FIGURE 12-4
Fetal hydantoin syndrome. **A.** Facial features including upturned nose, mild midfacial hypoplasia, and long upper lip with thin vermilion border. **B.** Distal digital hypoplasia. (Reproduced with permission from Buehler BA1, Delimont D, van Waes M, et al: Prenatal prediction of risk of the fetal hydantoin syndrome, N Engl J Med. 1990 May 31;322(22):1567–1572.)



These risks do not appear to hold for the newer agents levetiracetam and lamotrigine, although the number of reported pregnancies to date is smaller (Mølgaard-Nielsen, 2011; Weston, 2016). The Motherisk Program reviewed eight studies of levetiracetam and concluded that monotherapy was associated with a 2-percent major malformation rate, which is no different from that for the general population (Chaudhry, 2014).

Providers are encouraged to enroll pregnant women treated with antiepileptic medication in the NAAED Pregnancy Registry. Management of epilepsy in pregnancy is discussed in Chapter 60 (Preconceptional Counseling).

Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs

These medications may result in *ACE-inhibitor fetopathy*. Normal renal development depends on the fetal renin-angiotensin system. ACE-inhibitor medication may cause fetal hypotension and renal hypoperfusion, with subsequent ischemia and anuria (Guron, 2000; Pryde, 1993). Reduced perfusion can result in fetal-growth restriction and calvarium maldevelopment, and oligohydramnios may lead to pulmonary hypoplasia and limb contractures (Barr, 1991). Because angiotensin-receptor blockers have a similar mechanism of action, concerns regarding fetotoxicity have been generalized to include this entire medication class.

Concerns were also raised about ACE-inhibitor embryotoxiciy, although these have largely been disproven. In 2006, a review of 29,000 infants from the Tennessee Medicaid database identified a two- to threefold greater risk for neonatal cardiac and CNS abnormalities among the 209 that had prenatal ACE-inhibitor exposure (Cooper, 2006). Subsequent larger studies have not corroborated these observations. First, in a retrospective cohort study of more than 460,000 pregnancies, risks for birth defects were not greater with ACE inhibitors than with other antihypertensive medications (Li, 2011). Similarly, Bateman and coworkers (2017) reviewed 1.3 million pregnancies from the Medicaid Analytic eXtract and found no higher risk for any malformation with ACE-inhibitor exposure after adjusting for confounding factors such as diabetes. Thus, women with inadvertent first-trimester exposure to these medications can be reassured. However, given the many therapeutic options for treating hypertension during pregnancy, discussed in Chapter 50 (Management During Pregnancy), it is recommended that ACE inhibitors and angiotensin receptor-blocking drugs be avoided in pregnancy.

Antifungal Medications

From this class of drugs, fluconazole has been associated with a pattern of congenital malformations resembling the autosomal recessive *Antley-Bixler syndrome*. Abnormalities include oral clefts, abnormal facies, and cardiac, skull, long-bone, and joint abnormalities. Such findings have been reported only with chronic, first-trimester, high-dose treatment at doses of 400 to 800 mg daily.

Regarding low-dose treatment of vulvovaginal candidiasis, the Motherisk Program recently conducted a systematic review of pregnancies with first-trimester fluconazole exposure of 150 or 300 mg in total (Alsaad, 2015). The overall risk for birth defects was not greater, although a small increase in rates of cardiac malformations could not be excluded. A population-based cohort study from Denmark identified a threefold greater risk for tetralogy of Fallot following exposure to low-dose fluconazole (Mølgaard-Nielsen, 2013). The birth prevalence of tetralogy of Fallot rose from 3 to 10 cases per 10,000. This is a risk so low that we would not endorse specialized sonography for this indication. Notably, investigators did not identify increased risks for 14 other birth defects previously associated with exposure to high-dose azole antifungal agents (Mølgaard-Nielsen, 2013).

Antiinflammatory Agents

Nonsteroidal Antiinflammatory Drugs

This drug class includes both aspirin and traditional NSAIDs such as ibuprofen and indomethacin. They exert their effects by inhibiting prostaglandin synthesis. In a report from the NBDPS, at least 20 percent of pregnant women recall first-trimester NSAID use, particularly ibuprofen and aspirin, and such exposure is not a major risk factor for birth defects (Hernandez, 2012).

However, when taken in late pregnancy, indomethacin may cause constriction of the fetal ductus arteriosus and subsequent pulmonary hypertension. Fetal ductal constriction is more likely when the drug is taken in the third trimester for longer than 72 hours. The risk is 15-fold higher among indomethacin-exposed pregnancies (Koren, 2006). The drug also may decrease fetal urine production and amnionic fluid volume (Rasanen, 1995; van der Heijden, 1994; Walker, 1994). In one systematic review, indomethacin tocolysis was associated with neonatal morbidity (Hammers, 2015a,b). Specifically, the risk for bronchopulmonary dysplasia, severe intraventricular hemorrhage, and necrotizing enterocolitis was increased approximately 50 percent (odds ratio 1.5).

With aspirin, a low dosage of 100 mg daily or less does *not* confer a greater risk for constriction of the ductus arteriosus or for adverse infant outcomes (Di Sessa, 1994; Grab, 2000). As with other NSAIDs, however, high-dose aspirin use should be avoided, particularly in the third trimester.

Leflunomide

This is a pyrimidine-synthesis inhibitor used to treat rheumatoid arthritis but is contraindicated in pregnancy. In several animal species, it results in fetal hydrocephalus, eye anomalies, skeletal abnormalities, and embryo death when given at or below human-equivalent doses (Sanofi-Aventis, 2016). The active metabolite, teriflunomide, is detectable in plasma for up to 2 years following discontinuation of the medication. Women who become pregnant while taking leflunomide, and even those of childbearing potential who have discontinued it, are recommended to undergo an accelerated drug elimination procedure with either cholestyramine or activated charcoal (Sanofi-Aventis, 2016). Reassuringly, in a cohort of 60 women with first-trimester leflunomide exposure who completed cholestyramine washout, the rate of birth defects was not increased (Chambers, 2010).

Antimicrobial Drugs

Medications used to treat infections are among those most frequently administered during pregnancy. Over the years, experience has accrued regarding their general safety. With a few exceptions cited below, most of the commonly used antimicrobial agents are considered safe for the embryo-fetus.

Aminoglycosides

Some preterm neonates treated with gentamicin or streptomycin have developed nephrotoxicity and ototoxicity. Despite theoretical concern for potential fetal toxicity, no adverse effects have been demonstrated, and no congenital defects resulting from prenatal exposure have been identified.

Chloramphenicol

This antimicrobial is not considered teratogenic and is no longer routinely used in the United States. More than 50 years ago, a constellation of findings termed the *gray baby syndrome* was described in neonates who received the medication. Preterm newborns were unable to conjugate and excrete the drug and manifested abdominal distention, respiratory abnormalities, an ashen-gray color, and vascular collapse (Weiss, 1960). Chloramphenicol was subsequently avoided in late pregnancy due to theoretical concerns.

Nitrofurantoin

From NBDPS results, first-trimester nitrofurantoin exposure is linked to a twofold risk for cleft lip (Ailes, 2016; Crider, 2009). Considering that the birth prevalence of clefts approximates 1 case per 1000, the likelihood that a nitrofurantoin-exposed fetus would *not* have a cleft would thus be 998 per 1000. For other birth defects, initial associations with this antibiotic did not persist in the final NBDPS cohort (Ailes, 2016).

In one systematic review of nitrofurantoin exposure in pregnancy, results of cohort and case-control studies differed (Goldberg, 2015). Five cohort studies included 9275 exposed pregnancies and nearly 1.5 million unexposed pregnancies, and the review found no higher risk for any malformation. However, among three case-control studies that had nearly 40,000 cases matched with 130,000 controls, the rate of hypoplastic left heart syndrome was threefold greater (Goldberg, 2015). For context, this increase in risk would result in a birth prevalence of fewer than 1 case per 1000 exposed infants. The American College of Obstetricians and Gynecologists (2017e) has concluded that first-trimester nitrofurantoin use is appropriate if no suitable alternatives are available.

Sulfonamides

These drugs are often combined with trimethoprim and used to treat infections during pregnancy. One indication is treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The NBDPS, which included 107 pregnancies with periconceptional trimethoprim-sulfamethoxazole exposure and birth defects, identified a fivefold greater risk to have offspring with esophageal atresia or diaphragmatic hernia (Ailes, 2016). Similar to findings with nitrofurantoin exposure, this degree of increase would confer a risk of approximately 1 case per 1000 exposed infants for these selected birth defects. However, these findings have not been corroborated by other reports. One review from the Medication Exposure in Pregnancy Risk Evaluation Program included more than 7500 infants with first-trimester exposure to trimethoprim-sulfamethoxazole (Hansen, 2016). Compared with either unexposed infants or those exposed to penicillins or cephalosporins, no greater risk for any congenital abnormality was identified. The American College of Obstetricians and Gynecologists (2017e) considers sulfonamides appropriate for first-trimester use if suitable alternatives are lacking.

Sulfonamides displace bilirubin from protein-binding sites. Thus, if given near the time of preterm delivery, these agents theoretically might worsen neonatal hyperbilirubinemia. However, a population-based review of more than 800,000 births from Denmark found no association between exposure to sulfamethoxazole in late pregnancy and neonatal jaundice (Klarskov, 2013).

Tetracyclines

These drugs are no longer commonly used in pregnant women. They are associated with yellowish-brown discoloration of deciduous teeth when used after 25 weeks' gestation. The risk for subsequent dental caries does not appear greater (Billings, 2004; Kutscher, 1966). In contrast, a recent systematic review of doxycycline in pregnancy identified no higher rates of either birth defects or staining of deciduous teeth (Cross, 2016).

Antineoplastic Agents

Cancer management in pregnancy includes many chemotherapeutic agents generally considered to be at least potentially toxic to the embryo, fetus, or both. For the many novel polyclonal antibody therapies designated as antineoplastics, there are few data concerning their safety. Some risks with these and with other antineoplastic agents are discussed in Chapter 63 (Cancer Therapy in Pregnancy). A few of the more common agents for which experience in pregnancy has accrued are considered next.

Cyclophosphamide

This alkylating agent inflicts a chemical insult on developing fetal tissues and leads to cell death and heritable DNA alterations in surviving cells. Pregnancy loss rates are increased, and reported malformations include skeletal abnormalities, limb defects, cleft palate, and eye abnormalities (Enns, 1999; Kirshon, 1988). Surviving infants may have growth abnormalities and developmental delays. Environmental exposure among health-care workers is associated with a higher risk for spontaneous abortion (Chap. 18, Paternal Factors).

Methotrexate

This folic-acid antagonist is a potent teratogen. It is used for cancer chemotherapy, immunosuppression of autoimmune diseases and psoriasis, nonsurgical treatment of ectopic pregnancy, and medical abortion. It is similar in action to aminopterin, which is no longer used clinically, and can cause defects known collectively as the fetal *methotrexate-aminopterin syndrome*. This includes craniosynostosis with a "clover-leaf" skull, wide nasal bridge, low-set ears, micrognathia, and limb abnormalities (Del Campo, 1999). The embryo is thought to be most vulnerable at 8 to 10 weeks postconception and at dosages of at least 10 mg/week. However, this is not universally accepted (Feldkamp, 1993).

The standard 50 mg/m^2 dose given to treat ectopic pregnancy or to induce elective abortion exceeds this threshold dose. Some reports have suggested an association with cardiac anomalies, particularly conotruncal defects, in intrauterine pregnancies inadvertently treated with methotrexate for suspected ectopic pregnancy (Dawson, 2014; Hyoun, 2012). Thus, ongoing pregnancies after treatment with methotrexate—especially if used in conjunction with misoprostol—raise serious concerns for fetal malformations (Nurmohamed, 2011).

Tamoxifen

This nonsteroidal selective estrogen-receptor modulator (SERM) is used as an adjuvant to treat breast cancer. No pattern of birth defects has been described in limited case reports and series (Braems, 2011). However, tamoxifen has been associated with malformations similar to those caused by diethylstilbestrol (DES) exposure in rodents, including vaginal adenosis. Consequently, women who become pregnant on therapy or within 2 months of its discontinuation should be apprised of the potential long-term risks of a DES-like syndrome.

Trastuzumab

This is a recombinant monoclonal antibody directed to the human epidermal growth factor receptor 2 (HER2) protein. Used to treat breast cancers that express HER2 protein, this drug has not been associated with fetal malformations. However, cases of oligohydramnios sequence resulting in pulmonary hypoplasia, renal failure, skeletal abnormalities, and neonatal deaths have been reported (Genentech, 2017). Surveillance for these complications is recommended for exposed pregnancies and for those treated at any time in the 7 months prior to conception. A trastuzumab pregnancy exposure registry

and a pregnancy pharmacovigilance program have been established to monitor pregnancy outcomes. These warnings also apply to those treated with ado-trastuzumab emtansine.

Antiviral Agents

The number of drugs used to treat viral infections has increased rapidly during the past 20 years. For most, experience in pregnant women is limited.

Ribavirin

This nucleoside analogue is a component of therapy for hepatitis C infection, discussed in Chapter 55 (Hepatitis D). Ribavirin causes birth defects in multiple animal species at doses significantly lower than those recommended for human use. Reported malformations include skull, palate, eye, skeleton, and gastrointestinal abnormalities. The drug has a half-life of 12 days and persists in extravascular compartments following therapy discontinuation. Treated women must use two forms of contraception and have monthly pregnancy tests while on therapy and for 6 months following drug discontinuation (Genentech, 2015). Ribavirin use is also contraindicated in men whose partners are pregnant.

Efavirenz

This is a nonnucleoside reverse transcriptase inhibitor used to treat HIV infection (Chap. 65, Delivery Planning). CNS and ocular abnormalities have been reported in cynomolgus monkeys treated with doses comparable to those used in humans. Several case reports also describe neural-tube defects following human exposure to efavirenz. Reassuringly, the Antiretroviral Pregnancy Registry has identified no increased birth defect rates in more than 800 pregnancies with first-trimester exposure (Bristol-Meyers Squibb, 2017b).

Endothelin-Receptor Antagonists

Bosentan, ambrisentan, and macitentan are three endothelin-receptor antagonists used to treat pulmonary arterial hypertension (Chap. 49, Cardiomyopathies). The endothelin-receptor signaling pathway is important for neural-crest development. Mice deficient in endothelin receptors develop neural-crest cell defects that include craniofacial and cardiac outflow tract abnormalities (de Raaf, 2015). Each of these three agents has been found to cause similar birth defects in multiple animal species (Actelion, 2017). No human data are available. Endothelin-receptor antagonists may be obtained only through restricted access programs, each of which has stringent requirements that include contraception and monthly pregnancy testing (Actelion, 2016, 2017; Gilead, 2015).

Sex Hormones

Some of the functions and effects of male and female hormones on the developing fetus are discussed in Chapter 3 (Sexual Differentiation). It is intuitive that exposure of female fetuses to excessive male sex hormones—and vice versa—might be detrimental.

Testosterone and Anabolic Steroids

Androgen exposure in reproductive-aged women typically stems from anabolic steroid use to accrue lean body mass and muscular strength. Exposure of a female fetus may cause varying degrees of virilization and may result in ambiguous genitalia similar to that encountered in congenital adrenal hyperplasia. Findings can include labioscrotal fusion with first-trimester exposure and phallic enlargement from later fetal exposure (Grumbach, 1960; Schardein, 1980).

Danazol

This ethinyl testosterone derivative has weak androgenic activity. It is used to treat endometriosis, immune thrombocytopenic purpura, migraine headaches, premenstrual syndrome, and fibrocystic breast disease. In a review of inadvertent exposure during early pregnancy, Brunskill (1992) reported that 40 percent of exposed female fetuses were virilized. There was a dose-related pattern of clitoromegaly, fused labia, and urogenital sinus malformation.

Diethylstilbestrol

This medication is included for historical context. From 1940 until 1971, between 2 and 10 million pregnant women were given this synthetic estrogen for ill-advised indications. It was removed from the market after Herbst and associates (1971) reported a series of eight women exposed to DES in utero who developed an otherwise rare neoplasm, vaginal clear-cell adenocarcinoma. With no relationship to drug dosage, the absolute cancer risk approximates 1 case per 1000 DES-exposed fetuses. Twofold greater rates of vaginal and cervical intraepithelial neoplasia were also described (Vessey, 1989).

DES exposure has further been associated with genital tract abnormalities in exposed fetuses of both genders. Women may have a hypoplastic, T-shaped uterine cavity; cervical collars, hoods, septa, and coxcombs; and “withered” fallopian tubes (Goldberg, 1999; Salle, 1996). Some are described and illustrated in Chapter 3 (Diethylstilbestrol Reproductive Tract Abnormalities (Class VII)). Later in life, women exposed in utero have slightly higher rates of earlier menopause and breast cancer (Hoover, 2011). Men may develop epididymal cysts, microphallus, hypospadias, cryptorchidism, and testicular hypoplasia (Klip, 2002; Stillman, 1982).

Immunosuppressant Medications

Some of the immune functions necessary for pregnancy maintenance are discussed in Chapter 5 (Amnion). Given these important interactions, immunosuppressant drugs logically might affect pregnancy.

Corticosteroids

These medications include glucocorticoids and mineralocorticoids, which have antiinflammatory and immunosuppressive actions. They are frequently used to treat serious disorders such as asthma and autoimmune disease. Corticosteroids have been associated with clefts in animal studies. In one metaanalysis of case-control studies by the Motherisk Program, systemic corticosteroid exposure was associated with a threefold increase in the rate of clefts. This is an absolute risk of 3 cases per 1000 exposed fetuses (Park-Wyllie, 2000). A 10-year prospective cohort study by the same group, however, did not identify higher risks for major malformations. Based on these findings, corticosteroids are not considered to represent a major teratogenic risk.

Unlike other corticosteroids, the active metabolite of prednisone, which is prednisolone, is inactivated by the placental enzyme 11β-hydroxysteroid dehydrogenase 2. Thus, it may not effectively reach the fetus.

Mycophenolate Mofetil

This inosine monophosphate dehydrogenase inhibitor, and a related agent, mycophenolic acid, are immunosuppressants. They are used to prevent rejection in organ-transplant recipients and to treat autoimmune disease (Chap. 59, Perinatal Mortality and Morbidity). Mycophenolate is a potent teratogen. From the National Transplantation Pregnancy Registry, of pregnancies in which mycophenolate was not discontinued until after the first trimester, birth defects complicated 30 percent, and another 30 percent spontaneously aborted (King, 2017). One prospective review by the European Network of Teratology Information Services similarly identified a spontaneous loss rate of nearly 30 percent in exposed pregnancies. More than 20 percent of liveborn infants had major anomalies (Hoeltzenbein, 2012).

Many affected infants have a pattern of defects termed *mycophenolate embryopathy.* This includes microtia, auditory canal atresia, clefts, coloboma and other eye anomalies, short fingers with hypoplastic nails, and cardiac defects (Anderka, 2009; Merlob, 2009). A Risk Evaluation and Mitigation Strategy (REMS) has been developed for mycophenolate prescribers who treat women with reproductive potential. REMS are safety strategies mandated by the FDA to help manage known risks associated with a medicine yet still allow patients to have access to the benefits of a given drug.

Radioiodine

Radioactive iodine-131 is used for treatment of thyroid cancer and thyrotoxicosis and for diagnostic thyroid scanning. It is also a component of iodine-131 tositumomab therapy, which is employed to treat a type of non-Hodgkin lymphoma. Radioiodine is contraindicated during pregnancy because it readily crosses the placenta and is then concentrated in the fetal thyroid gland by 12 weeks' gestation. It may cause severe or irreversible fetal and neonatal hypothyroidism, which can lead to decreased mental capacity and delayed skeletal maturation (Jubilant DraxImage, 2016). Pregnancy testing should be performed before administration of radioiodine-131.

Lead

Prenatal lead exposure is associated with fetal-growth abnormalities and with childhood developmental delay and behavioral abnormalities. According to the CDC (2010), no level of lead exposure is considered safe in pregnancy. Care and testing for at-risk pregnancies is discussed in Chapter 9 (Common Concerns).

Mercury

Environmental spills of methyl mercury in Minamata Bay, Japan, and rural Iraq demonstrated that the developing nervous system is particularly susceptible to this heavy metal. Prenatal exposure causes disturbances in neuronal cell division and migration. This leads to a range of defects from developmental delay to microcephaly and severe brain damage (Choi, 1978).

The principal concern for prenatal mercury exposure is the consumption of certain species of large fish (Chap. 9, Common Concerns). The FDA (2017a) advises that pregnant women and breastfeeding mothers avoid consumption of king mackerel, marlin, orange roughy, shark, swordfish, tilefish, and bigeye tuna.

Psychiatric Medications

Treatment of psychiatric illness in pregnancy, including a discussion of the risks and benefits of various psychiatric medications, is described in Chapter 61 (Psychological Adjustments to Pregnancy). Selected birth defects and adverse effects associated with specific medications are presented here.

Lithium

This medication has been associated with Ebstein anomaly, a rare cardiac abnormality that otherwise complicates only 1 per 20,000 births. Ebstein anomaly is characterized by apical displacement of the tricuspid valve, often resulting in severe tricuspid regurgitation and marked right atrial enlargement that confer significant morbidity. A report from the Lithium Baby Registry initially suggested that the risk for Ebstein anomaly was as high as 3 percent. However,

subsequent series have identified an attributable risk for Ebstein anomaly and co-occurring right-sided cardiac anomalies of only 1 to 4 per 1000 exposed pregnancies (Patorno, 2017; Yacobi, 2008). In a review of four case-control studies that included more than 200 infants with Ebstein anomaly, no cases were attributed to lithium exposure (Cohen, 1994).

Neonatal lithium toxicity stems from exposure near delivery. The manufacturer recommends that if possible, the dosage should be decreased or drug discontinued 2 to 3 days prior to delivery to reduce this risk (West-Ward, 2016). Findings typically persist for 1 to 2 weeks and may include neonatal hypothyroidism, diabetes insipidus, cardiomegaly, bradycardia, electrocardiogram abnormalities, cyanosis, and hypotonia (American College of Obstetricians and Gynecologists, 2016).

Selective Serotonin- and Norepinephrine-Reuptake Inhibitors

As a class, these medications are not considered major teratogens (American College of Obstetricians and Gynecologists, 2016). The one exception is paroxetine, which has been associated with a higher risk for cardiac anomalies, particularly atrial and ventricular septal defects. Three large databases—a Swedish national registry, a United States insurance claims database, and the Motherisk Program—each identified a 1.5- to twofold greater risk for cardiac malformations following first-trimester paroxetine exposure (Bar-Oz, 2007; Sebela, 2017). For these reasons, the American College of Obstetricians and Gynecologists (2016) recommends that paroxetine be avoided in women planning pregnancy. Fetal echocardiography should be considered for those with first-trimester paroxetine exposure.

Neonatal effects have been associated with prenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) and selective norepinephrine-reuptake inhibitors (SNRIs). Approximately 25 percent of neonates exposed to SSRIs in late pregnancy manifest one or more nonspecific findings considered to represent poor neonatal adaptation (Chambers, 2006; Costei, 2002; Jordan, 2008). Collectively termed the *neonatal behavioral syndrome*, findings can include jitteriness, irritability, hyper- or hypotonia, feeding abnormalities, vomiting, hypoglycemia, thermoregulatory instability, and respiratory abnormalities. Fortunately, these neonatal behaviors are typically mild and self-limited and last approximately 2 days. Jordan and coworkers (2008) reported that affected newborns were not more likely to require a higher level of care, to experience respiratory abnormalities, or to have prolonged hospitalization. Rarely, neonates exposed to SSRIs in late pregnancy demonstrated more severe adaptation abnormalities (Ornoy, 2017).

Another concern with late-pregnancy exposure is the possible association of SSRI medications with *persistent pulmonary hypertension of the newborn (PPHN)*. The baseline incidence approximates 2 cases per 1000 term newborns. PPHN is characterized by elevated pulmonary vascular resistance with right-to-left shunting and resultant hypoxemia. Two recent population-based cohort studies—together involving more than 5 million pregnancies—identified an attributable risk of only 1 to 2 cases per 1000 births (Huybrechts, 2015; Kieler, 2012). Not only is the risk for this condition quite low, but cases associated with SSRI medication have not been severe (Ornoy, 2017).

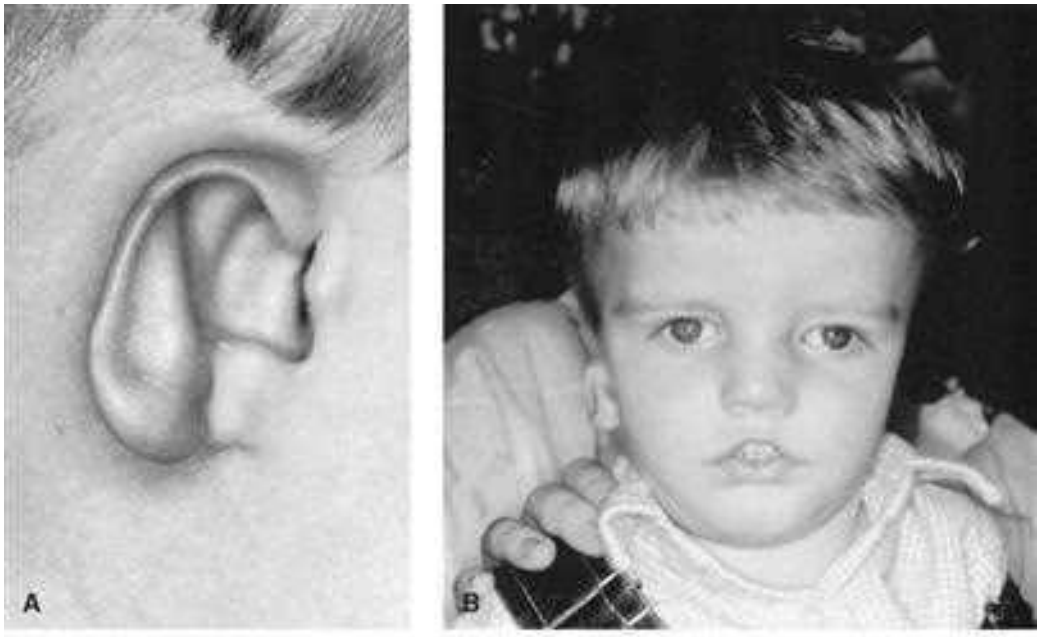
Antipsychotic Medications

No antipsychotic medications are considered teratogenic. Exposed neonates can manifest abnormal extrapyramidal muscle movements and withdrawal symptoms that include agitation, abnormally enhanced or diminished muscle tone, tremor, sleepiness, feeding difficulty, and respiratory abnormalities. These findings are nonspecific and transient, similar to the neonatal behavioral syndrome that can follow SSRI exposure. An FDA (2011) alert cites all medications in this class. These include older drugs such as haloperidol and chlorpromazine, as well as newer medications such as aripiprazole, olanzapine, quetiapine, and risperidone.

Retinoids

These vitamin A derivatives are among the most potent human teratogens. Three retinoids available in the United States are highly teratogenic when orally administered—isotretinoin, acitretin, and bexarotene. By inhibiting neural-crest cell migration during embryogenesis, they create a pattern of cranial neural-crest defects—termed *retinoic acid embryopathy*—that involve the CNS, face, heart, and thymus (Fig. 12-5). Specific anomalies may include ventriculomegaly, maldevelopment of the facial bones or cranium, microtia or anotia, micrognathia, cleft palate, conotruncal heart defects, and thymic aplasia or hypoplasia.

FIGURE 12-5
Isotretinoin embryopathy. **A.** Bilateral microtia or anotia with stenosis of external ear canal. **B.** Flat, depressed nasal bridge and ocular hypertelorism. (Used with permission from Dr. Edward Lammer.)



Isotretinoin

13-*cis*-Retinoic acid is a vitamin A isomer that stimulates epithelial cell differentiation and is used for dermatological disorders, especially cystic nodular acne. First-trimester exposure is associated with a high rate of pregnancy loss, and up to a third of fetuses have malformations (Lammer, 1985). The iPLEDGE program is an FDA-mandated REMS for isotretinoin and is found at: www.ipledgeprogram.com. This web-based, restricted-distribution program requires participation for all patients, physicians, and pharmacies to help eliminate embryonic–fetal exposure. Although other countries have instituted similar programs, inadvertent exposure remains a global concern (Crijns, 2011).

Acitretin

This retinoid is used to treat severe psoriasis and was introduced to replace etretinate. The latter is a lipophilic retinoid with such a long half-life (120 days) that birth defects resulted more than 2 years after therapy was discontinued. Although acitretin has a short half-life, it is metabolized to etretinate, and thus remains in the body for prolonged periods (Stiefel Laboratories, 2015). To obviate exposure, the manufacturer of acitretin has developed a pregnancy risk management program. Called "Do Your P.A.R.T"—Pregnancy prevention Actively Required during and after Treatment, this program promotes a delay of conception for at least 3 years following therapy discontinuation.

Bexarotene

This retinoid is used to treat cutaneous T-cell lymphoma. When given to rats in doses comparable to those for human therapy, fetuses developed eye and ear abnormalities, cleft palate, and incomplete ossification. For a woman to receive this medication, the manufacturer requires two forms of contraception that are initiated 1 month before therapy and are continued for 1 month after bexarotene discontinuation. This is coupled with monthly pregnancy testing during treatment (Valeant Pharmaceuticals, 2015). Males who have partners who could become pregnant are advised to use condoms during sexual intercourse while taking bexarotene and for 1 month after discontinuing therapy.

Topical Retinoids

These compounds, initially used to treat acne, have become so popular for the treatment of sun damage that they are called *cosmeceuticals* (Panchaud, 2012). The most commonly used topical agents are tretinoin, isotretinoin, and adapalene. Systemic absorption is low, and this argues against plausible teratogenicity.

Isolated case reports have described malformations following topical tretinoin, and it is unknown whether this is due to variability in absorption or perhaps potential individual susceptibility (Kaplan, 2015). A prospective study by the European Network of Teratology Information Services found no higher rates of birth defects or spontaneous losses, and no case of retinoid embryopathy (Panchaud, 2012). One systematic review by the Motherisk Program included 635 pregnancies with exposure to topical retinoids. Investigators similarly identified no higher risk for congenital malformations, spontaneous abortion, stillbirth, low birthweight, or preterm delivery (Kaplan, 2015). These results may be reassuring to pregnant women with inadvertent exposure.

Notably, the manufacturer of tazarotene cautions that application over a sufficient body surface area could be comparable to oral treatment. Accordingly, its use in pregnancy is not recommended (Allergan, 2017).

Vitamin A

There are two natural forms of vitamin A. Beta-carotene, which is a precursor of provitamin A, is found in fruits and vegetables and has never been shown to cause birth defects (Oakley, 1995). Retinol is preformed vitamin A, which has been associated with cranial neural-crest defects when more than 10,000 IU per day is consumed in the first trimester (Rothman, 1995). It seems reasonable to avoid doses of preformed preparations that exceed the recommended 3000 IU daily allowance (American Academy of Pediatrics, 2017).

Thalidomide and Lenalidomide

Possibly the most notorious human teratogen, thalidomide causes malformations in 20 percent of fetuses exposed between 34 and 50 days menstrual age. The characteristic malformation is *phocomelia*—an absence of one or more long bones. As a result, hands or feet are attached to the trunk, occasionally by a small rudimentary bone. Cardiac malformations, gastrointestinal abnormalities, external ear malformations, eye anomalies, and other limb-reduction defects are also common following thalidomide exposure. The manufacturer reports that up to 40 percent of affected newborns do not survive the neonatal period (Celgene, 2017a).

Thalidomide was marketed outside the United States from 1956 to 1960, before its teratogenicity was appreciated. The ensuing disaster, with thousands of affected children, was instructive of several important teratological principles. First, the placenta is not an effective barrier to the transfer of toxic substances from mother to embryo (Dally, 1998). Second, different species show extreme variability in their susceptibility to drugs and chemicals. Namely, thalidomide produced no defects in multiple rodent species and was assumed to be safe for humans. Last, exposure timing and defect type are often closely related (Vargesson, 2015). For example, upper-limb amelia may develop with thalidomide exposure during days 24 to 30 postconception, upper-limb phocomelia with exposure during days 24 to 33, and lower-limb phocomelia with exposure during days 27 to 33.

Thalidomide was first approved in the United States in 1999 and currently is used to treat erythema leprosum nodosum and multiple myeloma (Celgene, 2017a). The FDA has mandated a web-based, restricted-distribution program for thalidomide, called THALOMID REMS, which is required before patients, physicians, and pharmacies can access the medication.

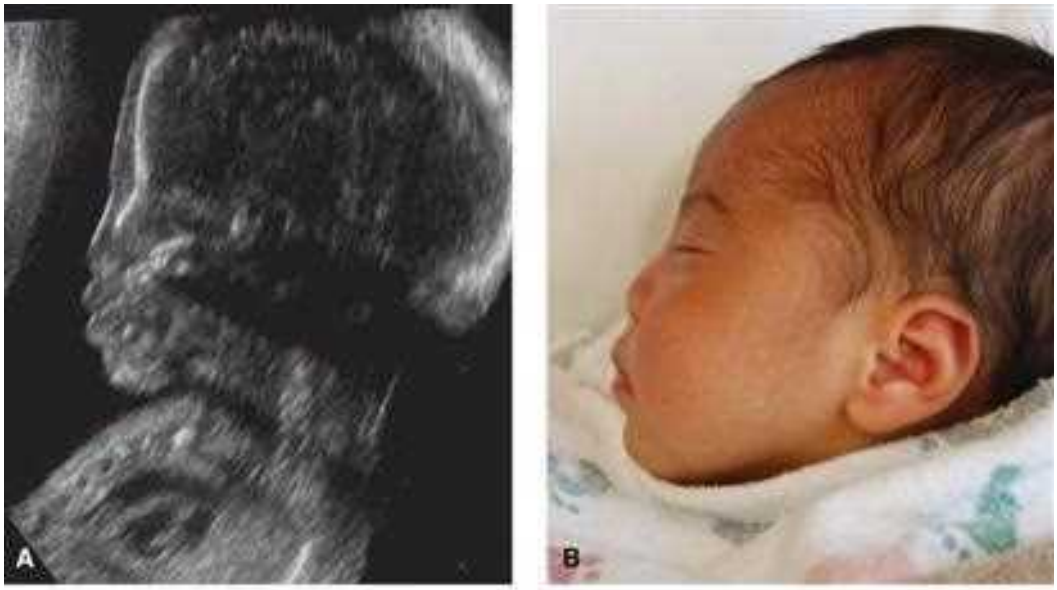
Lenalidomide is an analogue of thalidomide that is used to treat some types of myelodysplastic syndrome and multiple myeloma. It crosses the placenta in multiple animal species, and it causes thalidomide-like limb abnormalities in monkeys (Celgene, 2017b). Because of obvious teratogenicity concerns, a restricted-distribution program similar to that used for thalidomide has been developed.

Warfarin

This anticoagulant is a vitamin K antagonist with a long half-life. Because of its low molecular weight, it readily crosses the placenta and may cause embryotoxic and fetotoxic effects. Warfarin analogues, such as Coumadin, are considered contraindicated in pregnancy. An exception, as discussed in Chapter 49 (Surgically Corrected Heart Disease), is treatment of women with mechanical heart valves who are at high risk for thromboembolism (Bristol-Myers Squibb, 2017a).

Warfarin embryopathy is characterized by stippled epiphyses and nasal hypoplasia (Fig. 12-6). In one review of 63 cases attributed to warfarin exposure, 80 percent displayed characteristic findings, which include depressed nasal bridge with nasal hypoplasia and choanal atresia, along with stippled epiphyses of the femur, humerus, calcanei, and distal phalanges (Van Driel, 2002). It may result from exposure between the 6th and 9th weeks' gestation (Hall, 1980). The prevalence of the warfarin embryopathy following exposure during this critical period is estimated to be 6 percent (van Driel, 2002). One metaanalysis of cases in which the warfarin dosage was ≤5 mg/d identified embryopathy in 1 percent of exposed fetuses. This suggests that risk may be dose dependent (Hassouna, 2014).

FIGURE 12-6
Warfarin embryopathy or fetal warfarin syndrome: nasal hypoplasia and depressed nasal bridge seen in a fetal sonographic image **(A)** and in the same newborn **(B)**.



If used beyond the first trimester, warfarin may lead to hemorrhage into fetal structures, which can cause abnormal growth and deformation from scarring (Warkany, 1976). Nearly 50 percent of reported embryopathy cases also have CNS anomalies (van Driel, 2002). Abnormalities can include agenesis of the corpus callosum; cerebellar vermian agenesis, which is the Dandy-Walker malformation; microphthalmia; and optic atrophy (Hall, 1980). Affected infants are also at risk for blindness, deafness, and developmental delays.

Herbal Remedies

With various herbal remedies, associated risks are more challenging to estimate because studies are few and because these compounds are not FDA-regulated. The European Committee of Herbal Medicinal Products provides assessment reports and monographs on selected herbal substances and preparations, but safety data are generally limited (Wiesner, 2017). Animal studies have not been conducted, and thus knowledge of complications often derives from reports of acute toxicity (Hepner, 2002; Sheehan, 1998). Further, the identity, quantity, and purity of each ingredient are usually unknown. Given these uncertainties, it seems prudent to counsel pregnant women to avoid these substances. A list of selected herbal compounds and their potential effects is shown in Table 12-5.

TABLE 12-5

Pharmacological Actions and Adverse Effects of Some Herbal Medicines

Herb and Common Name	Relevant Pharmacological Effects	Concerns
Aloe (oral ingestion) Black cohosh	Smooth-muscle stimulant Smooth-muscle stimulant	May cause uterine contractions Causes uterine contractions; also has an estrogenic compound
Blue cohosh	Smooth-muscle stimulant	Causes uterine contractions; contains compounds teratogenic in multiple animal species
Echinacea: *purple coneflower root*	Activates cell-mediated immunity	Allergic reactions; decreases immunosuppressant effectiveness; possible immunosuppression with long-term use
Ephedra: *ma huang*	Direct and indirect sympathomimetic; tachycardia and hypertension	Hypertension, arrhythmias, myocardial ischemia, stroke; depletes endogenous catecholamines; life-threatening interaction with monoamine oxidase inhibitors
Evening primrose oil	Contains linoleic acids, a prostaglandin precursor	Possible complications if used for labor induction
Garlic: *ajo*	Inhibits platelet aggregation; increased fibrinolysis; antihypertensive activity	Risk of bleeding, especially when combined with other platelet aggregation inhibitors
Ginger	Cyclooxygenase inhibitor, thromboxane synthetase inhibitor	Increased risk of bleeding
Ginkgo biloba	Anticoagulant	Risk of bleeding; interferes with monoamine oxidase inhibitors
Ginseng	Lowers blood glucose; inhibition of platelet aggregation	Hypoglycemia; hypertension; risk of bleeding
Kava: *awa, intoxicating pepper, kawa*	Sedation, anxiolysis	Sedation; tolerance and withdrawal
Valerian: *all heal, garden heliotrope, vandal root*	Sedation	Sedation; hepatotoxicity, benzodiazepine-like acute withdrawal
Yohimbe		Hypertension, arrhythmias

Data from Ang-Lee, 2001; Briggs, 2015; Hall, 2012; Wiesner, 2017.

Recreational Drugs

Not uncommonly, fetuses are exposed to one or more illicit drugs. Assessment of outcomes attributable to these drugs may be confounded by factors such as poor maternal health, malnutrition, infectious disease, and polysubstance abuse. Moreover, illegal substances may contain toxic contaminants such as lead, cyanide, herbicides, and pesticides. Impurities added as diluents may independently have serious adverse perinatal effects. As noted in Known and Suspected Teratogens, alcohol is a significant teratogen. Because it is legally obtained and ubiquitous, its use also confounds the study of illicit drug teratogenicity.

Amphetamines

These sympathomimetic amines are not considered to be major teratogens. Methamphetamine enhances dopamine release and blocks its reuptake. It is prescribed to treat attention-deficit/hyperactivity disorder and narcolepsy. Methamphetamine abuse has been rising in the United States since the late 1980s (American College of Obstetricians and Gynecologists, 2017b). In utero exposure has been consistently associated with higher rates of small-for-gestational age newborns (Gorman, 2014; Smith, 2006). Hypertensive complications, placental abruption, preterm birth, and stillbirth are other associated complications (Gorman, 2014). Behavioral abnormalities have been described in both infants and school-aged children (Eze, 2016).

Cocaine

With this CNS stimulant, most adverse outcomes result from its vasoconstrictive and hypertensive effects. Serious potential maternal complications are cerebrovascular hemorrhage, myocardial damage, and placental abruption. Studies of congenital abnormalities and cocaine exposure have yielded conflicting results, but associations with cleft palate, cardiovascular abnormalities, and urinary tract anomalies have been reported (Chasnoff, 1988; Lipshultz, 1991; van Gelder, 2009). Cocaine use is also associated with fetal-growth restriction and preterm delivery. Children exposed as fetuses have risks for behavioral abnormalities and cognitive impairments (Bada, 2011; Gouin, 2011).

Opioids–Narcotics

The dramatic rise in narcotic use among non-pregnant and pregnant individuals has been aptly termed an epidemic. Opioids are not considered to be major teratogens. The NBDPS did identify a slightly greater risk for spina bifida, gastroschisis, and cardiac abnormalities with periconceptional opioid exposure (Broussard, 2011). The American College of Obstetricians and Gynecologists (2017c) stresses that this potential, small increase in birth defects with maintenance therapy should be weighed against the risks associated with uncontrolled opioid abuse. Heroin addiction is associated with adverse pregnancy outcomes from the effects of repeated narcotic withdrawal on the fetus and placenta (American College of Obstetricians and Gynecologists, 2017c). These include preterm birth, placental abruption, fetal-growth restriction, and fetal death.

Neonatal narcotic withdrawal, called the *neonatal abstinence syndrome*, may manifest in 40 to 90 percent of exposed newborns (Blinick, 1973; Creanga, 2012; Dashe, 2002; Zelson, 1973). As discussed in Chapter 33 (Neonatal Abstinence Syndrome), CNS irritability may progress to seizures if untreated and may be accompanied by tachypnea, apneic episodes, poor feeding, and failure to thrive. At-risk neonates are closely monitored using a scoring system, and those severely affected are treated with opioids (Finnegan, 1975). The proportion of exposed newborns developing neonatal abstinence syndrome has risen significantly in recent years (Creanga, 2012; Lind, 2015).

The American College of Obstetricians and Gynecologists (2017c) recommends that pregnant women with opioid-use disorder be maintained on opioid-agonist therapy to reduce the risks associated with illicit opioid abuse and associated behaviors. Treatment includes either methadone, usually through a licensed outpatient opioid treatment program, or buprenorphine, which may be given in an office-based setting by a licensed buprenorphine prescriber. A multidisciplinary treatment program is recommended to reduce the likelihood of additional opioid abuse while on maintenance therapy. The College (2017c) discourages withdrawal from methadone during pregnancy because of high relapse rates. At Parkland Hospital, pregnant opioid users who decline maintenance therapy are offered inpatient hospitalization for controlled methadone taper, with the goal of reducing the likelihood of neonatal abstinence syndrome (Dashe, 2002; Stewart, 2013).

Marijuana

This is the illicit drug most commonly used in pregnancy (American College of Obstetricians and Gynecologists, 2017a). Based on data from the National Survey on Drug Use and Health, the prevalence of marijuana use in pregnancy was nearly 4 percent in 2014 (Brown, 2017). Cannabinoids are not considered to be major teratogens, but there is concern because endogenous cannabinoids play key roles in human brain development. In one metaanalysis of nearly 8000 exposed pregnancies, adverse outcomes such as preterm birth and low birthweight were increased only in the presence of concomitant tobacco use (Conner, 2016).

Miscellaneous Drugs

Phencyclidine (PCP) or angel dust is not associated with congenital anomalies. More than half of exposed newborns, however, experience withdrawal symptoms characterized by tremors, jitteriness, and irritability. *Toluene* is a common solvent used in paints and glue. Occupational exposure is reported to have significant fetal risks (Wilkins-Haug, 1997). When abused by women in early pregnancy, it is associated with *toluene embryopathy*, which is phenotypically similar to fetal alcohol syndrome. Abnormalities include pre- and postnatal growth deficiency, microcephaly, midface hypoplasia, short palpebral fissures, and wide nasal bridge (Pearson, 1994). Up to 40 percent of exposed children have developmental delays (Arnold, 1994).

Tobacco

Cigarette smoke contains a complex mixture of nicotine, cotinine, cyanide, thiocyanate, carbon monoxide, cadmium, lead, and various hydrocarbons (Stillerman, 2008). In addition to being fetotoxic, many of these substances have vasoactive effects or reduce oxygen levels. Tobacco is not considered a major teratogen, although selected birth defects have been reported to occur with greater frequency among newborns of women who smoke. It is plausible that the vasoactive properties of tobacco smoke could produce congenital defects related to vascular disturbances. For example, the prevalence of Poland sequence, which is caused by an interruption in the vascular supply to one side of the fetal chest and ipsilateral arm, is twofold greater in smokers (Martinez-Frias, 1999). A small increased risk for cardiac anomalies has also been reported and may be dose related (Alverson, 2011; Malik, 2008; Sullivan, 2015). One study analyzing more than 6 million births found an association between maternal smoking and hydrocephaly, microcephaly, omphalocele, gastroschisis, cleft lip and palate, and hand abnormalities (Honein, 2001). Electronic nicotine delivery systems are not considered safe, as nicotine may have adverse effects on fetal brain and lung development (American College of Obstetricians and Gynecologists, 2017d).

The best-documented adverse reproductive outcome from smoking is a dose-response reduction in fetal growth. Newborns of mothers who smoke weigh on average 200 g less than newborns of nonsmokers (D'Souza, 1981). Smoking doubles the risk of low birthweight and raises the risk of fetal-growth restriction two- to threefold (Werler, 1997). Even secondhand smoke increases the risk for low birthweight (Hegaard, 2006). Women who stop smoking early in pregnancy may have neonates with normal birthweights (Cliver, 1995). Other adverse outcomes associated with cigarette smoking include preterm birth,

placenta previa, placenta abruption, spontaneous abortion, and sudden infant death syndrome (American College of Obstetricians and Gynecologists, 2017d). Risks of childhood asthma and obesity are also increased.

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CHAPTER 13: Genetics

Foetal death may be due to abnormalities in the ovum itself or due to some disease on the part of the mother, and now and again of the father. The death of the foetus is frequently due to abnormalities in the development of the embryo which are inconsistent with foetal life.

—J. Whitridge Williams (1903)

INTRODUCTION

In Williams' first edition of *Obstetrics*, he rarely referenced inherited conditions that Gregor Mendel had described 50 years earlier. Fast-forward to 2017, when the science of genetics is a major obstetrical discipline.

Genetics is the study of genes, heredity, and the variation of inherited characteristics. Medical genetics deals with the etiology and pathogenesis of human diseases that are at least partially genetic in origin, along with their prediction and prevention. Thus, it is closely linked to *genomics*, which is the study of gene function and interaction. In addition to chromosomal, mendelian, and nonmendelian genetic conditions reviewed in this chapter, medical genetics includes prenatal and preimplantation genetic diagnosis, as well as newborn genetic screening, which are discussed in Chapters 14 and 32, respectively.

Genetic disease is common. Between 2 and 3 percent of newborns have a recognized structural defect. In another 3 percent of individuals, a defect is diagnosed by age 5, and another 8 to 10 percent of persons are discovered by age 18 to have one or more functional or developmental abnormalities. Advances in genomics are used increasingly to provide information regarding susceptibility to genetic diseases, and every indication suggests that this field will reshape prenatal diagnosis.

GENOMICS IN OBSTETRICS

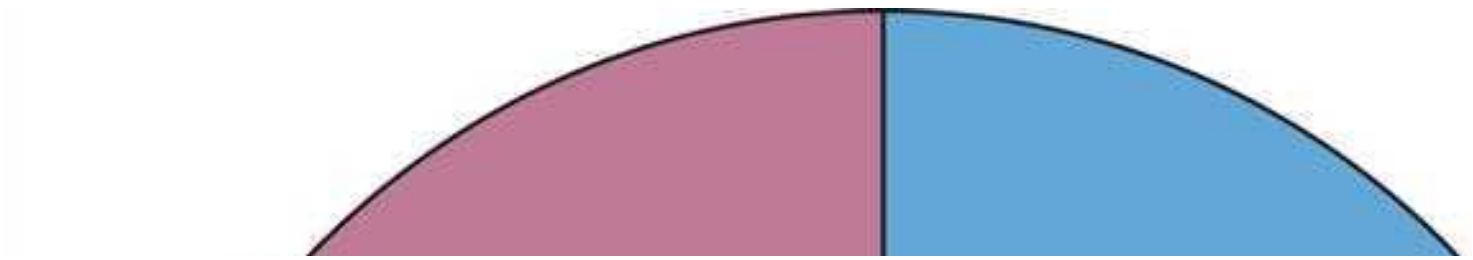
Completed in 2003, the Human Genome Project identified more than 25,000 human genes and led to rapid expansion of genomic research to better understand disease biology (McKusick, 2003). More than 99 percent of our DNA is identical. However, genetic code varies every 200 to 500 base pairs, usually as a single-nucleotide polymorphism. The human genome contains more than 80 million such genetic variants, and understanding their potential role in disease requires not only sophisticated interpretation but also integration of resources (Rehm, 2015).

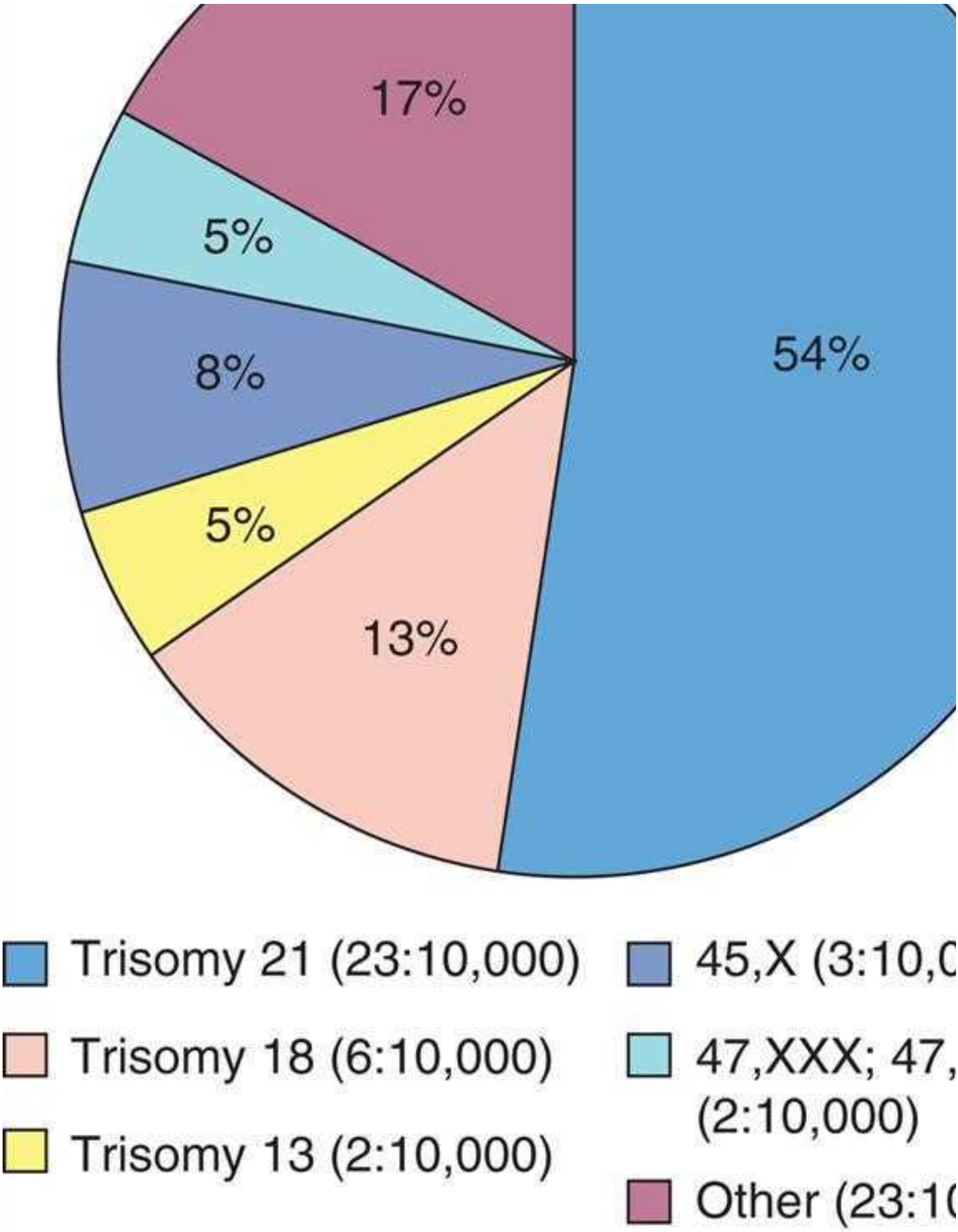
The National Center for Biotechnology Information (NCBI) maintains genetic and genomic databases that are freely accessible to clinicians and researchers. Several of these databases are particularly useful in obstetrics and maternal-fetal medicine practice. The *GeneReviews* database provides in-depth clinical information for nearly 700 genetic conditions, including diagnostic criteria, management, and genetic counseling considerations (National Center for Biotechnology Information, 2017a). The *Genetic Testing Registry (GTR)* database contains information regarding the benefits and limitations of available tests for a given disorder. It lists more than 48,000 genetic tests and instructions for specimen collection and transport to individual laboratories throughout the world (National Center for Biotechnology Information, 2017b). Another database, *Online Mendelian Inheritance in Man* (OMIM), is a comprehensive catalog of human genes and phenotypes that allows clinicians to search for syndromes based on particular traits or abnormalities. As of early 2017, OMIM included more than 15,000 genes and nearly 5000 mendelian and mitochondrial conditions with a known molecular basis (Johns Hopkins University, 2017). The National Library of Medicine (2017) has also established a database of genetic information intended for patients—one that trainees may find especially helpful—the *Genetics Home Reference (GHR)*. This database contains data on more than 2400 genetic conditions and genes, including resources for families.

CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities figure prominently in genetic disease. Aneuploidy accounts for more than 50 percent of first-trimester miscarriages, approximately 20 percent of second-trimester losses, and 6 to 8 percent of stillbirths and early-childhood deaths (Reddy, 2012; Stevenson, 2004; Wou, 2016). In the European Surveillance of Congenital Anomalies (EUROCAT) network of population-based registries, chromosomal abnormalities were identified in 0.4 percent of births (Wellesley, 2012). Of recognized pregnancies with aneuploidy, trisomy 21 composes just more than half of all cases. Trisomy 18 accounts for almost 15 percent, and trisomy 13 for 5 percent (Fig. 13-1).

FIGURE 13-1
Prevalence and relative proportion of selected chromosomal abnormalities from EUROCAT (European Surveillance of Congenital Anomalies) population-based registries that included >10,000 aneuploid live births, fetal deaths, and pregnancy terminations, 2000–2006. (Data from Wellesley, 2012.)





Standard Nomenclature

Karyotypes are described using the International System for Human Cytogenomic Nomenclature (McGowan-Jordan, 2016). Abnormalities fall into two broad categories—those of *chromosome number*, such as trisomy, and those of *chromosome structure*, such as a deletion or translocation. Each chromosome has a short arm, termed the "p" or petit arm, and a long arm, known as the "q" arm, selected because it is the next letter in the alphabet. The two arms are separated by the centromere.

When reporting a karyotype, the total number of chromosomes is listed first, corresponding to the number of centromeres. This is followed by the sex chromosomes, XX or XY, and then by a description of any structural variation. Specific abnormalities are indicated by standard abbreviations, such as del (deletion) and inv (inversion). The affected region or bands of the p or q arms are then designated, so that the reader will know the exact abnormality location and type. Examples are shown in Table 13-1.

TABLE 13-1

Examples of Karyotype Designations Using the 2016 International System for Human Cytogenetic Nomenclature

Karyotype	Description
46,XX	Normal female chromosome constitution
47,XY,+21	Male with trisomy 21
47,XX,+21/46,XX	Female who is a mosaic of trisomy 21 cells and cells with normal constitution
46,XY,del(4)(p14)	Male with terminal deletion (del) of the short arm of chromosome 4 at band p14
46,XX,dup(5)(p14p15.3)	Female with duplication (dup) of the short arm of chromosome 5 from band p14 to band p15.3
45,XY,der(13;14)(q10;q10)	Male with balanced robertsonian translocation (der) of the long arms of chromosomes 13 and 14—the karyotype now has one normal 13, one normal 14, and the translocation chromosome, reducing the normal 46 chromosome complement to 45
46,XX,t(11;22)(q23;q11.2)	Female with a balanced reciprocal translocation (t) between chromosomes 11 and 22, with breakpoints at 11q23 and 22q11.2
46,XY,inv(3)(p21q13)	Male with inversion (inv) of chromosome 3 that extends from p21 to q13—a pericentric inversion because it includes the centromere
46,X,r(X)(p22.1q27)	Female with one normal X and one ring (r) X chromosome, with the regions distal to p22.1 and q27 deleted from the ring
46,X,i(X)(q10)	Female with one normal X chromosome and an isochromosome (i) of the long arm of the other X
ish 22q11.2(HIRAx2)	FISH of metaphase cells using a probe for the HIRA locus of the 22q11.2 region, with 2 signals identified (no evidence of microdeletion)
ish del(22)(q11.2q11.2) (HIRA-)	FISH of metaphase cells using a probe for the HIRA locus of the 22q11.2 region, with only one signal identified, consistent with the microdeletion
arr[GRCh38] 18p11.32q23 (102328_79093443)x3	Microarray analysis (arr), genome build GRCh38, showing a single copy gain on chromosome 18 from band p11.32 to band q23 (essentially the entire chromosome), consistent with trisomy 18
arr[GRCh38] 4q32.2q35.1 (163146681_183022312)x1	Microarray analysis (arr), genome build GRCh38, showing a copy loss on the long arm of chromosome 4 at bands q32.2 through q35.1 (19.9 Mb)
arr[GRCh38] 15q11.2q26 (23123715_101888908)x2 hmz	SNP microarray analysis (arr), genome build GRCh 38, showing homozygosity for the entire long arm of chromosome 15

FISH = fluorescence in situ hybridization; GRCh38 = Genome Reference Consortium human build 38; HIRA = histone cell cycle regulator; SNP = single nucleotide pleomorphism.

Used with permission from Dr. Kathleen S. Wilson.

Terminology is similar for fluorescence in situ hybridization. Described in Genetic Tests, this technique is used to rapidly identify of a specific chromosome abnormality and verify suspected microdeletion or microduplication syndromes. The report begins with the designation *ish* for in situ hybridization performed on metaphase cells and *nuc ish* for hybridization performed on interphase nuclei. If no abnormality is identified, this is followed by the probe's specific chromosomal region, such as 22q11.2, and then the name of the probe and the number of signals visualized—for example, HIRAx2. If a deletion is identified, *del* is included before the chromosomal region, and the name of the probe is followed by a minus sign (HIRA-), as shown in Table 13-1. The 22q11.2 microdeletion syndrome is discussed in Abnormalities of Chromosome Structure.

A recent addition to the standard nomenclature is terminology to represent copy number variants identified by *chromosomal microarray analysis*, which is discussed in Chromosomal Microarray Analysis. *Copy number variant* is another term for a microdeletion or microduplication of DNA too small to be visualized with a standard karyotype. The array designation begins with the abbreviation *arr* and the version of the genome build to which the nucleotide designations are aligned, such as GRCh38 for Genome Reference Consortium human build 38. This is followed by the number of the chromosome on which the abnormality is identified, by the p or q arm, and by the specific bands in question. Array reports next include the affected base pair coordinates, thus conveying the exact size and location within the genome for every abnormality identified—including copy number variants of uncertain significance.

Abnormalities of Chromosome Number

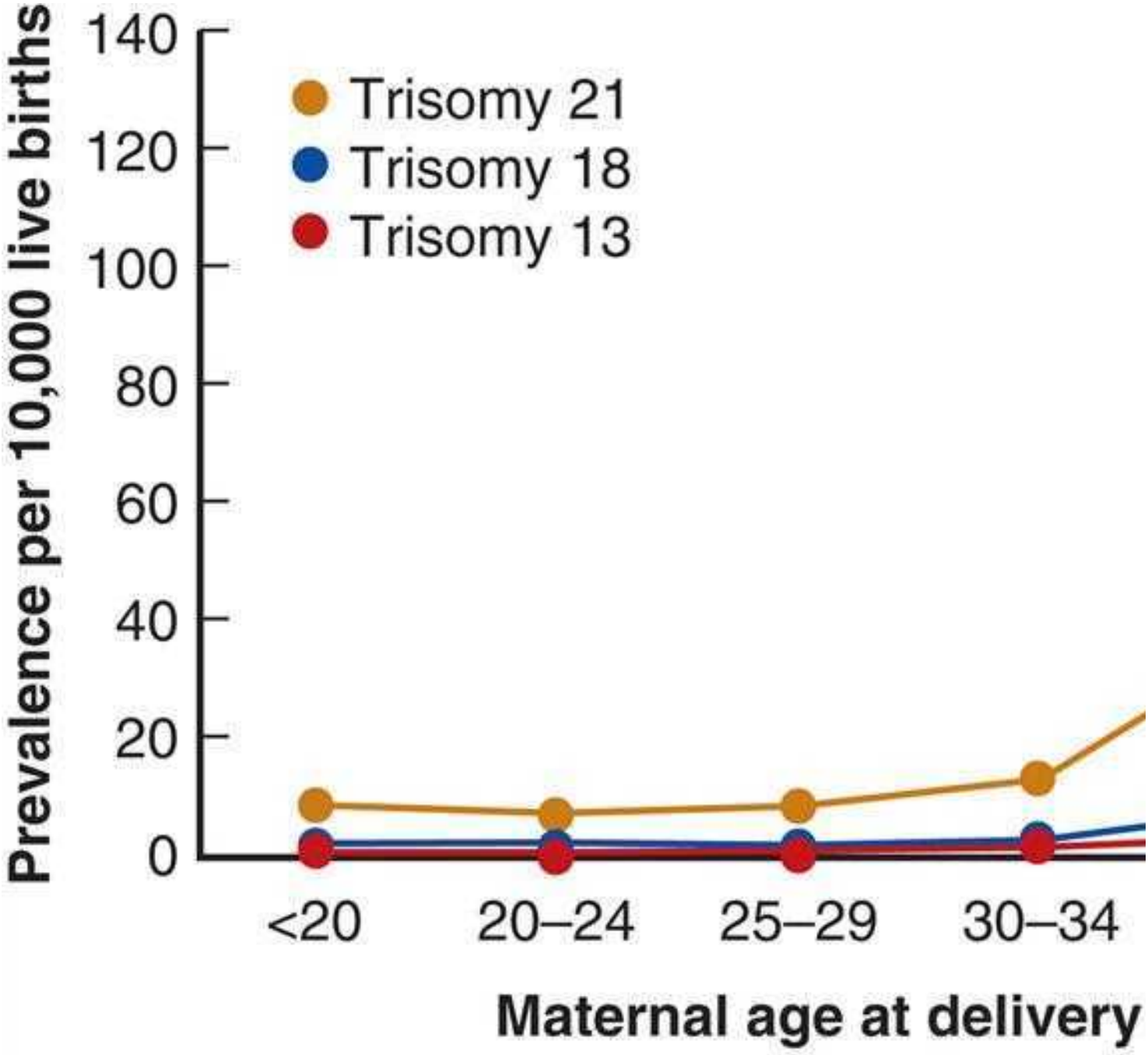
The most easily recognized chromosomal abnormalities are numerical. *Aneuploidy* is inheritance of either an extra chromosome—resulting in trisomy, or loss of a chromosome—*monosomy*. These differ from *polyploidy*, which is an abnormal number of haploid chromosome sets, such as triploidy. The estimated incidence of various numerical chromosomal abnormalities is shown in Figure 13-1.

Autosomal Trisomies

These account for approximately half of all chromosomal abnormalities. In most cases, trisomy results from nondisjunction, which is failure of normal chromosomal pairing and separation during meiosis. Nondisjunction may occur if the chromosomes: (1) fail to pair up, (2) pair up properly but separate prematurely, or (3) fail to separate.

The risk of any autosomal trisomy rises steeply with maternal age, particularly after age 35 (Fig. 13-2). Oocytes are suspended in midprophase of meiosis I from birth until ovulation, in some cases for 50 years. Following completion of meiosis at ovulation, nondisjunction results in one gamete having two copies of the affected chromosome, leading to trisomy if fertilized. The other gamete, receiving no copy of the affected chromosome, will be monosomic if fertilized. It is estimated that 10 to 20 percent of oocytes are aneuploid secondary to meiotic errors, compared with 3 to 4 percent of sperm. Although each chromosome pair is equally likely to have a segregation error, it is rare for trisomies other than 21, 18, or 13 to result in a term pregnancy, and most fetuses with trisomies 18 and 13 die before term.

FIGURE 13-2
Prevalence of autosomal trisomies according to maternal age found in population-based birth defects surveillance programs in the United States, 2006–2010, which included live births, stillbirths, and pregnancy terminations. (Data from Mai, 2013. Redrawn with permission from Dashe JS: Aneuploidy screening. Obstet Gynecol 128(1):181, 2016.)



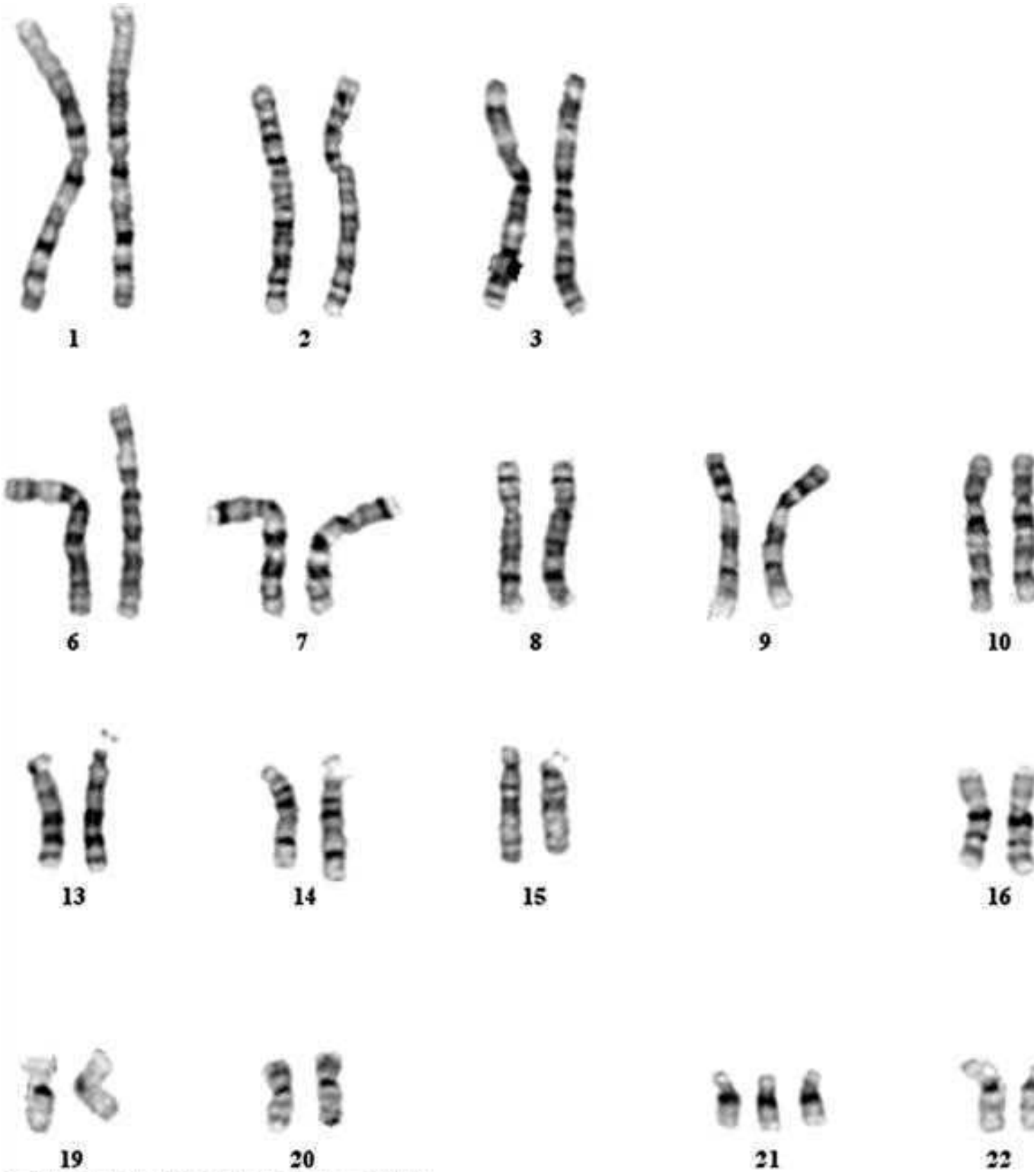
Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

After a pregnancy with an autosomal trisomy, the risk for any autosomal trisomy in a future pregnancy approximates 1 percent until the woman's age-related risk exceeds this. Accordingly, prenatal diagnosis with chorionic villus sampling or amniocentesis is offered in these subsequent pregnancies (Chap. 14, Technique). Parental chromosomal studies are not indicated unless the affected pregnancy was caused by an unbalanced translocation or other structural rearrangement.

Trisomy 21—Down Syndrome

In 1866, J. L. H. Down described a group of intellectually disabled children with distinctive physical features. Nearly 100 years later, Lejeune (1959) demonstrated that Down syndrome is caused by an autosomal trisomy (Fig. 13-3). Trisomy 21 causes 95 percent of Down syndrome cases, whereas 3 to 4 percent of cases are due to a robertsonian translocation, described later (Isochromosomes). The remaining 1 to 2 percent results from an isochromosome or from mosaicism. The nondisjunction that yields trisomy 21 occurs during meiosis I in approximately 75 percent of cases, and the remaining events are during meiosis II.

FIGURE 13-3
Abnormal male karyotype with trisomy 21, consistent with Down syndrome (47,XY,+21). (Used with permission from Dr. Frederick Elder.)



Down syndrome is the most common nonlethal trisomy. Its approximate prevalence is 1 in 500 recognized pregnancies. However, fetal losses and pregnancy terminations yield an estimated prevalence of 13.5 in 10,000 births in the United States—1 per 740 (Mai, 2013; Parker, 2010). The fetal death rate beyond 20 weeks' gestation approximates 5 percent (Loane, 2013). Coinciding with the older maternal age distribution during the past four decades, the prevalence of Down syndrome has risen approximately 33 percent (Loane, 2013; Parker, 2010; Shin, 2009).

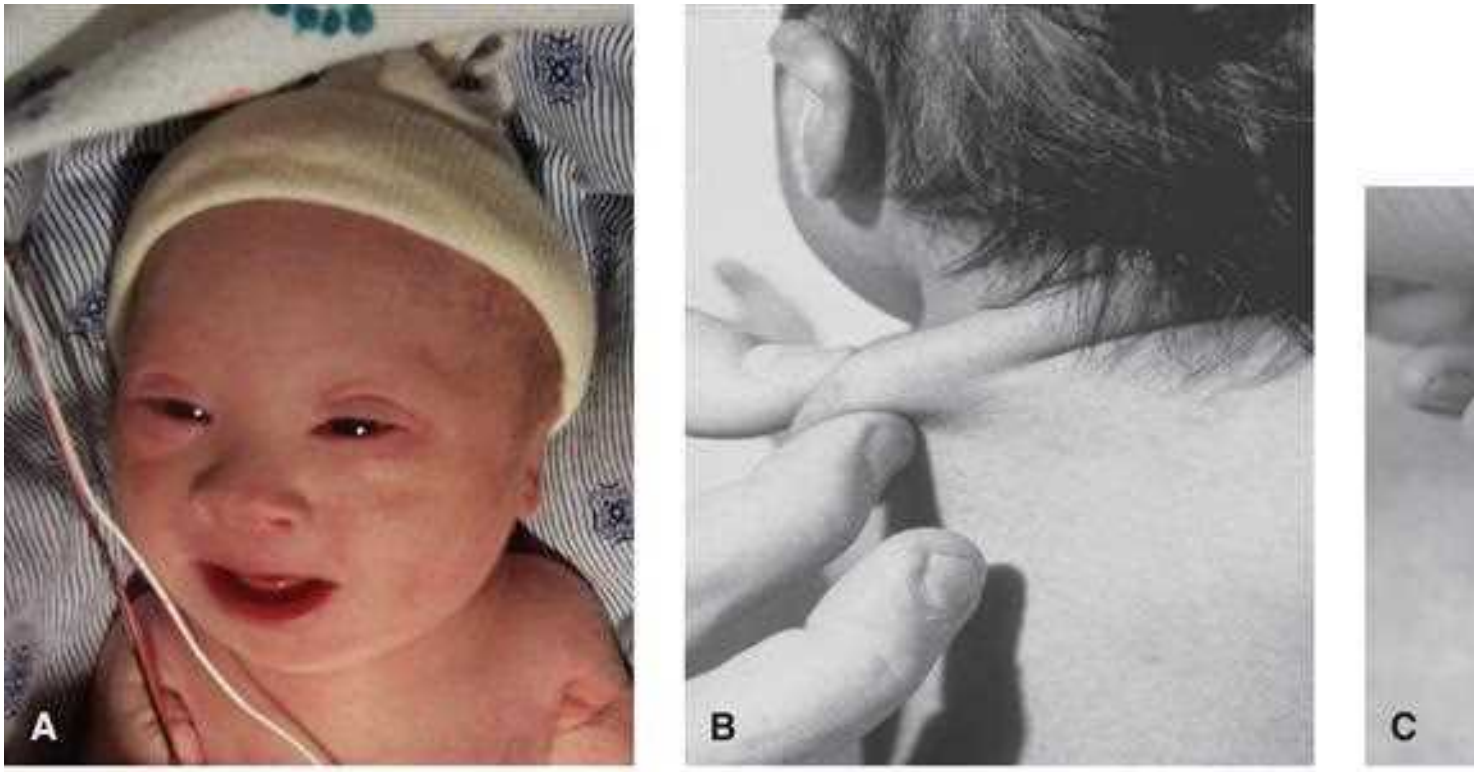
Notably, adult women with Down syndrome are fertile, and a third of their offspring will have Down syndrome (Scharrer, 1975). Males with Down syndrome are almost always sterile because of markedly reduced spermatogenesis.

Approximately 30 percent of second-trimester fetuses with Down syndrome have a major malformation that can be identified sonographically (Hussamy, 2017; Vintzileos, 1995). As discussed in Chapter 14 (Sonographic Screening), when both major anomalies and minor aneuploidy markers are considered, an estimated 50 to 60 percent of Down syndrome pregnancies can be detected sonographically (American College of Obstetricians and Gynecologists, 2016d). Approximately half of liveborn neonates with Down syndrome are found to have cardiac defects, particularly ventricular septal defects and endocardial cushion defects (Figs. 10-29 and 10-30) (Bergstrom, 2016; Freeman, 2008). Gastrointestinal abnormalities are identified in 12 percent and include esophageal atresia, Hirschsprung disease, and duodenal atresia (Fig. 10-38) (Bull, 2011).

Characteristic features of Down syndrome are shown in Figure 13-4. Typical findings include brachycephaly; epicanthal folds and up-slanting palpebral fissures; Brushfield spots, which are grayish spots on the periphery of the iris; a flat nasal bridge; and hypotonia. Infants often have loose skin at the nape of the neck, short fingers, a single palmar crease, hypoplasia of the middle phalanx of the fifth finger, and a prominent space or "sandal-toe gap" between the first and second toes. Some of these findings are prenatal sonographic markers for Down syndrome, reviewed in Chapter 14 (Sonographic Screening).

FIGURE 13-4

Trisomy 21—Down syndrome. **A.** Characteristic facial appearance. **B.** Redundant nuchal tissue. **C.** Single transverse palmar crease. (Used with permission from Dr. Charles P. Read and Dr. Lewis Waber.)



Health problems common in children with Down syndrome include hearing loss in 75 percent, severe optical refractive errors in 50 percent, cataracts in 15 percent, obstructive sleep apnea in 60 percent, thyroid disease in 15 percent, and a higher incidence of leukemia (Bull, 2011). The degree of mental impairment is usually mild to moderate, with an average intelligence quotient (IQ) score of 35 to 70. Social skills in affected children are often higher than predicted by their IQ scores.

Data suggest that approximately 95 percent of liveborn infants with Down syndrome survive the first year. The 10-year survival rate is at least 90 percent overall and is 99 percent if major malformations are absent (Rankin, 2012; Vendola, 2010). Several organizations offer education and support for prospective parents faced with prenatal diagnosis of Down syndrome. These include the March of Dimes, National Down Syndrome Congress (www.ndsccenter.org), and National Down Syndrome Society (www.ndss.org).

Trisomy 18—Edwards Syndrome

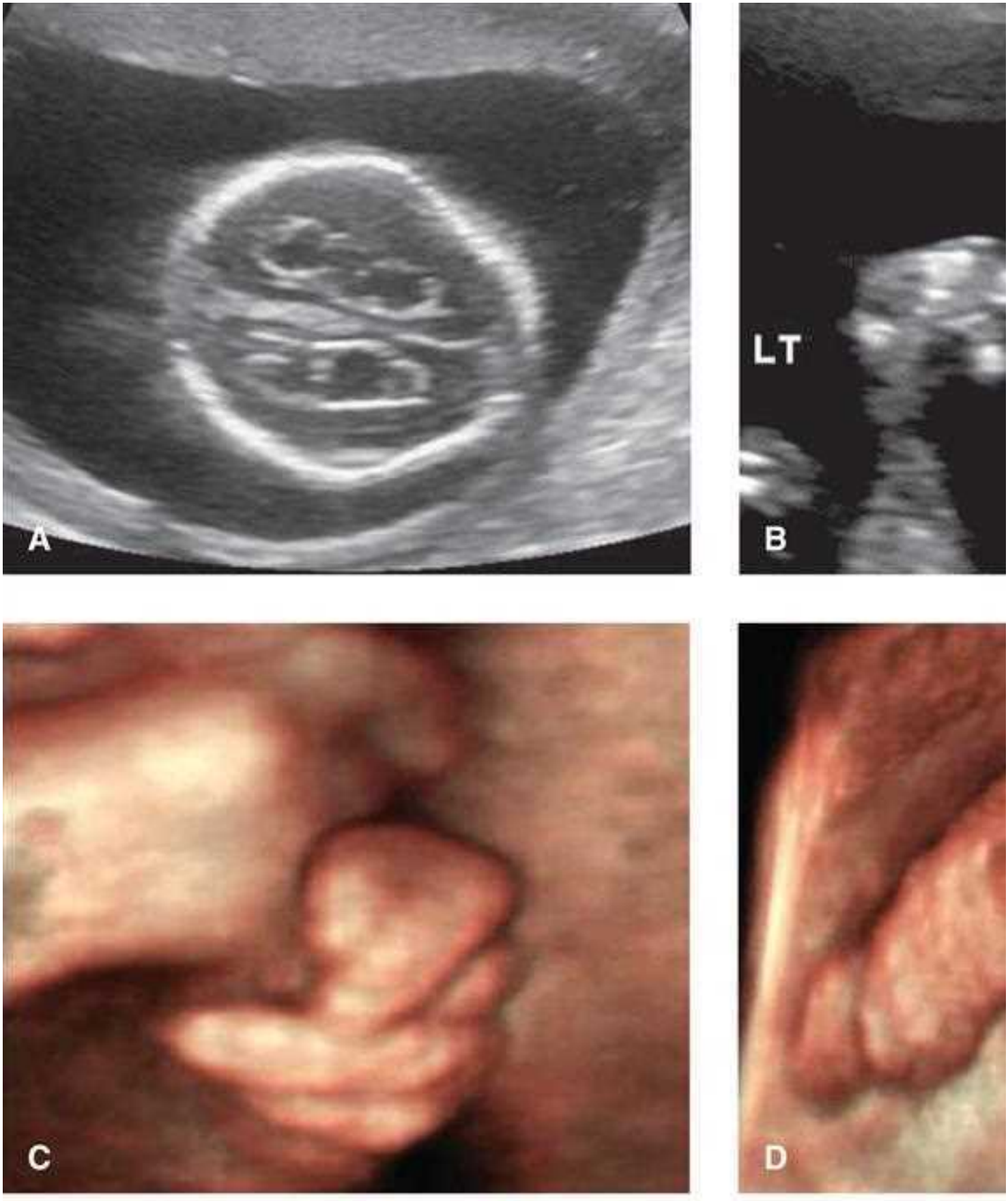
The association between this constellation of abnormalities and an autosomal trisomy was first described by Edwards (1960). In population-based series, prevalence of trisomy 18 approximates 1 in 2000 recognized pregnancies—including abortuses, stillbirths, and live births, and approximately 1 in 6600 liveborn neonates (Loane, 2013; Parker, 2010). The difference in prevalence is explained by the high in-utero lethality of the condition and the termination of many affected pregnancies. Perhaps not surprisingly, survival of liveborn neonates is likewise bleak. More than half die within the first week, and the 1-year survival rate approximates only 2 percent (Tennant, 2010; Vendola, 2010). The syndrome is three- to fourfold more common in females (Lin, 2006; Rosa, 2011). Unlike Down and Patau syndromes, which involve acrocentric chromosomes and thus may stem from a robertsonian translocation, Edwards syndrome uncommonly results from a chromosomal rearrangement.

Virtually every organ system can be affected by trisomy 18. Common major anomalies include heart defects in more than 90 percent—particularly ventricular septal defects, as well as cerebellar vermian agenesis, myelomeningocele, diaphragmatic hernia, omphalocele, imperforate anus, and renal anomalies such as horseshoe kidney (Lin, 2006; Rosa, 2011; Yeo, 2003). Sonographic images of several of these are shown in Chapter 10.

Cranial and extremity abnormalities are also frequent and include a prominent occiput, posteriorly rotated and malformed ears, micrognathia, clenched hands with overlapping digits, radial aplasia with hyperflexion of the wrists, and rockerbottom or clubbed feet (Fig. 13-5). A “strawberry-shaped” cranium is noted in approximately 40 percent of cases, abnormally wide cavum septum pellucidum in more than 90 percent, and choroid plexus cysts in up to 50 percent (Abele, 2013; Yeo, 2003). Importantly, isolated choroid plexus cysts are not associated with trisomy 18. These cysts only raise the risk for trisomy 18 if fetal structural abnormalities or an abnormal aneuploidy screening test result is also present (Reddy, 2014).

FIGURE 13-5

Trisomy 18—Edwards Syndrome. **A.** This transventricular sonographic view shows fetal choroid plexus cysts and an angulated “strawberry-shaped” skull. **B.** Radial clubhand is manifested as a single forearm bone (radius), with the hands in a fixed, hyperflexed position at right angles to the forearms. **C.** This three-dimensional (3-D) sonographic image shows the characteristic hand position of clenched fists with overlapping digits. **D.** 3-D sonographic image displays a rockerbottom foot.



Pregnancies with trisomy 18 that reach the third trimester often develop fetal-growth restriction, and the mean birthweight is <2500 g (Lin, 2006; Rosa, 2011). Because abnormal fetal heart rate tracings are common during labor, mode of delivery and management of heart rate abnormalities should be discussed in advance. In older reports, more than half of undiagnosed fetuses underwent cesarean delivery for “fetal distress” (Schneider, 1981).

Trisomy 13—Patau Syndrome

This constellation of fetal abnormalities and their association with an autosomal trisomy was first described by Patau and colleagues (1960). The prevalence of trisomy 13 approximates 1 in 12,000 live births and 1 in 5000 recognized pregnancies, which includes abortuses and stillbirths (Loane, 2013; Parker, 2010). As with trisomy 18, trisomy 13 is highly lethal, and most affected fetuses are lost or terminated.

Approximately 80 percent of pregnancies with Patau syndrome result from trisomy 13. The remainder is caused by a robertsonian translocation involving chromosome 13. The most frequent structural chromosomal rearrangement is a translocation between chromosomes 13 and 14, der(13;14)(q10;q10). This translocation is carried by approximately 1 in 1300 individuals, although the risk of an affected liveborn neonate is less than 2 percent (Nussbaum, 2007).

Trisomy 13 is associated with abnormalities of virtually every organ system. One characteristic finding is holoprosencephaly (Fig. 10-15). This is present in approximately two thirds of cases and may be accompanied by microcephaly, hypotelorism, and nasal abnormalities that range from a single nostril to a proboscis. Cardiac defects are found in up to 90 percent of fetuses with trisomy 13 (Shipp, 2002). Other abnormalities that suggest trisomy 13 include neural-tube defects—particularly cephalocele, microphthalmia, cleft lip-palate, omphalocele, cystic renal dysplasia, polydactyly, rockerbottom feet, and areas of skin aplasia (Lin, 2007). For the fetus or newborn with a cephalocele, cystic kidneys, and polydactyly, the differential diagnosis includes trisomy 13 and the autosomal-recessive Meckel-Gruber syndrome. Sonographic images of several of these are shown in Chapter 10 (Neural-Tube Defects).

Few fetuses with trisomy 13 survive until birth. Of those that do, the 1-week survival rate approximates 40 percent, and 1-year survival rate is only about 3 percent (Tennant, 2010; Vendola, 2010). Counseling regarding prenatal diagnosis and management options is similar to that described for trisomy 18.

Unlike other aneuploidies, fetal trisomy 13 confers risk to the pregnant woman. Hyperplacentosis and preeclampsia develop in up to half of pregnancies with trisomy 13 carried beyond the second trimester (Tuohy, 1992). Chromosome 13 contains the gene for soluble fms-like tyrosine kinase-1 (sFlt-1), which is an antiangiogenic protein associated with preeclampsia (Chap. 40, Endothelial Cell Injury). Investigators have documented overexpression of the sflt-1 protein by trisomic 13 placentas and in serum of women with preeclampsia (Bdolah, 2006; Silasi, 2011).

Other Trisomies

In the absence of mosaicism, discussed later (Chromosomal Mosaicism), other autosomal trisomies rarely yield a liveborn neonate. Case of live births with trisomy 9 and with trisomy 22 have been noted (Kannan, 2009; Tinkle, 2003). Trisomy 16 is the most common trisomy found with first-trimester losses and accounts for 16 percent of these losses. However, it is not identified later in gestation. Trisomy 1 has never been reported.

Monosomy

Nondisjunction creates an equal number of nullisomic and disomic gametes. As a rule, missing chromosomal material is more devastating than extra chromosomal material, and almost all monosomic conceptuses are lost before implantation. The one exception is monosomy for the X chromosome (45,X), Turner syndrome, which is discussed subsequently. Despite the strong association between maternal age and trisomy, maternal age and monosomy are not linked.

Polyploidy

This is an abnormal number of complete haploid chromosomal sets. Polyploidy accounts for approximately 20 percent of spontaneous abortions but is rare in later gestations.

Triploid pregnancies have three haploid sets—69 chromosomes. One parent must contribute two sets, and the phenotypic presentation differs according to the parent of origin. With *diandric triploidy*, also known as type I triploidy, the extra chromosomal set is paternal, resulting from fertilization of one egg by two sperm or by a single diploid—and thus abnormal—sperm. Diandric triploidy produces a partial molar pregnancy, discussed in Chapter 20 (Epidemiology and Risk Factors). Diandric triploidy accounts for most triploid conceptions, but their first-trimester loss rate is extremely high. As a result, two thirds of triploid pregnancies identified beyond the first trimester are caused instead by *digynic triploidy* (Jauniaux, 1999). With a digynic triploid pregnancy, also known as type II triploidy, the extra chromosomal set is maternal, and the egg fails to undergo the first or second meiotic division before fertilization. Digynic triploid placentas do not develop molar changes. However, the fetus usually displays asymmetrical growth restriction.

The prevalence of recognized triploid pregnancies approximates 1 in 5000 pregnancies (Zalel, 2016). Triploidy is a lethal aneuploidy, and more than 90 percent of fetuses with either the diandric or digynic form have multiple structural anomalies. These include central nervous system defects—particularly involving the posterior fossa, as well as cardiac, renal, and extremity anomalies (Jauniaux, 1999; Zalel, 2016). Counseling, prenatal diagnosis, and delivery options are similar to those for trisomies 18 and 13. The recurrence risk for a woman whose triploid fetus survived past the first trimester is 1 to 1.5 percent, and thus prenatal diagnosis is offered in future pregnancies (Gardner, 1996).

Tetraploid pregnancies have four haploid sets of chromosomes, resulting in either 92,XXXX or 92,XXYY. This suggests a postzygotic failure to complete an early cleavage division. The conceptus invariably succumbs, and the recurrence risk is minimal.

Sex Chromosome Abnormalities

45, X—Turner Syndrome

First described by Turner (1938), this syndrome later was found to be caused by monosomy X (Ford, 1959). The prevalence of Turner syndrome is approximately 1 in 2500 liveborn girls (Cragan, 2009; Dolk, 2010). The missing X chromosome is paternally derived in 80 percent of cases (Cockwell, 1991; Hassold, 1990). Screening for Turner syndrome with cell-free DNA is discussed in Chapter 14 (Cell-Free DNA Screening).

Turner syndrome is the only monosomy compatible with life, but it is also the most common aneuploidy in first-trimester losses, accounting for 20 percent. This is explained by the wide range in phenotype. Approximately 98 percent of affected conceptuses are so abnormal that they abort early in the first trimester. Of the remainder, many manifest large, septated cystic hygromas in the late first or early second trimester (Fig. 10-22). When cystic hygromas are accompanied by hydrops

fetalis, fetuses nearly always die in utero (Chap 15, Hydrops Fetalis). Less than 1 percent of pregnancies with Turner syndrome yield a liveborn neonate. And, only half of these actually have monosomy X. Approximately a fourth have mosaicism, such as 45,X/46,XX or 45,X/46,XY, and another 15 percent have isochromosome X, that is, 46,X,i(Xq)(Milunsky, 2004; Nussbaum, 2007).

Abnormalities associated with Turner syndrome include left-sided cardiac defects—such as coarctation of the aorta, hypoplastic left heart syndrome, or bicuspid aortic valve—in 30 to 50 percent; renal anomalies, particularly horseshoe kidney; and hypothyroidism. Other features are short stature, broad chest with widely spaced nipples, congenital lymphedema—puffiness over the dorsum of hands and feet, and a "webbed" posterior neck resulting from cystic hygromas. Intelligence scores are generally in the normal range, but affected individuals are at risk for difficulties with visual-spatial organization, nonverbal problem solving, and interpretation of social cues (Jones, 2006). Growth hormone is typically administered in childhood to ameliorate short stature (Kappelgaard, 2011). More than 90 percent have ovarian dysgenesis and require estrogen repletion starting just before adolescence. An exception is mosaicism involving the Y chromosome, as this confers risk for germ cell neoplasm—regardless of whether the child is phenotypically male or female. Accordingly, eventual prophylactic bilateral gonadectomy is indicated (Cools, 2011; Schorge, 2016).

47,XXX

Approximately 1 in 1000 female newborns has an additional X chromosome—47,XXX. The extra X is maternally derived in more than 90 percent of cases (Milunsky, 2004). Affected infants do not have a characteristic appearance, and in the past most children did not come to attention until school age. However, the incidence of 47,XXX is weakly associated with maternal age, and cell-free DNA screening has resulted in increased diagnoses (Table 14-5). Frequent features include tall stature, hypertelorism, epicanthal folds, kyphoscoliosis, clinodactyly, and hypotonia (Tartaglia, 2010; Wigby, 2016). More than a third are diagnosed with a learning disability, half have attention deficit disorder, and overall cognitive scores are in the low-average range. No specific pattern of malformations has been described, but genitourinary problems and seizure disorders are more common (Wigby, 2016). Pubertal development is unaffected. Primary ovarian insufficiency has been reported (Holland, 2001). Because of variable presentation and subtle abnormal findings, it is estimated that this diagnosis is ascertained clinically in only 10 percent of affected children.

Females with two or more extra X chromosomes—48,XXXX or 49,XXXXX—are likely to have physical abnormalities apparent at birth. These abnormal X complements are associated with intellectual disability. For both males and females, the IQ score is lower with each additional X chromosome.

47,XXY—Klinefelter Syndrome

This is the most common sex chromosome abnormality and found in approximately 1 in 600 male infants. The additional X chromosome is maternally or paternally derived with equal propensity (Jacobs, 1995; Lowe, 2001). The association with either advanced maternal or paternal age is weak (Milunsky, 2004).

Like 47,XXX, newborns with 47,XXY usually appear phenotypically normal and do not have a higher incidence of anomalies. As children, boys are typically taller than average and have normal prepubertal development. However, they have gonadal dysgenesis, do not undergo normal virilization, and require testosterone supplementation beginning in adolescence. They may develop gynecomastia. IQ scores usually lie in the average to low-average range, and many have delays in language development and reading (Boada, 2009; Girardin, 2011).

47,XYY

This aneuploidy occurs in approximately 1 in 1000 male newborns. As with 47,XXX and XXY individuals, affected boys tend to be tall. A third have macrocephaly, nearly two thirds demonstrate hypotonia, and tremors are also common (Bardsley, 2013). Rates of major anomalies are not elevated, although hypertelorism and clinodactyly may be identified in more than half. Pubertal development is normal, and fertility is unimpaired. Affected children carry risks for oral and written language impairments, attention deficit disorder is diagnosed in more than half, and the rate of autism spectrum disorder is also increased (Bardsley, 2013; Ross, 2009). Intelligence scores generally lie in the normal range.

Males with more than two Y chromosomes—48,XYYY—or with both additional X and Y chromosomes—48,XXYY or 49,XXXYY—are more likely to have congenital abnormalities, medical problems, and intellectual disability (Tartaglia, 2011).

Abnormalities of Chromosome Structure

Structural chromosomal abnormalities include deletions, duplications, translocations, isochromosomes, inversions, ring chromosomes, and mosaicism (see Table 13-1). Their overall birth prevalence approximates 0.3 percent (Nussbaum, 2007). Identification of a structural chromosomal abnormality raises two primary questions. First, what phenotypic abnormalities or later developmental abnormalities are associated with this finding? Second, is evaluation of parental karyotype indicated—specifically, are the parents at increased risk of carrying this abnormality? If so, what is their risk of having future affected offspring?

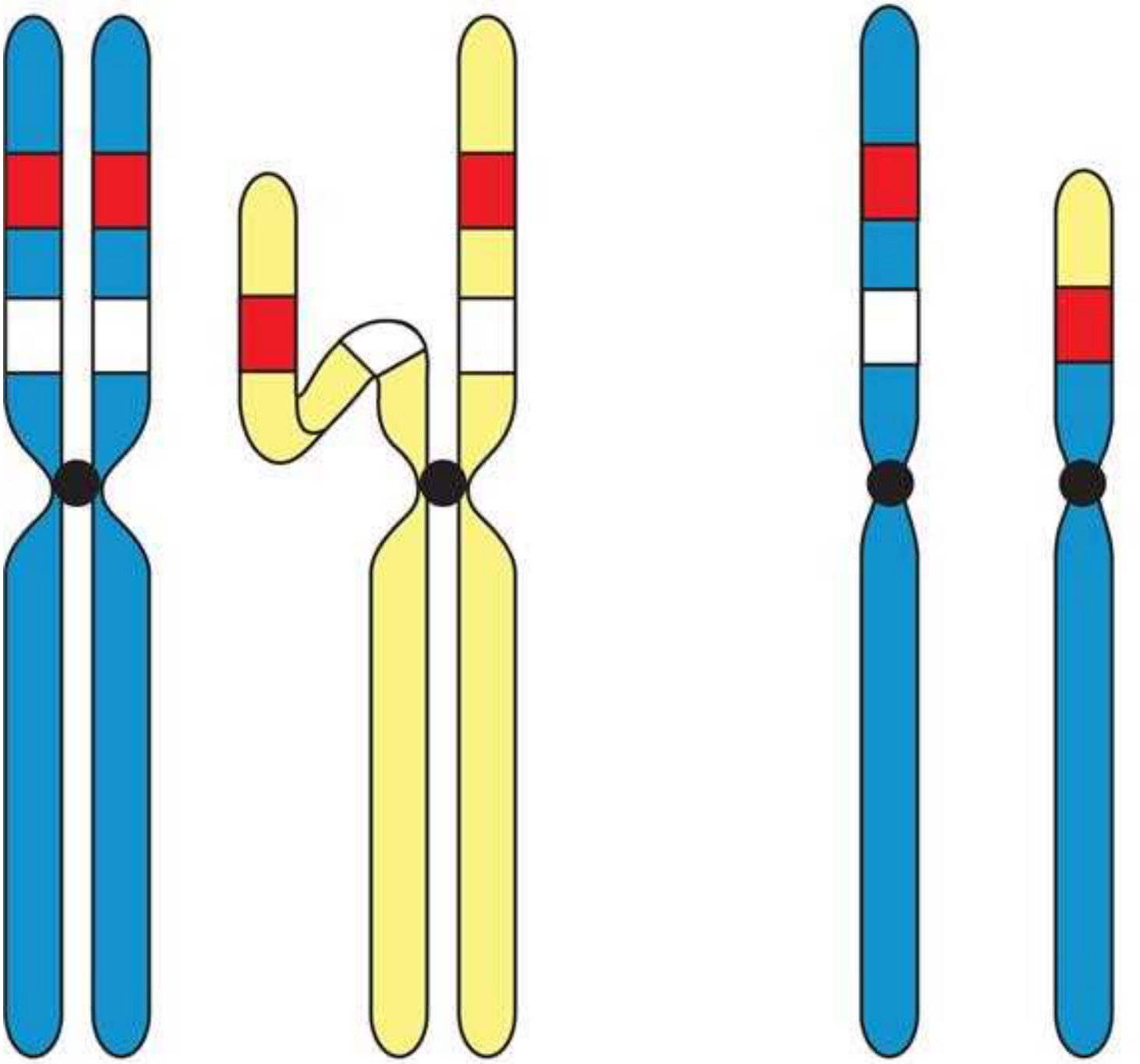
Deletions and Duplications

A chromosomal deletion indicates that a portion of a chromosome is missing, whereas a duplication means that a portion has been included twice. Most deletions and duplications occur during meiosis and result from malalignment or mismatching during the pairing of homologous chromosomes. The misaligned segment may then be deleted, or if the mismatch remains when the two chromosomes recombine, it may result in a deletion in one chromosome and duplication in the other (Fig. 13-6). When a deletion or duplication is identified in a fetus or infant, parental karyotyping should be offered, because if either parent carries a balanced translocation, the recurrence risk in subsequent pregnancies is significantly increased. Deletions involving DNA segments large enough to be seen with standard cytogenetic karyotyping are identified in approximately 1 in 7000 births (Nussbaum, 2007). Common deletions may be referred to by eponyms—for example, del 5p is called *cri du chat syndrome*.

FIGURE 13-6

A mismatch during pairing of homologous chromosomes may lead to a deletion in one chromosome and a duplication in the other. Del = deletion; Dupl = duplication.

Meiosis I



Normal Del

Microdeletions and Microduplications

These chromosomal deletions or duplications—smaller than 3 to 5 million base pairs—are too small to be detected with standard karyotyping. However, prenatal chromosomal microarray analysis (CMA), described later (Chromosomal Microarray Analysis), permits identification of syndromes associated with these microdeletion or duplications. When CMA is used, the region of DNA that is missing or duplicated is termed a *genomic copy number variant*. Despite the relatively small size, a microdeletion or duplication may involve a stretch of DNA that contains multiple genes—causing a *contiguous gene syndrome*, which can encompass serious but unrelated phenotypic abnormalities (Schmickel, 1986). In some cases, a microduplication may involve the exact DNA region that causes a recognized microdeletion syndrome (Table 13-2). When a specific microdeletion syndrome is suspected clinically, it is confirmed using either CMA or fluorescence in situ hybridization.

TABLE 13-2

Selected Microdeletion Syndromes

Syndrome	Prevalence	Location	Features
Alagille	1:70,000	20p12.2	Cholestasis (paucity of intrahepatic bile ducts), cardiac disease, skeletal disease, ocular abnormalities, dysmorphic facies
Angelman	1:12,000 to 1:20,000	15q11.2–q13 (maternal genes)	Dysmorphic facies—"happy puppet" appearance, mental retardation, ataxia, hypotonia, seizures
Cri-du-chat	1:20,000 to 1:50,000	5p15.2–15.3	Abnormal laryngeal development with "cat-like" cry, hypotonia, mental retardation
Kallmann syndrome	1:10,000 to 1:86,000	Xp22.3	Hypogonadotropic hypogonadism, anosmia
Langer-Giedion	Rare	8q23.3	Trichorhinophalangeal syndrome, dysmorphic facies, sparse hair, redundant skin, mental retardation
Miller-Dieker	Rare	17p13.3	Neuronal migration abnormalities with lissencephaly, microcephaly, dysmorphic facies
Prader-Willi	1:10,000 to 1:30,000	15q11.2–q13 (paternal genes)	Obesity, hypotonia, mental retardation, hypogonadotropic hypogonadism, small hands and feet
Retinoblastoma	1:280,000	13q14.2	Retinoblastoma, retinoma (benign neoplasm), non-retinal (second primary) tumors
Rubenstein-Taybi	1:100,000 to 1:125,000	16p13.3	Dysmorphic facies, broad thumbs/toes, mental retardation, increased tumor risk
Smith-Magenis	1:15,000 to 1:25,000	17p11.2	Dysmorphic facies, speech delay, hearing loss, sleep disturbances, self-destructive behaviors
Velocardiofacial/DiGeorge/Shprintzen	1:4,000	22q11.2	Conotruncal cardiac defects, cleft palate, velopharyngeal incompetence, thymic and parathyroid abnormalities, developmental delay
WAGR	1:500,000	11p13	Wilms tumor, aniridia, genitourinary anomalies (including ambiguous genitalia), mental retardation
Williams-Beuren	1:7500 to 1:10,000	7q11.23	Dysmorphic facies, dental malformation, mental retardation, aortic and peripheral pulmonary artery stenosis
Wolf-Hirschhorn	1:20,000 to 1:50,000	4p16.3	Dysmorphic facies, delayed growth and development, cleft lip/palate, coloboma, cardiac septal defects
X-linked ichthyosis	1:6,000	Xp22.3	Steroid sulfatase deficiency, corneal opacities

Prevalence reflects live births.

Data from National Library of Medicine, 2017; Johns Hopkins University, 2017.

22q11.2 Microdeletion Syndrome

This syndrome is also known as DiGeorge syndrome, Shprintzen syndrome, and velocardiofacial syndrome. It is the most common microdeletion, with a prevalence of 1 in 3000 to 6000 births. Although inherited in an autosomal dominant fashion, more than 90 percent of cases arise from de novo mutations. The full deletion

includes 3 million base pairs, encompasses 40 genes, may include 180 different features, and thus poses some counseling challenges (Shprintzen, 2008). Features can vary widely, even among affected family members. Previously, different constellations of features were thought to characterize the DiGeorge and Shprintzen phenotypes, but it is now accepted that they represent the same microdeletion (McDonald-McGinn, 2015).

In approximately 75 percent of affected individuals, associated abnormalities include conotruncal cardiac anomalies, such as tetralogy of Fallot, truncus arteriosus, interrupted aortic arch, and ventricular septal defects (McDonald-McGinn, 2015). Immune deficiency, such as T-cell lymphopenia, also develops in approximately 75 percent. More than 70 percent have velopharyngeal insufficiency or cleft palate. Learning disabilities, autism spectrum disorder, and intellectual disability are also common. Other manifestations include hypocalcemia, renal anomalies, esophageal dysmotility, hearing loss, behavioral disorders, and psychiatric illness—particularly schizophrenia. Short palpebral fissures, bulbous nasal tip, micrognathia, short philtrum, and small or posteriorly rotated ears are characteristic facial features.

Chromosomal Translocations

These are DNA rearrangements in which a segment of DNA breaks away from one chromosome and attaches to another. The rearranged chromosomes are called derivative (der) chromosomes. There are two types—reciprocal and robertsonian translocations.

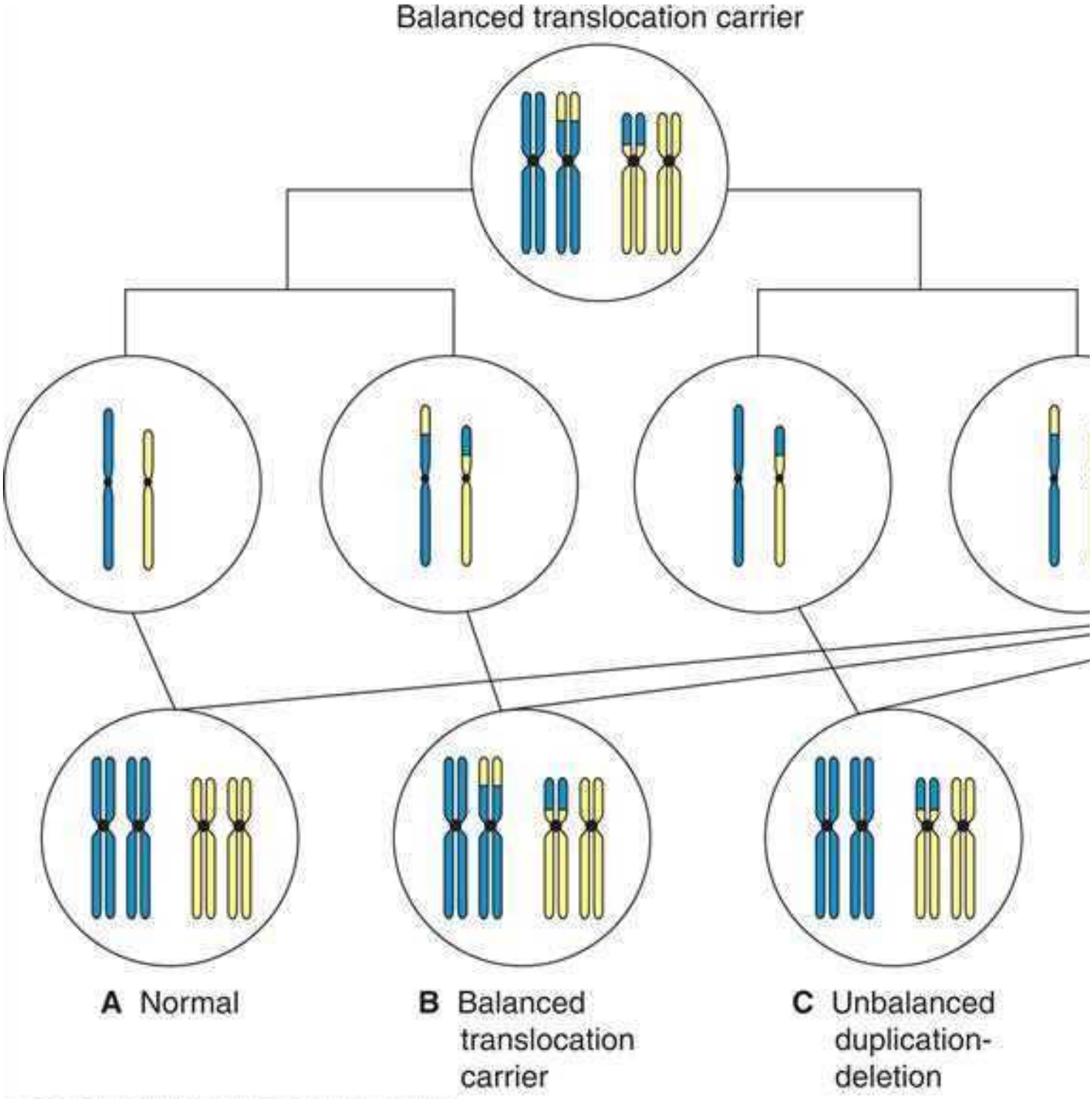
Reciprocal Translocations

A double-segment or reciprocal translocation begins when breaks occur in two different chromosomes. The broken fragments are then exchanged, so that each affected chromosome contains a fragment of the other. If no chromosomal material is gained or lost in this process, the translocation is considered balanced. The prevalence of reciprocal translocations approximates 1 in 600 births (Nussbaum, 2007). Although the balanced translocation carrier is usually normal phenotypically, repositioning of specific genes within chromosomal segments can cause abnormalities. The risk of a major structural or developmental abnormality in an apparent balanced translocation carrier is approximately 6 percent. Interestingly, using CMA technology, up to 20 percent of individuals who appear to have a balanced translocation are found instead to have missing or redundant DNA segments (Manning, 2010).

Balanced translocation carriers are at risk to produce unbalanced gametes, resulting in abnormal offspring. As shown in Figure 13-7, if an oocyte or sperm contains a translocated chromosome, fertilization results in an unbalanced translocation—monosomy for part of one affected chromosome and trisomy for part of the other. The observed risk of a specific translocation can often be estimated by a genetic counselor. In general, translocation carriers identified after the birth of an abnormal child have a 5- to 30-percent risk of producing liveborn offspring with an unbalanced translocation. Carriers identified for other reasons, for example, during an infertility evaluation, have only a 5-percent risk. This is likely because the gametes are so abnormal that conceptions are nonviable.

FIGURE 13-7

A carrier of a balanced translocation may produce offspring who are also carriers of the balanced rearrangement **(B)**, offspring with unbalanced translocations **(C, D)**, or offspring with normal chromosomal complements **(A)**.



Robertsonian Translocations

These involve only *acrocentric* chromosomes, which are chromosomes 13, 14, 15, 21, and 22. The acrocentric chromosomes have extremely short p arms. In a robertsonian translocation, the q arms of two acrocentric chromosomes fuse at one centromere to form a derivative chromosome. The other centromere and both sets of p arms are lost. Because the number of centromeres determines the chromosome count, a robertsonian translocation carrier has only 45 chromosomes. Fortunately, the p arms of the acrocentric chromosomes—the satellite regions—contain redundant copies of genes that code for ribosomal RNA. As these are present in multiple copies on other acrocentric chromosomes, their loss does not affect the translocation carrier, who is usually phenotypically normal. However, when the derivative chromosome is paired during fertilization with a haploid chromosome from the partner, resulting offspring will be trisomic for that chromosome.

Robertsonian translocations are found in 1 in 1000 individuals. The incidence of abnormal offspring approximates 15 percent if a robertsonian translocation is carried by the mother and 2 percent if carried by the father. Robertsonian translocations are not a major cause of miscarriage and are found in fewer than 5 percent of couples with recurrent pregnancy loss. When a fetus or child is found to have a translocation trisomy, both parents should be offered karyotype analysis. If neither parent is a carrier, the recurrence risk is extremely low.

Balanced robertsonian carriers have reproductive difficulties for a number of reasons. If the fused chromosomes are homologous, that is, from the same chromosome pair, the carrier can produce only unbalanced gametes. Each egg or sperm contains either both copies of the translocated chromosome, which would result in trisomy if fertilized, or no copy, which would result in monosomy. If the fused chromosomes are nonhomologous, four of the six possible gametes would be abnormal. The most common robertsonian translocation is der(13;14)(q10;q10), which accounts for up to 20 percent of cases of Patau syndrome (Trisomy 18—Edwards Syndrome).

Isochromosomes

These abnormal chromosomes are composed of either two q arms or two p arms of one chromosome fused together. Isochromosomes are thought to arise when the centromere breaks transversely instead of longitudinally during meiosis II or mitosis. They can also result from a meiotic error in a chromosome with a robertsonian translocation. An isochromosome containing the q arms of an acrocentric chromosome behaves like a homologous robertsonian translocation, and such a carrier can produce only abnormal unbalanced gametes. When an isochromosome involves nonacrocentric chromosomes, with p arms containing important genetic material, the fusion and abnormal centromere break results in two isochromosomes. One is composed of both p arms, and one is composed of both q arms. It is likely that one of these isochromosomes would be lost during cell division, resulting in the deletion of all the genes located on the lost arm. Thus, a carrier is usually phenotypically abnormal and produces abnormal gametes. The most common isochromosome involves the long arm of the X chromosome, i(Xq), which is the etiology of 15 percent of cases of Turner syndrome.

Chromosomal Inversions

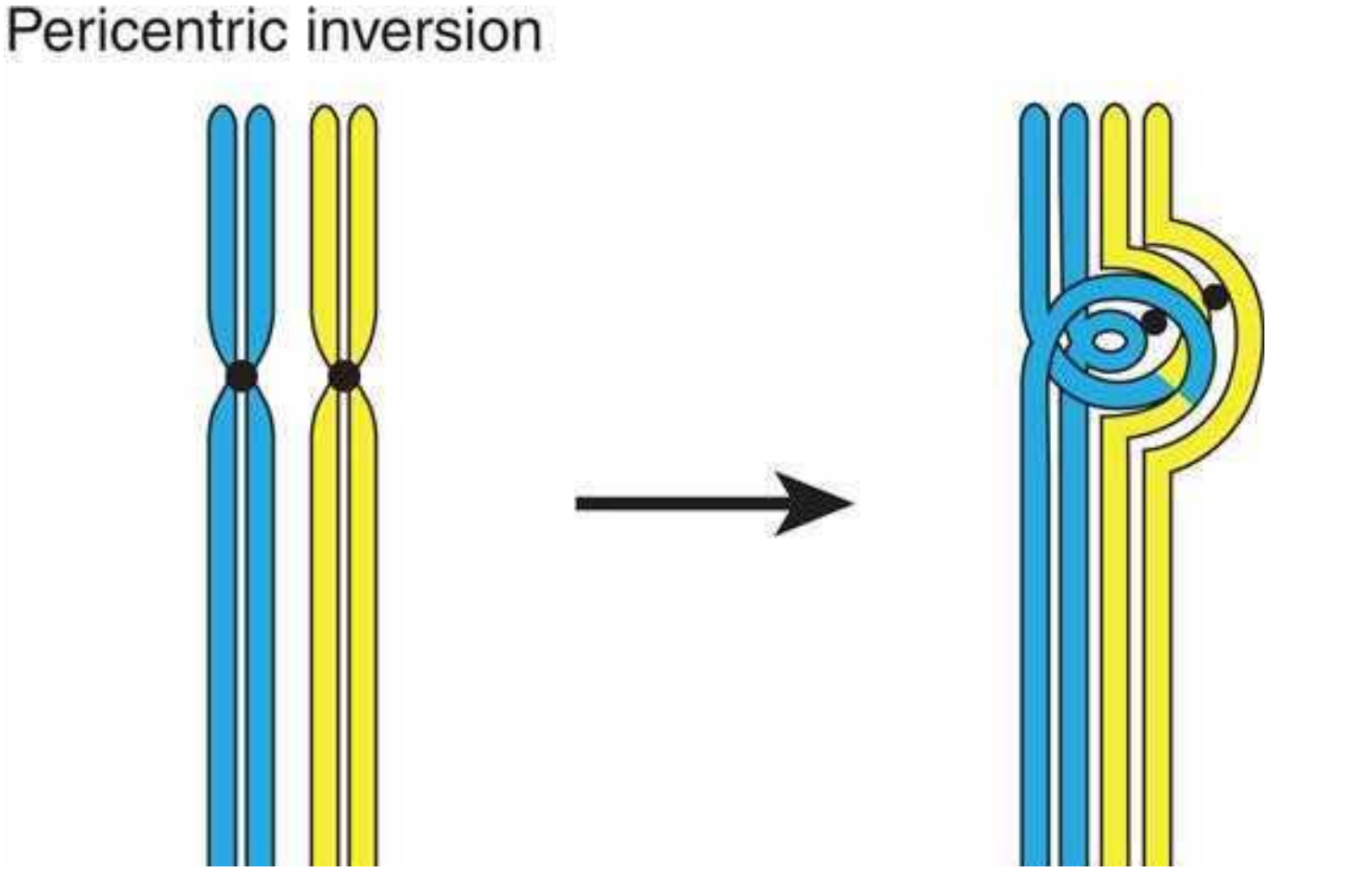
When there are two breaks in the same chromosome, and the intervening genetic material is inverted before the breaks are repaired, the result is a chromosomal inversion. Although no genetic material is lost or duplicated, the rearrangement may alter gene function. There are two types—pericentric and paracentric inversions.

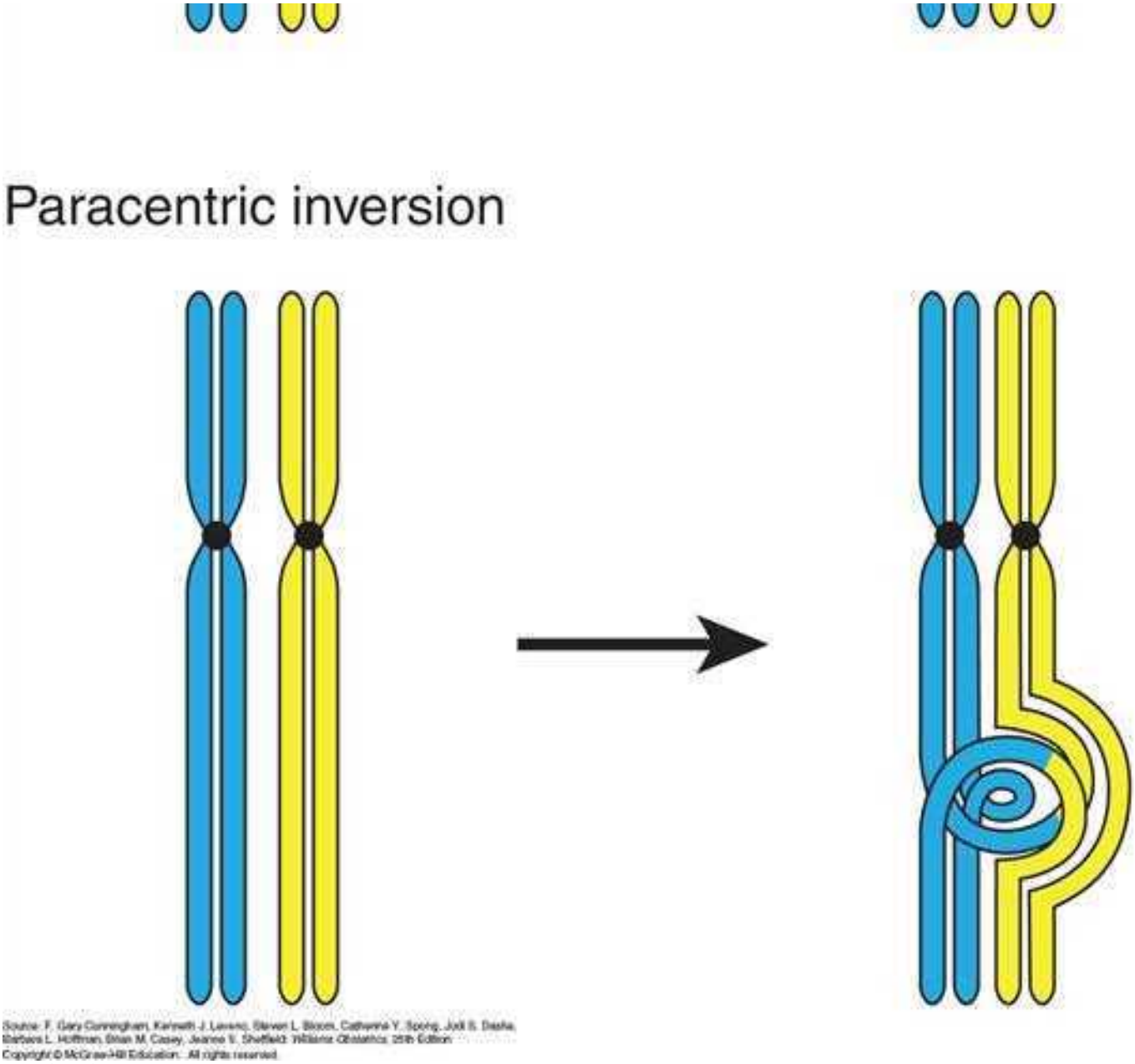
Pericentric Inversion

This results from breaks in both the p and q arms of a chromosome, such that the inverted material includes the centromere (Fig. 13-8). A pericentric inversion causes problems in chromosomal alignment during meiosis and confers significant risk for the carrier to produce abnormal gametes and abnormal offspring. In general, the observed risk of abnormal offspring in a pericentric inversion carrier is 5 to 10 percent if ascertainment was made after the birth of an abnormal child. But the risk is only 1 to 3 percent if prompted by another indication. An important exception is a pericentric inversion on chromosome 9. This is inv(9)(p11q12), which is a normal variant present in approximately 1 percent of the population.

FIGURE 13-8

Mechanism of meiosis in the setting of either pericentric inversion (one involving the centromere) or paracentric inversion (not involving the centromere). Individuals with pericentric inversions are at increased risk for producing offspring with a duplication/deletion. Those with paracentric inversions are at increased risk for early pregnancy loss.





Paracentric Inversion

If there are two breaks within one arm of a chromosome—either p or q—the inverted material does not include the centromere, and the inversion is paracentric (see Fig. 13-8). The carrier makes either normal balanced gametes or gametes that are so abnormal as to preclude fertilization. Thus, although infertility may be a problem, the risk of having an abnormal offspring is extremely low.

Ring Chromosome

If there are deletions at each end of the same chromosome, the ends may come together to form a ring chromosome. The telomere regions, which are the ends of a chromosome, contain specialized nucleoprotein complexes that stabilize the chromosome. If just the telomeres are lost, all necessary genetic material is retained, and the carrier is essentially balanced. If a deletion extends more proximally than the telomere, the carrier is likely to be phenotypically abnormal. An example of this is a ring X chromosome, which may result in Turner syndrome.

Chromosomal Mosaicism

A mosaic individual has two or more cytogenetically distinct cell lines that are derived from a single zygote. Phenotypic expression of mosaicism depends on several factors, including whether the cytogenetically abnormal cells involve the fetus, part of the fetus, just the placenta, or some combination. Of amnionic fluid cultures, mosaicism is found in approximately 0.3 percent but may not reflect the fetal chromosomal complement (Carey, 2014). When the abnormal cells are present in only a single flask of amnionic fluid, the finding is likely pseudomosaicism, caused by cell-culture artifact (Bui, 1984; Hsu, 1984). When abnormal cells involve multiple cultures, however, true mosaicism is more likely, and further testing may be warranted. A second cell line is verified in 60 to 70 percent of these fetuses (Hsu, 1984; Worton, 1984).

Confined Placental Mosaicism

With chorionic villus sampling, studies demonstrate that up to 2 percent of placentas are mosaic, with the mosaicism confined to the placenta in most of these cases (Baffero, 2012; Henderson, 1996). Amniocentesis should be offered. In a series of more than 1000 pregnancies with mosaicism found from chorionic villus sampling, subsequent amniocentesis identified true fetal mosaicism in 13 percent. Uniparental disomy, discussed later (Imprinting), was found in 2 percent, and the remainder resulted from confined placental mosaicism (Malvestiti, 2015). If mosaicism is detected for a chromosome known to contain imprinted genes—such as chromosomes 6, 7, 11, 14, or 15—testing for uniparental disomy should be considered, as there may be fetal consequences (Grati, 2014a).

Although outcomes with confined placental mosaicism are generally good, fetal-growth restriction is more common, and the stillbirth risk is also higher (Reddy, 2009). Fetal-growth restriction may stem from impaired functioning of the aneuploid placental cells (Baffero, 2012). Placental mosaicism for trisomy 16 confers a particularly poor prognosis.

Gonadal Mosaicism

Mosaicism confined to the gonads likely arises from a mitotic error in cells destined to become the gonad, resulting in a population of abnormal germ cells. Because spermatogonia and oogonia divide throughout fetal life, and spermatogonia continue to divide throughout adulthood, gonadal mosaicism may also follow a meiotic error in previously normal germ cells. Gonadal mosaicism can account for de novo diseases in the offspring of normal parents. Autosomal dominant examples are achondroplasia and osteogenesis imperfecta, and X-linked ones include Duchenne muscular dystrophy. Gonadal mosaicism also explains the 6-percent recurrence risk after the birth of a child with a disease caused by a “new” mutation.

MODES OF INHERITANCE

A monogenic or *mendelian* disorder is caused by a mutation or alteration in a single locus or gene in one or both members of a gene pair. Types of mendelian inheritance include autosomal dominant, autosomal recessive, X-linked, and Y-linked. Other monogenic inheritance patterns, described subsequently, include mitochondrial inheritance, uniparental disomy, imprinting, and trinucleotide repeat expansion—also termed anticipation. By age 25, approximately 0.4 percent of the population exhibits an abnormality attributed to a monogenic disorder, and 2 percent will have at least one such disorder during their lifetime (Table 13-3).

TABLE 13-3

Selected Monogenic (Mendelian) Disorders

Autosomal Dominant
Achondroplasia
Acute intermittent porphyria
Adult polycystic kidney disease
Antithrombin III deficiency
BRCA1 and BRCA2 breast and/or ovarian cancer
Ehlers-Danlos syndrome
Familial adenomatous polyposis
Familial hypercholesterolemia
Hereditary hemorrhagic telangiectasia
Hereditary spherocytosis
Huntington disease
Hypertrophic obstructive cardiomyopathy
Long QT syndrome
Marfan syndrome
Myotonic dystrophy
Neurofibromatosis type 1 and 2
Tuberous sclerosis
von Willebrand disease
Autosomal Recessive
α_1-Antitrypsin deficiency
Congenital adrenal hyperplasia
Cystic fibrosis
Gaucher disease
Hemochromatosis
Homocystinuria
Phenylketonuria
Sickle-cell anemia
Tay-Sachs disease
Thalassemia syndromes
Wilson disease
X-Linked
Androgen insensitivity syndrome
Chronic granulomatous disease
Color blindness
Fabry disease
Fragile X syndrome
Glucose-6-phosphate deficiency
Hemophilia A and B
Hypophosphatemic rickets
Muscular dystrophy—Duchenne and Becker
Ocular albinism type 1 and 2

Relationship between Phenotype and Genotype

When considering inheritance, it is the phenotype that is dominant or recessive, not the genotype. With a dominant disease, the normal gene may direct the production of normal protein, but the phenotype is abnormal because it is determined by protein produced by the abnormal gene. With a recessive disease, a heterozygous carrier may produce detectable levels of an abnormal gene product but have no features of the condition because the phenotype is directed by the product of the normal co-gene. For example, erythrocytes from carriers of sickle-cell anemia contain approximately 30 percent hemoglobin S, but because the other 70 percent is hemoglobin A, these cells do not usually sickle in vitro.

Heterogeneity

Genetic heterogeneity explains how different genetic mechanisms can result in the same phenotype. *Locus heterogeneity* indicates that a specific disease phenotype can be caused by mutations in different genetic loci. It also explains why some diseases appear to follow more than one type of inheritance. An example is retinitis pigmentosa, which may develop following mutations in at least 35 different genes or loci and may result in autosomal dominant, autosomal recessive, or X-linked forms.

Allelic heterogeneity describes how different mutations of the same gene may affect presentation of a particular disease. For example, although only one gene has been associated with cystic fibrosis—the *cystic fibrosis conductance transmembrane regulator* gene—more than 2000 mutations in this gene have been described and result in variable disease severity (Chaps. 14 and 51, Cystic Fibrosis and Sarcoidosis).

Phenotypic heterogeneity explains how different disease states can arise from different mutations in the same gene. As an example, mutations in the *fibroblast growth factor receptor 3 (FGFR3)* gene may result in several different skeletal disorders, including achondroplasia and thanatophoric dysplasia, both of which are discussed in Chapter 10 (Skeletal Abnormalities).

Autosomal Dominant Inheritance

If only one copy of a gene pair determines the phenotype, that gene is considered to be dominant. Carriers have a 50-percent chance of passing on the affected gene with each conception. A gene with a dominant mutation generally specifies the phenotype in preference to the normal gene. That said, not all individuals will necessarily manifest an autosomal dominant condition the same way. Factors that affect the phenotype of an autosomal dominant condition include penetrance, expressivity, and occasionally, presence of codominant genes.

Penetrance

This characteristic describes whether or not a dominant gene is expressed at all. A gene with recognizable phenotypic expression in all individuals is 100-percent penetrant, whereas penetrance is incomplete if some carriers express the gene but some do not. This may be quantitatively expressed—for example, a gene that is expressed in some way in 80 percent of individuals who have that gene is 80-percent penetrant. Importantly, incomplete penetrance explains why some autosomal dominant diseases may appear to "skip" generations.

Expressivity

Individuals with the same autosomal dominant trait may manifest the condition differently, even within the same family. Genes with variable expressivity can produce disease manifestations that range from mild to severe. Examples include neurofibromatosis, tuberous sclerosis, and adult polycystic kidney disease.

Codominant Genes

If two different alleles in a gene pair are both expressed in the phenotype, they are considered to be codominant. Blood type, for example, is determined by expression of dominant A and B red-cell antigens that can be expressed simultaneously. Another example of codominance is the group of genes responsible for hemoglobin production. An individual with one gene directing production of hemoglobin S and the other directing production of hemoglobin C will produce both S and C hemoglobin (Chap. 56, Pregnancy and Sickle-Cell Syndromes).

Advanced Paternal Age

Paternal age older than 40 is associated with increased risk for spontaneous genetic mutations, particularly single base substitutions. This may result in offspring with new autosomal dominant disorders or X-linked carrier states. In particular, advanced paternal age has been associated with mutations in the *fibroblast growth factor receptor 2 (FGFR2)* gene, which may cause craniosynostosis syndromes such as Apert, Crouzon, and Pfeiffer syndromes; mutations in the *FGFR3* gene, which may result in achondroplasia and thanatophoric dysplasia; and mutations in the *RET proto-oncogene,* which may cause multiple endocrine neoplasia syndromes (Jung, 2003; Toriello, 2008). Using whole genome sequencing, described later (Whole Genome Sequencing and Whole Exome Sequencing), Kong and associates (2012) also demonstrated that paternal age contributes to a rise in the rate of single-nucleotide polymorphisms among offspring. This rate is approximately two mutations for each year of paternal age. Because individual autosomal dominant disorders are uncommon, the actual risk for any specific condition is low, and no screening or testing is specifically recommended.

Advanced paternal age has also been associated with a slightly greater risk for fetal Down syndrome and for isolated structural abnormalities (Grewal, 2012; Toriello, 2008; Yang, 2007). It is not generally considered to pose an elevated risk for other aneuploidies, probably because the aneuploid sperm cannot fertilize an egg.

Autosomal Recessive Inheritance

Recessive diseases develop only when both gene copies are abnormal. Many enzyme deficiency diseases display autosomal recessive inheritance, and enzyme activity in the carrier is usually about half of normal. Unless carriers are screened for a specific disease, such as cystic fibrosis, they usually are recognized only after the birth of an affected child or the diagnosis of an affected family member (Chap. 14, Cystic Fibrosis). If a couple has a child with an autosomal recessive disease, the recurrence risk is 25 percent for each subsequent pregnancy. Thus, 1/4 of offspring will be homozygous normal, 2/4 will be heterozygous carriers, and 1/4 will be homozygous abnormal. In other words, three of four children will be phenotypically normal, and 2/3 of phenotypically normal siblings are actually carriers.

A heterozygous carrier of a recessive condition is only at risk to have affected children if his or her partner is heterozygous or homozygous for the disease. Genes for rare autosomal recessive conditions have low prevalence in the general population. Thus, the likelihood that a partner will be a gene carrier is small, unless there is consanguinity or the partner is a member of an at-risk group. Heterozygous carriers are usually undetectable clinically but may have biochemical test abnormalities

that can be used for carrier screening. Other recessive conditions can be identified only by molecular genetic testing (Chap. 14, Carrier Screening for Genetic Disorders).

Inborn Errors of Metabolism

Most of these autosomal recessive diseases result from absence of a crucial enzyme, leading to incomplete metabolism of proteins, lipids, or carbohydrates. The metabolic intermediates that build up are toxic to various tissues and may result in intellectual disability or other abnormalities.

Phenylketonuria

Also known as phenylalanine hydroxylase (PAH) deficiency, this autosomal recessive disease is caused by mutations in the *PAH* gene. PAH metabolizes phenylalanine to tyrosine, and homozygotes have diminished or absent enzyme activity. This leads to abnormally high levels of phenylalanine, resulting in progressive intellectual impairment, autism, seizures, motor deficits, and neuropsychological abnormalities (Blau, 2010). Because phenylalanine competitively inhibits tyrosine hydroxylase—which is essential for melanin production, affected individuals also have hair, eye, and skin hypopigmentation. More than 500 *PAH* gene mutations have been characterized, and the carrier frequency is 1 in 60, such that the disease affects approximately 1 in 15,000 newborns (American College of Obstetricians and Gynecologists, 2017c). Prompt diagnosis and restriction of dietary phenylalanine beginning early in infancy are essential to prevent neurological damage, and all states mandate newborn screening for phenylketonuria (PKU).

Phenylalanine restriction alone would result in inadequate protein consumption, and phenylalanine-free amino acid-based supplementation is required. Also, in 2007, a synthetic form of the PAH cofactor tetrahydrobiopterin (sapropterin) was approved for PKU treatment. Approximately 25 to 50 percent of affected individuals are sapropterin-responsive and may experience a significant decline in phenylalanine levels and improvement in neuropsychiatric symptoms (Vockley, 2014). Lifelong maintenance of phenylalanine concentrations in the range of 2 to 6 mg/dL (120 to 360 µmol/L) is necessary to prevent worsening neurocognitive and psychiatric problems (American College of Obstetricians and Gynecologists, 2017c). Fortunately, even those who have previously discontinued therapy may experience improved neuropsychological function with treatment.

During pregnancy, women with PKU whose phenylalanine levels remain above the recommended range are at risk to have otherwise normal (heterozygous) offspring who sustain in utero damage as a result of being exposed to toxic phenylalanine concentrations. Phenylalanine is actively transported to the fetus. Hyperphenylalaninemia raises the risk for miscarriage and for PKU embryopathy, characterized by intellectual disability, microcephaly, seizures, growth impairment, and cardiac anomalies. Among women on unrestricted diets, the risk to have a child with intellectual disability exceeds 90 percent, microcephaly occurs in more than 70 percent, and as many as 1 in 6 children have cardiac defects (Lenke, 1980). The Maternal Phenylketonuria Collaborative Study, which included 572 pregnancies followed more than 18 years, reported that maintenance of serum phenylalanine levels in the recommended range between 2 and 6 mg/dL significantly reduced the fetal abnormality risk and resulted in childhood IQ scores in the normal range (Koch, 2003; Platt, 2000). Preconceptional counseling and consultation with providers from experienced PKU centers is recommended.

Consanguinity

Two individuals are considered consanguineous if they have at least one recent ancestor in common. Although uncommon in Western countries, more than 1 billion people are estimated to live in countries in which 20 to 50 percent of marriages are consanguineous (Romeo, 2014). In medical genetics, a union is consanguineous if between second cousins or closer relatives. First-degree relatives share half of their genes, second-degree relatives share a fourth, and third-degree relatives—first cousins—share one eighth. Because of the potential for shared deleterious genes, consanguinity confers an increased risk to have offspring with otherwise rare autosomal recessive diseases or multifactorial disorders. In population-based series, first cousins are reported to have a twofold risk for congenital anomalies (Sheridan, 2013; Stoltenberg, 1997). Consanguinity also is associated with a greater rate of stillbirth (Kapurubandara, 2016). Because CMA performed using a single-nucleotide polymorphism platform may identify consanguinity, it is important that preprocedural counseling include this possibility.

Incest is defined as a sexual relationship between first-degree relatives such as parent-child or brother-sister and is universally illegal. Progeny of such unions carry the highest risk of abnormal outcomes, and older studies reported that up to 40 percent of offspring were abnormal as a result of recessive and multifactorial disorders (Baird, 1982; Freire-Maia, 1984).

X-Linked and Y-Linked Inheritance

Most X-linked diseases are recessive. Common examples include color blindness, hemophilia A and B, and Duchenne and Becker muscular dystrophy. Males with an X-linked recessive gene are usually affected by the disease it causes, because they lack a second X chromosome to express the normal dominant gene. A male with an X-linked disease cannot have affected sons because they cannot receive his X chromosome. When a woman carries a gene causing an X-linked recessive condition, each of her sons has a 50-percent risk of being affected, and each daughter has a 50-percent chance of being a carrier.

Women with an X-linked recessive gene are generally unaffected by the disease it causes. In some cases, however, the random inactivation of one X chromosome in each cell—termed lyonization—is skewed, and female carriers may have features of the condition. For example, approximately 10 percent of female carriers of hemophilia A will have factor VIII levels less than 30 percent of normal, and a similar proportion of female hemophilia B carriers have factor IX levels less than 30 percent. Levels below these thresholds confer a greater risk for abnormal bleeding when affected women give birth (Plug, 2006). Indeed, even with higher levels, carriers are reported to be at increased risk for bleeding complications (Olsson, 2014). Similarly, female carriers of Duchenne or Becker muscular dystrophy carry an elevated risk for cardiomyopathy, and periodic evaluation for cardiac dysfunction and neuromuscular disorders is recommended (American Academy of Pediatrics, 2008).

X-linked dominant disorders mainly affect females, because they tend to be lethal in males. Two examples are vitamin D-resistant rickets and incontinentia pigmenti. One exception is fragile X syndrome, which is discussed subsequently.

The prevalence of Y-linked chromosomal disorders is low. This chromosome carries genes important for sex determination and various cellular functions related to spermatogenesis and bone development. Deletion of genes on the long arm of Y results in severe spermatogenic defects, whereas genes at the tip of the short arm are critical for chromosomal pairing during meiosis and for fertility.

Mitochondrial Inheritance

Human cells contain hundreds of mitochondria, each with its own genome and associated replication system. Oocytes contain approximately 100,000 mitochondria. Sperm hold only about 100, and these are destroyed after fertilization. Each mitochondrion has multiple copies of a 16.5-kb circular DNA molecule that contains 37 genes. Mitochondrial DNA encodes peptides required for oxidative phosphorylation and encodes ribosomal and transfer RNAs.

Mitochondria are inherited exclusively from the mother. Thus, although males and females both can be affected by a mitochondrial disorder, transmission is only through the mother. When a cell replicates, mitochondrial DNA sorts randomly into each of the daughter cells, a process termed replicative segregation. A consequence of replicative segregation is that any mitochondrial mutation will be propagated randomly into the daughter cells. Because each cell holds multiple copies of mitochondrial DNA, the mitochondrion may contain only normal or only abnormal DNA, termed *homoplasmy.* Alternatively, it may contain both normal and mutated DNA, namely *heteroplasmy.* If a heteroplasmic oocyte is fertilized, the relative proportion of mutated DNA may affect whether the individual manifests a given mitochondrial disease. It is not possible to predict the potential degree of heteroplasmy among offspring, and this poses challenges for genetic counseling.

As of 2016, 33 mitochondrial diseases or conditions with known molecular basis were described in Online Mendelian Inheritance in Man (Johns Hopkins University, 2017). Examples include myoclonic epilepsy with ragged red fibers (MERRF), Leber optic atrophy, Kearns-Sayre syndrome, Leigh syndrome, several forms of mitochondrial myopathy and cardiomyopathy, and susceptibility to chloramphenicol toxicity.

DNA Triplet Repeat Expansion—Anticipation

Mendel's first law is that genes are passed unchanged from parent to progeny, and barring new mutations, this is true for many genes or traits. However, certain genes are unstable, and their size, and thus function, may be altered during parent-to-child transmission. This is manifested clinically by anticipation—a phenomenon in which disease symptoms seem to be more severe and to appear at an earlier age in each successive generation. Examples of some DNA triplet (trinucleotide) repeat diseases are shown in Table 13-4.

TABLE 13-4

Some Disorders Caused by DNA Triplet Repeat Expansion

Dentatorubral-pallidoluysian atrophy
Fragile X syndrome
Friedreich ataxia
Huntington disease
Spinal and bulbar muscular atrophy
Myotonic dystrophies
Spinocerebellar ataxias

Fragile X Syndrome

This is the most common inherited form of intellectual disability and affects approximately 1 in 3600 males and 1 in 4000 to 6000 females (American College of Obstetricians and Gynecologists, 2017a). Fragile X syndrome is caused by expansion of a repeated trinucleotide DNA segment—cytosine-guanine-guanine (CGG)—at chromosome Xq27.3. When the CGG repeat number reaches a critical size—the full mutation—the *fragile X mental retardation 1 (FMR1)* gene becomes methylated. Methylation inactivates the gene, which halts expression of FMR1 protein. This protein is most abundant in nerve cells and is essential for normal cognitive development.

Although transmission of the syndrome is X-linked, both the sex of the affected individual and the number of CGG repeats determine the degree of clinical normalcy or impairment. Intellectual disability is generally more severe in males, in whom average IQ scores are 35 to 45 (Nelson, 1995). Affected individuals may have speech and language problems and attention-deficit/hyperactivity disorder. Fragile X syndrome is also the most common known cause of autism or "autistic like" behavior. Associated phenotypic abnormalities become more prominent with age and include a narrow face with large jaw, prominent ears, connective tissue abnormalities, and macroorchidism in postpubertal males. Clinically, four groups have been described (American College of Obstetricians and Gynecologists, 2017a):

Full mutation—more than 200 repeats

Premutation—55 to 200 repeats

Intermediate—45 to 54 repeats

Unaffected—fewer than 45 repeats

Full mutations are expressed (penetrant) in all males and many females. When a full mutation is present, males typically have significant cognitive and behavioral abnormalities and phenotypic features. In females, random X-inactivation, however, results in variable expression, and the disability may be much less severe. With

rare exception, the parent of origin of repeat expansion that leads to a full mutation is female (Monaghan, 2013).

For individuals with a premutation, evaluation and counseling are more complex. A female with the fragile X premutation is at risk to have offspring with the full mutation, depending on the repeat number. The risk of a full mutation in an offspring is 5 percent or less if the CGG repeat number is <70 but exceeds 95 percent with 100 to 200 CGG repeats (Nolin, 2003). Expansion is extremely unlikely in a male premutation carrier, but all of his daughters will carry the premutation. Among women with no risk factors, approximately 1 in 250 carries a fragile X premutation, and the risk approximates 1 in 90 in those with a family history of intellectual disability (Cronister, 2008). Premutation carriers may themselves experience significant health consequences. Males with the premutation are at increased risk for the fragile X tremor ataxia syndrome (FXTAS). This syndrome is characterized by memory loss, executive function deficits, anxiety, and dementia (Monaghan, 2013). Females are at risk for FXTAS as well, although less so. They also have a 20-percent risk for fragile X-associated primary ovarian insufficiency.

The American College of Obstetricians and Gynecologists (2016c, 2017a) recommends carrier screening for women with a family history of fragile X syndrome; individuals with unexplained intellectual disability, developmental delay, or autism; and women with primary ovarian insufficiency. Prenatal diagnosis can be accomplished by amniocentesis or chorionic villus sampling. Specimens obtained by either can define the CGG repeat number, although chorionic villus sampling may not accurately determine *FMR1* gene methylation status.

Imprinting

This term describes some genes that are inherited but not expressed, depending on whether they are inherited from the mother or father. Thus, the resulting phenotype varies according to the parent of origin. Imprinting affects gene expression by epigenetic control, which modifies genetic structure using methods other than altering the underlying nucleotide sequence. For example, methyl group addition may alter gene expression and thereby affect the phenotype without changing the genotype. Importantly, the effect may be reversed in a subsequent generation, because a female who inherits an imprinted gene from her father will pass it in her oocytes with a maternal—rather than paternal—imprint, and vice versa.

Selected diseases that can involve imprinting are shown in Table 13-5. A useful example includes two very different diseases that affect the same region of DNA. First, *Prader-Willi syndrome* is characterized by obesity and hyperphagia; short stature; small hands, feet, and external genitalia; and mild mental retardation. In more than 70 percent of cases, Prader-Willi syndrome is caused by microdeletion or disruption for the paternal 15q11.2-q13. The remaining cases are due to maternal uniparental disomy or due to maternal gene imprinting with the paternal gene inactivated.

TABLE 13-5

Some Disorders That Can Involve Imprinting

Disorder	Chromosomal Region	Parental Origin
Angelman	15q11.2-q13	Maternal
Beckwith-Wiedemann	11p15.5	Paternal
Myoclonus-dystonia	7q21	Maternal
Prader-Willi	15q11.2-q13	Paternal
Pseudohypoparathyroidism	20q13.2	Variable
Russell-Silver syndrome	7p11.2	Maternal

Data from Online Mendelian Inheritance in Man (Johns Hopkins University, 2017.)

In contrast, *Angelman syndrome* includes severe intellectual disability; normal stature and weight; absent speech; seizure disorder; ataxia and jerky arm movements; and paroxysms of inappropriate laughter. In approximately 70 percent of cases, Angelman syndrome is caused by microdeletion for the maternal 15q11.2-q13. In 2 percent, the syndrome is caused by paternal uniparental disomy, and another 2 to 3 percent is due to paternal gene imprinting with the maternal genes inactivated.

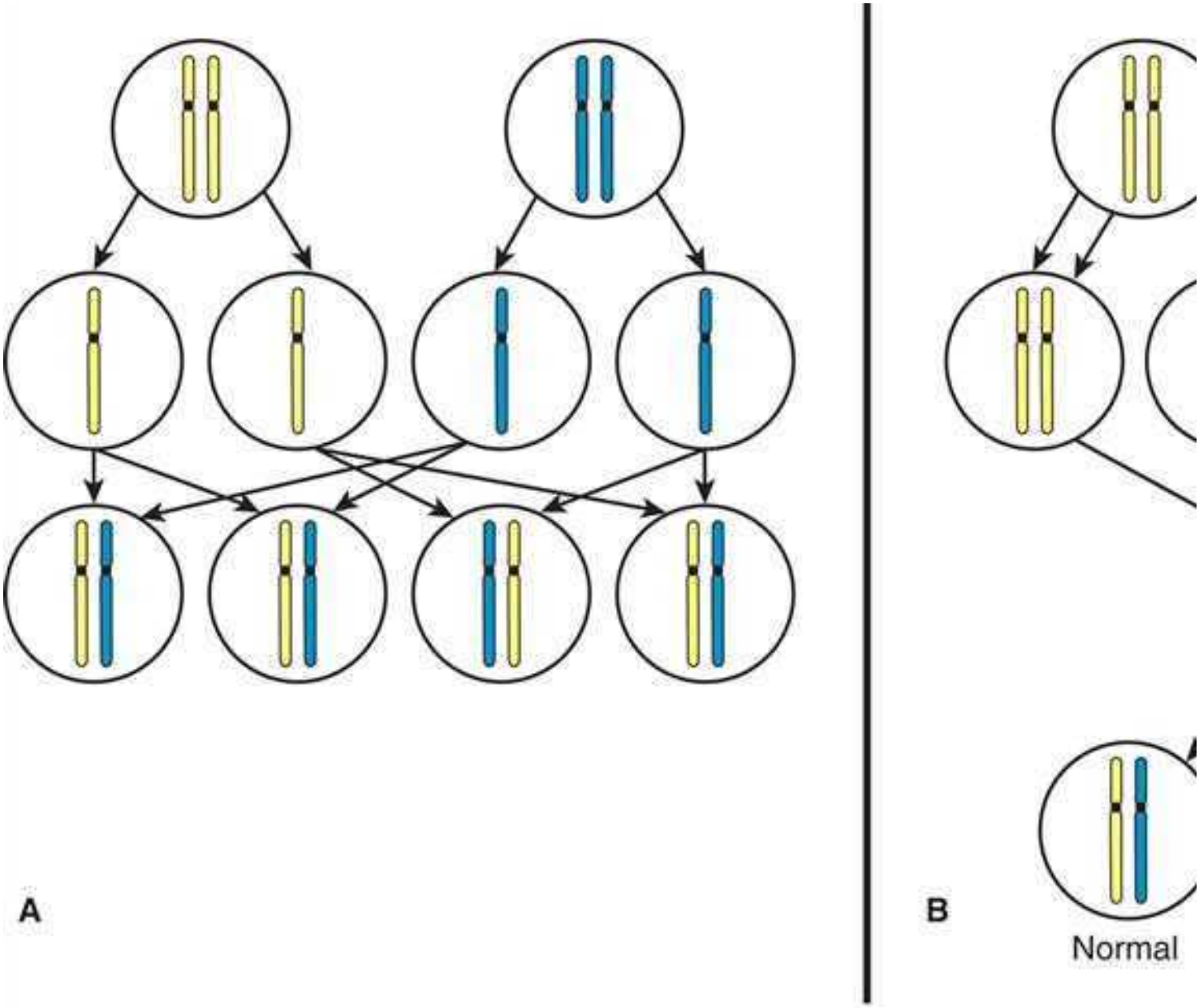
There are other examples of imprinting important to obstetrics. Complete hydatidiform mole, with a paternally derived diploid chromosomal complement, is characterized by abundant placental growth with no fetal structures (Chap. 20, Epidemiology and Risk Factors). Conversely, an ovarian teratoma, with a maternally derived diploid chromosomal complement, is characterized by the growth of various fetal but no placental tissues (Porter, 1993).

Uniparental Disomy

This occurs when both members of a chromosome pair are inherited from the same parent. Often, uniparental disomy does not have clinical consequences. Although both copies are inherited from one parent, they are not identical. However, if chromosomes 6, 7, 11, 14, or 15 are involved, offspring are at increased risk for an abnormality because of parent-of-origin differences in gene expression (Shaffer, 2001). Several genetic mechanisms may cause uniparental disomy, the most common of which is trisomic rescue, shown in Figure 13-9. After a nondisjunction event produces a trisomic conceptus, one of the three homologues may be lost. This will result in uniparental disomy for that chromosome in approximately one third of cases.

FIGURE 13-9

Mechanism of uniparental disomy arising from trisomic "rescue." **A.** In normal meiosis, one member of each pair of homologous chromosomes is inherited from each parent. **B.** If nondisjunction results in a trisomic conceptus, one homologue is sometimes lost. In a third of cases, loss of one homologue leads to uniparental disomy.



Isodisomy is the unique situation in which an individual receives two *identical* copies of one chromosome in a pair from one parent. This mechanism explains some cases of cystic fibrosis, in which only one parent is a carrier but the fetus inherits two copies of the same abnormal chromosome from that parent (Spence, 1988; Spotila, 1992). It also has been implicated in abnormal growth related to placental mosaicism.

Multifactorial Inheritance

Traits or diseases are considered to have multifactorial inheritance if they are determined by the combination of multiple genes and environmental factors (Table 13-6). Polygenic traits are determined by the combined effects of more than one gene. Most congenital and acquired conditions, as well as common traits, display multifactorial inheritance. Examples include malformations such as clefts and neural-tube defects, diseases such as diabetes and heart disease, and features or traits such as head size or height. Abnormalities that display multifactorial inheritance tend to recur in families, but not according to a mendelian pattern. If a couple has had a child with a multifactorial birth defect, their empirical risk to have another affected child is 3 to 5 percent. This risk declines exponentially with successively more distant relationships.

TABLE 13-6

Characteristics of Multifactorial Diseases

There is a genetic contribution: No mendelian pattern of inheritance No evidence of single-gene disorder
Nongenetic factors are also involved in disease causation: Lack of penetrance despite predisposing genotype Monozygotic twins may be discordant
Familial aggregation may be present: Relatives are more likely to have disease-predisposing alleles
Expression more common among close relatives: Becomes less common in less closely related relatives—fewer predisposing alleles Greater concordance in monozygotic than dizygotic twins

Adapted from Nussbaum, 2007.

Multifactorial traits that have a normal distribution in the population are termed continuously variable. A measurement that is more than two standard deviations above or below the population mean is considered abnormal. Continuously variable traits tend to be less extreme in the offspring of affected individuals, because of the statistical principle of regression to the mean.

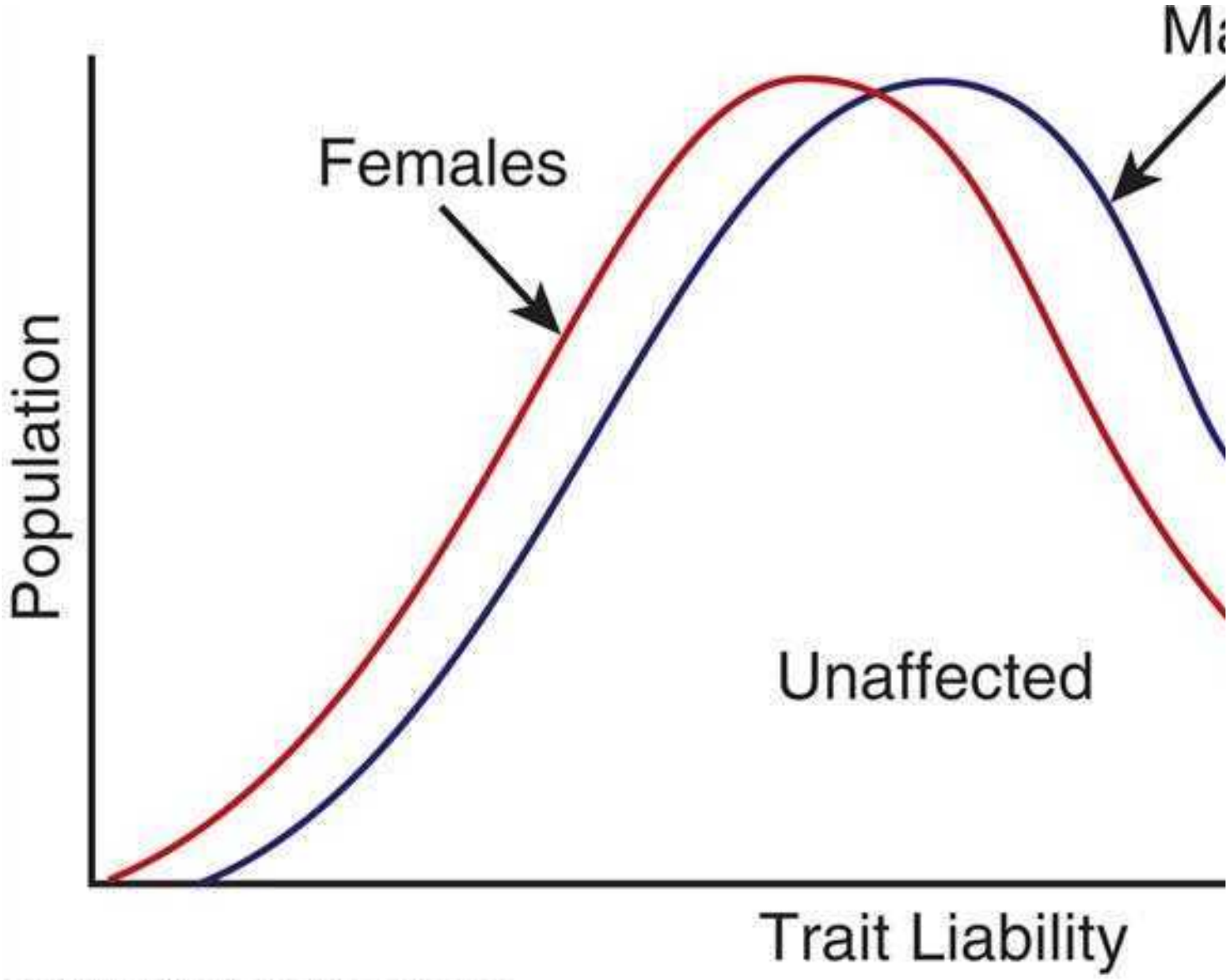
Threshold Traits

Some multifactorial traits do not appear until a threshold is exceeded. Genetic and environmental factors that create propensity or liability for the trait are themselves normally distributed, and only individuals at the extreme of the distribution exceed the threshold and exhibit the trait or defect. Phenotypic abnormality is thus an all-or-none phenomenon. Examples include cleft lip-palate and pyloric stenosis.

Certain threshold traits have a clear male or female predominance. If an individual of the less common gender has the characteristic or defect, the recurrence risk is greater in his or her offspring (Fig. 13-10). An example is pyloric stenosis, which is approximately four times more common in males (Krogh, 2012). A female with pyloric stenosis has likely inherited more predisposing genetic factors than are necessary to produce the defect in a male, and the recurrence risk for her children or siblings is thus higher than the expected 3 to 5 percent. Her male siblings or male offspring would have the highest liability because they not only will inherit more than the usual number of predisposing genes but also are the more susceptible gender.

FIGURE 13-10

Schematic example of a threshold trait, such as pyloric stenosis, which has a predilection for males. Each gender is normally distributed, but at the same threshold, more males than females will develop the condition.



The recurrence risk for threshold traits is also greater if the defect is severe. For example, the recurrence risk after the birth of a child with bilateral cleft lip and palate is approximately 8 percent, but it is only about 4 percent following a child with unilateral cleft lip alone.

Cardiac Defects

Structural cardiac anomalies are the most common birth defects, with a birth prevalence of 8 cases per 1000. More than 100 genes believed to be involved in cardiovascular morphogenesis have been identified, including those directing production of various proteins, protein receptors, and transcription factors (Olson, 2006; Weismann, 2007).

The risk of having a child with a cardiac anomaly is approximately 5 to 6 percent if the mother has the defect and 2 to 3 percent if the father has the defect (Burn, 1998). Selected left-sided lesions, including hypoplastic left heart syndrome, coarctation of the aorta, and bicuspid aortic valve, may have recurrence risks four- to sixfold higher (Lin, 1988; Lupton, 2002; Nora, 1988). Observed recurrence risks for specific cardiac malformations are listed in Table 49-4.

Neural-Tube Defects

These disorders are also classic examples of multifactorial inheritance. Development of neural-tube defects (NTDs) may be influenced by hyperthermia, hyperglycemia, teratogen exposure, ethnicity, family history, fetal gender, and various genes. Selected risks are more strongly associated with the specific defect location. Hyperthermia has been linked with anencephaly risk; pregestational diabetes with cranial and cervical-thoracic defects; and valproic acid exposure with lumbosacral defects (Becerra, 1990; Hunter, 1984; Lindhout, 1992). Sonographic features of NTDs are described in Chapter 10 (Neural-Tube Defects), their prevention with folic acid is discussed in Chapter 9 (Pragmatic Nutritional Surveillance), and fetal therapy for myelomeningocele is reviewed in Chapter 16 (Open Fetal Surgery).

More than 50 years ago, Hibbard and Smithells (1965) postulated that abnormal folate metabolism was responsible for many NTDs. For a woman with a prior affected child, the recurrence risk of 3 to 5 percent is decreased by at least 70 percent—and potentially by as much as 85 to 90 percent—with periconceptional oral folic acid supplementation at a dosage of 4 mg/d (Grosse, 2007; MRC Vitamin Study Research Group, 1991). However, most NTD cases do not occur in the setting of

maternal folic acid deficiency, and it has become clear that the gene-nutrient interactions underlying folate-responsive NTDs are complex. The NTD risk may be affected by genetic variation in folate transport or accumulation, impaired folate utilization via secondary nutrient deficiencies such as vitamin B_{12} or choline deficiency, and genetic variation in activity of folate-dependent metabolic enzymes (Beaudin, 2009).

GENETIC TESTS

All pregnant women should have the option of prenatal aneuploidy *screening* and prenatal genetic *diagnosis* (American College of Obstetricians and Gynecologists, 2016b). Aneuploidy screening may be performed with serum analyte-based screening or with a DNA-based screen, namely, cell-free DNA found in the maternal circulation. Prenatal genetic screening of the parents also aids carrier status determination in at-risk individuals (Chap. 14, Carrier Screening for Genetic Disorders).

For prenatal genetic diagnosis, the most commonly used tests are cytogenetic analysis (karyotyping), fluorescence in situ hybridization (FISH), and chromosomal microarray analysis. Testing may be performed on amnionic fluid or chorionic villi. In selected circumstances, whole genome or whole exome sequencing may be considered, but these are not recommended for routine use. To diagnose a specific disease whose genetic basis is known, DNA-based tests are often employed, typically using polymerase chain reaction (PCR) for rapid amplification of DNA sequences.

Cytogenetic Analysis

Karyotype analysis is commonly performed to test for chromosomal abnormalities. Any tissue containing dividing cells or cells that can be stimulated to divide is suitable for cytogenetic analysis. Karyotyping detects numerical abnormalities, that is, aneuploidy. It also identifies balanced or unbalanced structural rearrangements of at least 5 to 10 megabases in size. Karyotyping has diagnostic accuracy exceeding 99 percent.

The dividing cells are arrested in metaphase, and their chromosomes are stained to reveal light and dark bands. The most commonly used technique is Giemsa staining, which yields the G-bands shown in Figure 13-3. Each chromosome has a unique banding pattern that permits its identification and detection of deleted, duplicated, or rearranged segments. The accuracy of cytogenetic analysis rises with the number of bands produced. High-resolution metaphase banding routinely yields 450 to 550 visible bands per haploid chromosome set. Banding of prophase chromosomes generally yields 850 bands.

Because only dividing cells can be evaluated, the rapidity with which results are obtained correlates with the rapidity of cell growth in culture. Amnionic fluid, which contains epithelial cells, gastrointestinal mucosal cells, and amniocytes, usually yields results in 7 to 10 days. Fetal blood cells may provide results in 36 to 48 hours but are rarely needed (Chap. 14, Fetal Blood Sampling). If fetal skin fibroblasts are evaluated postmortem, stimulation of cell growth can be more difficult, and cytogenetic analysis may take 2 to 3 weeks (Chap. 35, Laboratory Evaluation).

Fluorescence In Situ Hybridization

This technique may be used for rapid identification of a specific chromosome abnormality and for verification of suspected microdeletion or duplication syndromes, such as the 22q11.2 microdeletion described earlier (Abnormalities of Chromosome Structure). Because of its 1- to 2-day turnaround time, FISH is often selected for cases in which findings may alter pregnancy management. To perform FISH, cells are fixed onto a glass slide, and fluorescent-labeled probes are hybridized to the fixed chromosomes (Figs. 13-11 and 13-12). Each probe is a DNA sequence that is complementary to a region of the chromosome or gene being investigated. If the DNA sequence is present, hybridization is detected as a bright signal visible by microscopy. The number of signals indicates the number of chromosomes or genes of that type in the cell being analyzed. Findings are probe-specific. Namely, FISH does not provide information on the entire chromosomal complement but merely the chromosomal or gene region of interest.

FIGURE 13-11
Steps in fluorescence in situ hybridization (FISH).

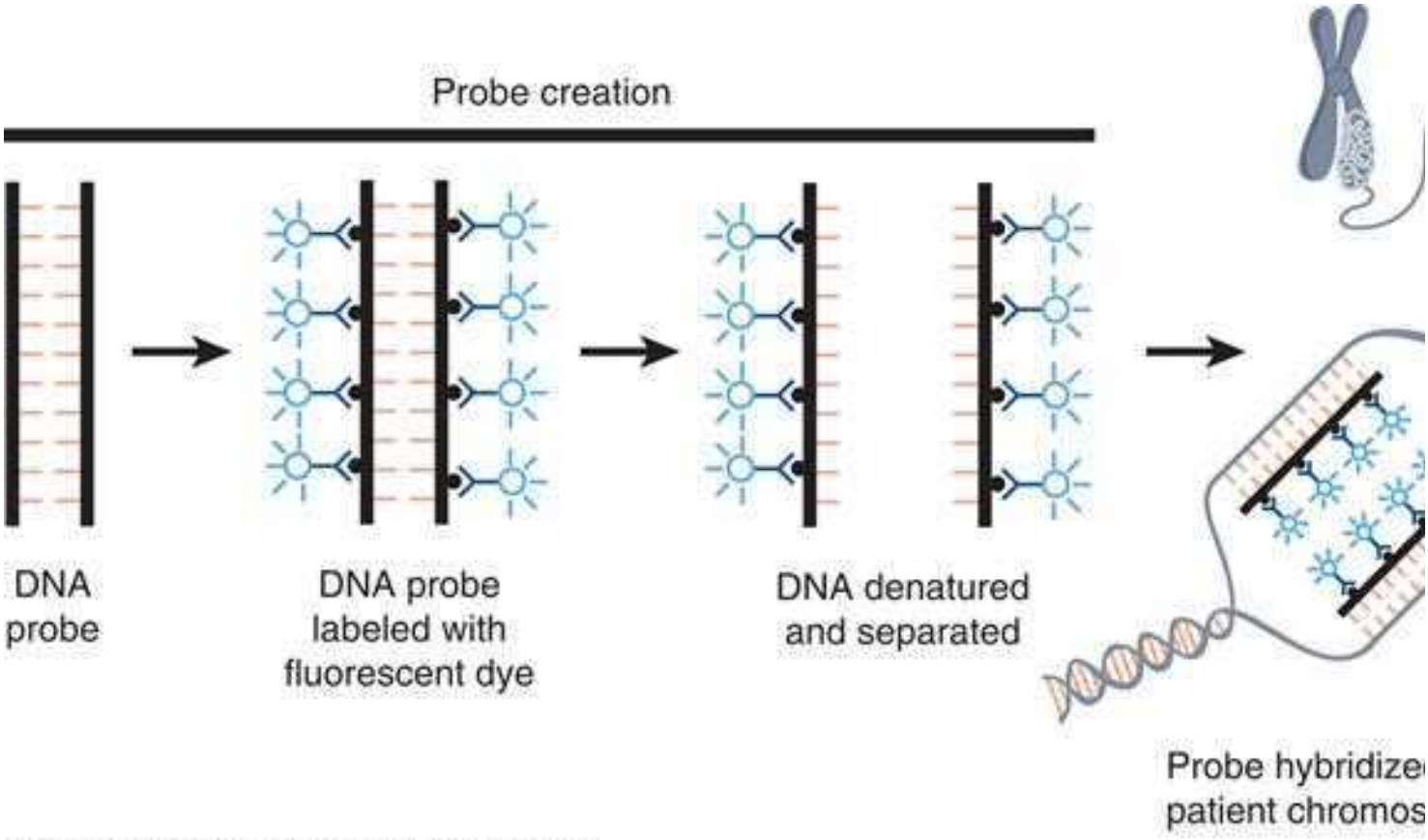
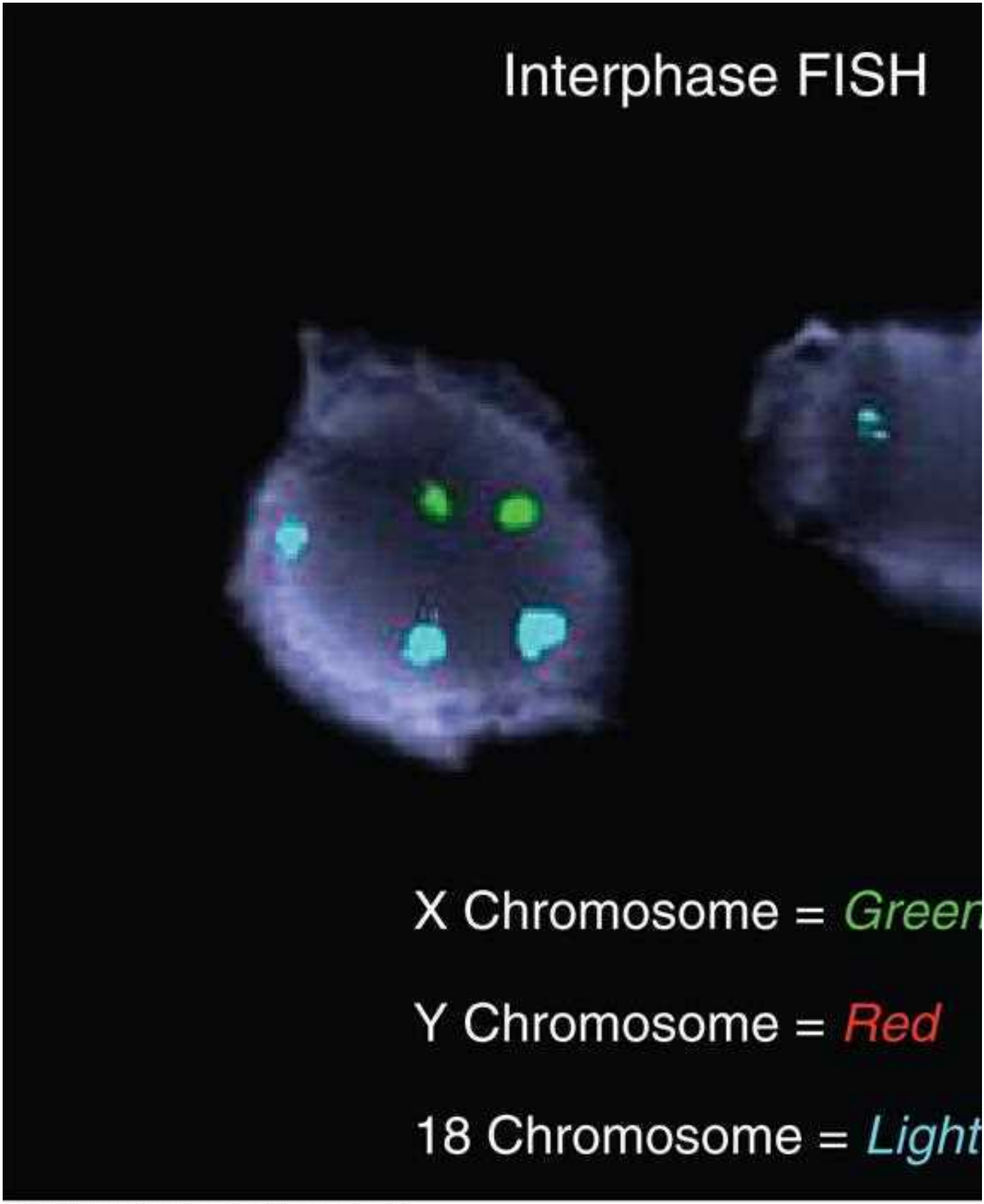


FIGURE 13-12

Interphase fluorescence in situ hybridization (FISH) using α-satellite probes for chromosomes 18, X, and Y. In this case, the three light blue signals, two green signals, and absence of red signals indicate that this is a female fetus with trisomy 18. (Used with permission from Dr. Frederick Elder.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

The most common prenatal application of FISH involves testing interphase chromosomes with DNA sequences specific to chromosomes 21, 18, 13, X, and Y. Figure 13-12 shows an example of interphase FISH using α-satellite probes for chromosomes 18, X, and Y to confirm trisomy 18. In a review of more than 45,000 samples, the concordance between FISH analysis and standard cytogenetic karyotyping was 99.8 percent (Tepperberg, 2001). The American College of Obstetricians and

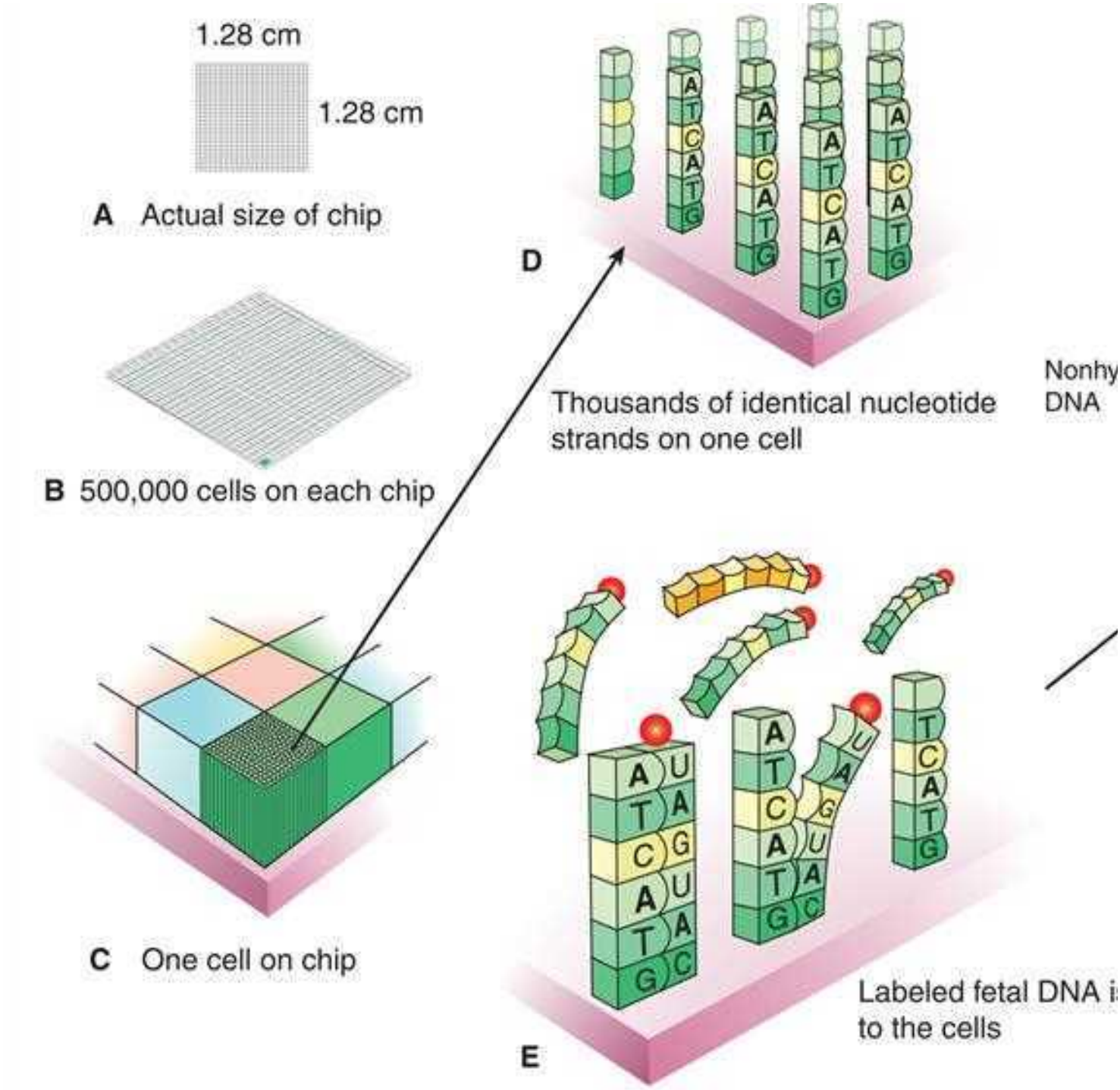
Gynecologists (2016b) recommends that clinical decision-making based on FISH incorporate clinical information consistent with the suspected diagnosis, such as an abnormal aneuploidy screening test result or sonographic finding, or incorporate a confirmatory diagnostic test such as karyotyping or CMA.

Chromosomal Microarray Analysis

This test is 100 times more sensitive than standard karyotyping and detects microduplications and microdeletions as small as 50 to 100 kilobases. Direct CMA can yield results in 3 to 5 days, whereas if cultured cells are required, results may take 10 to 14 days (American College of Obstetricians and Gynecologists, 2016b). Microarrays use either a comparative genomic hybridization (CGH) platform, a single-nucleotide polymorphism (SNP) platform, or a combination of the two. The CGH microarray platform compares test specimen DNA with a normal control sample. Shown in Figure 13-13, the CGH chip contains reference DNA fragments of known sequence—oligonucleotides. Fetal DNA from the amniocentesis or chorionic villus sampling specimen is labeled with a fluorescent dye and then hybridized to the DNA on the chip. Normal control DNA is labeled with a different probe and also hybridized to the chip. Then, the intensity of the fluorescent signals from the two samples is compared. With an SNP array, the chip contains known DNA sequence variants—single-nucleotide polymorphisms. When fetal DNA is labeled and hybridized to the chip, the fluorescent signal intensity indicates copy number variation.

FIGURE 13-13

Chromosomal microarray analysis. **A.** Actual microarray chip size. **B.** Each chip contains thousands of cells (squares). **C & D.** Each cell contains thousands of identical oligonucleotides on its surface, and each cell is unique in its nucleotide content. **E.** During genetic analysis, a mixture containing tagged fetal DNA is presented to the chip. Complementary DNA sequences bind. **F.** If a laser is shined on the chip, DNA sequences that have bound will glow. This identifies a matching sequence. (Modified with permission from Doody KJ: Treatment of the infertile couple. In Hoffman BL, Schorge JO, Schaffer JI, et al (eds): Williams Gynecology, 2nd ed. New York, McGraw-Hill, 2012.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Both types of platforms detect aneuploidy, unbalanced translocations, and microdeletions and microduplications. Neither type of array platform currently detects balanced chromosomal rearrangements. For this reason, couples with recurrent pregnancy loss should be offered karyotyping as the first-line test (Society for Maternal-Fetal Medicine, 2016). In addition, SNP arrays are able to identify triploidy and can detect *absence of heterozygosity.* The latter can occur with uniparental disomy when both copies of a chromosome are inherited from one parent. Further, absence of heterozygosity may occur when there is consanguinity, and counseling prior to performance of an SNP array should include this possibility.

Arrays may be genome-wide or may be targeted to known genetic syndromes. Genome-wide arrays are typically used in research settings, for example, to identify novel microdeletion syndromes in individuals with intellectual disability (Slavotinek, 2008). Targeted arrays are generally preferred prenatally because the likelihood of detecting a *copy number variant of uncertain clinical significance* is lower. In a systematic review, Hillman and colleagues (2013) identified copy number variants of uncertain significance in 1 to 2 percent of prenatal specimens. Not unexpectedly, this may be a source of significant distress to families, even with comprehensive pretest counseling.

Clinical Applications

In pregnancies at increased risk for autosomal trisomy based on aneuploidy screening, karyotyping or FISH plus karyotyping should be offered, and CMA should be made available (American College of Obstetricians and Gynecologists, 2016b). When the karyotype is normal, CMA has identified clinically relevant copy number variants in approximately 6.5 percent of pregnancies with fetal abnormalities and in 1 to 2 percent with no obvious fetal abnormality (Callaway, 2013). The American College of Obstetricians and Gynecologists (2016b) and the Society for Maternal-Fetal Medicine (2016) recommend that CMA be offered as a first-tier test when fetal structural abnormalities are identified, replacing fetal karyotyping in these cases. If a particular anomaly that strongly suggests a specific aneuploidy is identified, such as an endocardial cushion defect (trisomy 21) or alobar holoprosencephaly (trisomy 13), karyotyping or FISH may be offered as the initial test. It is recommended that genetic counseling include information about the benefits and limitations of both CMA and karyotyping, and that each be made available to women who elect prenatal diagnosis (Society for Maternal-Fetal Medicine, 2016). CMA may identify instances of autosomal dominant genetic disorders that have not yet manifested in an affected parent, and it may also identify instances of nonpaternity.

For stillbirth evaluation, CMA is more likely than standard karyotyping to provide a genetic diagnosis, in part because it does not require dividing cells. The Stillbirth Collaborative Research Network found that when karyotyping was uninformative, approximately 6 percent of cases had either aneuploidy or a pathogenic copy number variant identified with CMA (Reddy, 2012). Overall, CMA yields results nearly 25 percent more often than standard karyotyping alone.

Whole Genome Sequencing and Whole Exome Sequencing

Most fetuses with structural abnormalities have a normal karyotype and a normal CMA result. Whole genome sequencing (WGS) is a technique for analyzing the entire genome. Whole exome sequencing (WES) analyzes just the DNA coding regions, which account for approximately 1 percent of the genome. These next-generation sequencing tools are increasingly used in the postnatal setting to evaluate suspected genetic syndromes and intellectual disability. The American College of Medical Genetics Board of Directors (2012) states that WGS and WES may be considered for evaluation of the fetus with a likely genetic disorder in which CMA has failed to arrive at a diagnosis. The American College of Obstetricians and Gynecologists (2016a) suggests that this be in only selected circumstances, for example, with recurrent or lethal anomalies in which other approaches have been noninformative. Importantly, WGS and WES have significant limitations in their current form, including turnaround times that may be prohibitively long and a high rate of variants of uncertain significance (American College of Medical Genetics, 2012; Atwal, 2014). As a result, the clinical utility of this promising technology for prenatal cases is currently limited.

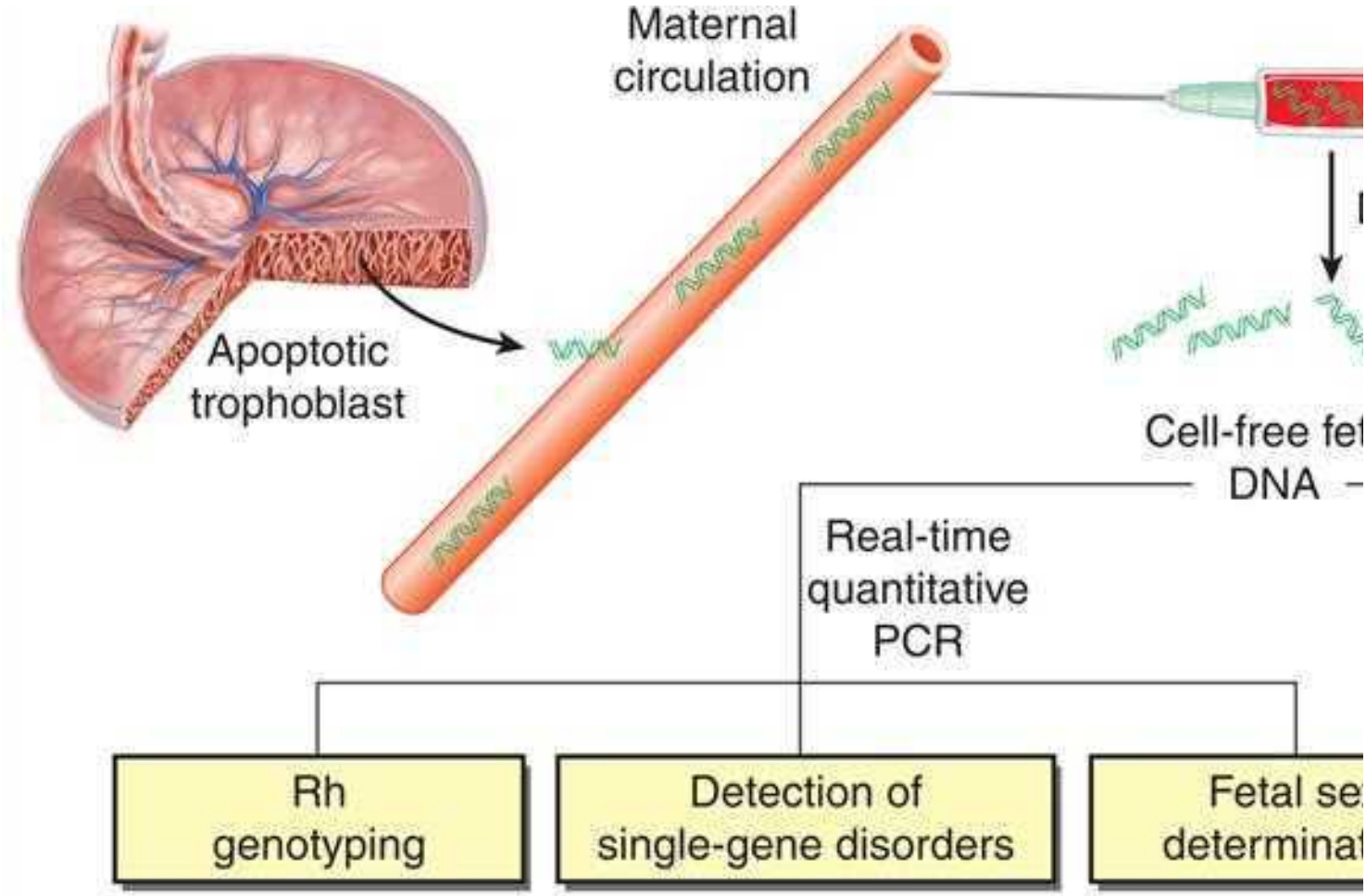
Fetal DNA in the Maternal Circulation

Fetal cells are present in maternal blood at a very low concentration, only 2 to 6 cells per milliliter (Bianchi, 2006). Sometimes, intact fetal cells may persist in the maternal circulation for decades following delivery. Persistent fetal cells may engraft in the mother and result in *microchimerism*, which has been implicated in maternal autoimmune diseases such as scleroderma, systemic lupus erythematosus, and Hashimoto thyroiditis. For prenatal diagnosis, the use of intact fetal cells from maternal blood is limited by low cell concentration, cell persistence into successive pregnancies, and difficulties in distinguishing fetal from maternal cells. In these cases, however, cell-free DNA overcomes these limitations.

Cell-Free DNA

These DNA fragments are derived from maternal cells and from apoptotic placental trophoblast cells—although DNA from the latter is often termed “fetal.” Cell-free DNA can be reliably detected in maternal blood after 9 to 10 weeks’ gestation (American College of Obstetricians and Gynecologists, 2017b). The proportion of cell-free DNA that is placental is called the fetal fraction, and it composes approximately 10 percent of the total circulating cell-free DNA in maternal plasma. Unlike intact fetal cells, cell-free DNA is cleared within minutes from maternal blood. In research settings, cell-free DNA has been used to detect numerous single-gene disorders transmitted through paternally inherited alleles. These include myotonic dystrophy, achondroplasia, Huntington disease, congenital adrenal hyperplasia, cystic fibrosis, and α-thalassemia (Wright, 2009). Clinical applications of cell-free DNA are aneuploidy screening, fetal sex determination, and Rh D genotyping (Fig. 13-14).

FIGURE 13-14
Cell-free DNA is actually derived from apoptotic trophoblast. The DNA is isolated from maternal plasma, and real-time quantitative polymerase chain reaction (PCR) may be used to target specific regions or sequences. This may be used for Rh D genotyping, detection of paternally inherited single-gene disorders, or fetal sex determination. Screening for autosomal trisomies and sex chromosomal aneuploidies is performed using whole-genome sequencing, chromosome selective or targeted sequencing, and analysis of single nucleotide polymorphisms.



Aneuploidy Screening

Several different types of assays are used to screen for fetal autosomal trisomies and sex chromosomal aneuploidies. These include whole-genome sequencing, which is also called massively parallel or shotgun sequencing; chromosome selective or targeted sequencing; and analysis of SNPs (American College of Obstetricians and Gynecologists, 2016a,b). By simultaneously sequencing millions of DNA fragments, investigators can identify whether the proportion or ratio of fragments from one chromosome is higher than expected. Sequences of fetal DNA are specific to individual chromosomes. Thus, samples from women with a Down syndrome fetus have a larger proportion of DNA sequences from chromosome 21.

The screening performance of cell-free DNA is excellent. In a metaanalysis of 37 studies of largely high-risk pregnancies, the pooled sensitivity to detect Down syndrome was 99 percent, and to identify trisomies 18 and 13, 96 and 91 percent, respectively. For each, the specificity was 99.9 percent (Gil, 2015). The false-positive rate is cumulative for each aneuploidy for which screening is performed, but it is usually below 1 percent. As a result, cell-free DNA screening is recommended as a screening option in those at greater risk for fetal autosomal trisomy (American College of Obstetricians and Gynecologists, 2017b; Society for Maternal-Fetal Medicine, 2015).

Unfortunately, cell-free DNA screens do not yield a result in 4 to 8 percent of cases. This may be due to assay failure, high assay variance, or low fetal fraction (Norton, 2012; Pergament, 2014; Quezada, 2015). Such pregnancies carry a greater risk for fetal aneuploidy. In addition, results may not reflect the fetal DNA complement but rather may indicate confined placental mosaicism, early demise of an aneuploid cotwin, maternal mosaicism, or rarely occult maternal malignancy (Bianchi, 2015; Curnow, 2015; Grati, 2014b; Wang, 2014). Recommendations for counseling are discussed in Chapter 14 (Cell-Free DNA for Secondary Screening).

Fetal Sex Determination

From the standpoint of genetic disease, fetal sex determination may be clinically useful if the fetus is at risk for an X-linked disorder. It may also be beneficial if the fetus is at risk for congenital adrenal hyperplasia because maternal corticosteroid therapy may be avoided if the fetus is male (Chap. 16, Congenital Adrenal Hyperplasia). In a metaanalysis of more than 6000 pregnancies by Devaney and associates (2011), the sensitivity of cell-free DNA testing for fetal sex determination approximated 95 percent between 7 and 12 weeks' gestation and improved to 99 percent after 20 weeks. The test specificity was 99 percent at both time periods, suggesting that cell-free fetal DNA is a reasonable alternative to invasive testing in selected cases.

Rh D Genotype Evaluation

In a predominantly white population, nearly 40 percent of fetuses of Rh D-negative women are themselves Rh D negative. Fetal Rh D genotype assessment from maternal blood can eliminate administration of anti-D immune globulin in these pregnancies, thereby reducing cost and potential risk. With Rh D alloimmunization, early identification of an Rh D-negative fetus might avoid unnecessary middle cerebral artery Doppler assessment or amniocentesis. Evaluation using cell-free DNA is done using real-time PCR to target several exons of the *RHD* gene. These are typically exons 4, 5, and 7.

Rh D-genotyping is performed routinely with cell-free DNA in Denmark and the Netherlands (Clausen, 2012; de Haas, 2016). In a population-based study of more than 25,000 Rh D-negative women screened at 27 weeks, the false-negative rate—in which Rh D-negative status was missed—was only 0.03 percent. The false-positive rate—in which Rh immune globulin would be given unnecessarily—was less than 1 percent (de Haas, 2016). Similar results were reported from the United Kingdom, although the false-negative rate was higher in the first trimester (Chitty, 2014). Investigators concluded that false-negative screening results might increase the alloimmunization risk, but by less than 1 case per million births (Chitty, 2014). Rh D alloimmunization is discussed in Chapter 15 (Red Cell Alloimmunization).

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CHAPTER 14: Prenatal Diagnosis

Careful examination should ordinarily lead to a correct diagnosis of hydrocephalus in the last weeks of pregnancy. In many cases the deformity can be detected by external palpation.

—J. Whitridge Williams (1903)

INTRODUCTION

In the initial edition of Williams Obstetrics, very few fetal disorders could be identified before delivery. Now, more than 100 years later, prenatal diagnosis has become a separate field of its own. Strictly speaking, prenatal diagnosis is the science of identifying congenital abnormalities, aneuploidies, and other genetic syndromes in the fetus. It encompasses the diagnosis of structural malformations with specialized sonography; routine screening tests for aneuploidy and neural-tube defects; diagnostic tests such as karyotyping and chromosomal microarray analysis performed on chorionic villi and amniocentesis specimens; and additional screening and diagnostic tests offered to those with pregnancies at risk for specific genetic disorders. The goal of prenatal diagnosis is to provide accurate information regarding short- and long-term prognosis, recurrence risk, and potential therapy, thereby improving patient counseling and optimizing outcomes.

Management of an affected pregnancy, including whether a woman would elect pregnancy termination, may be incorporated into the discussion of screening and testing options. However, nondirective counseling is central to prenatal diagnosis. This practice provides the patient with unbiased knowledge regarding a diagnosis and preserves her autonomy (Flessel, 2011). Fetal imaging of congenital anomalies is discussed in Chapter 10, and pregnancy termination is discussed in Chapter 18.

HISTORICAL PERSPECTIVE

More than 40 years ago, Brock (1972, 1973) observed that pregnancies complicated by neural-tube defects had higher levels of alpha-fetoprotein (AFP) in maternal serum and amnionic fluid. This formed the basis for the first maternal serum screening test for a fetal condition. The beginning of widespread serum screening came in 1977, after a collaborative trial from the United Kingdom established the association between elevated maternal serum AFP levels (MSAFP) and fetal open neural-tube defects (Wald, 1977). When screening was performed at 16 to 18 weeks' gestation, detection approached 90 percent for pregnancies with fetal anencephaly and 80 percent for those with myelomeningocele (spina bifida). These sensitivities are comparable to current testing (American College of Obstetricians and Gynecologists, 2016a).

The terms *level I* and *level II* sonography were coined in this context. In the California MSAFP Screening Program of the 1980s and early 1990s, women received serum screening prior to sonography, and those with an elevated MSAFP level would undergo level I sonography to identify an incorrect gestational age, multifetal gestation, or fetal demise (Filly, 1993). A third of pregnancies with an elevated MSAFP level had one of these three etiologies. Although birth defects were occasionally detected during level I sonography, this was not the expectation. If level I sonography did not identify an etiology for the MSAFP level elevation, amniocentesis would be offered. Then, only if the amnionic fluid AFP concentration were elevated would the woman undergo level II sonography. This more detailed and comprehensive survey of fetal anatomy was performed to detect and characterize the fetal abnormality.

If the amnionic fluid AFP level was elevated, an assay for amnionic fluid acetylcholinesterase was concurrently performed. This capitalized on the tendency of acetylcholinesterase to leak directly from exposed neural tissue into the amnionic fluid. The presence of both analytes in the amnionic fluid was considered diagnostic for neural-tube defects (American College of Obstetricians and Gynecologists, 2016a).

The overall sensitivity of amniocentesis to diagnose open neural-tube defects approximates 98 percent, with a false-positive rate of 0.4 percent (Milunsky, 2004). Importantly, other fetal abnormalities are associated with elevated amnionic fluid AFP levels and positive assay results for acetylcholinesterase. These include ventral wall defects, esophageal atresia, fetal teratoma, cloacal exstrophy, and skin abnormalities such as epidermolysis bullosa. Thus, by current standards, these amnionic fluid analytes would be considered ancillary screening tests, understanding that a positive result would prompt additional fetal imaging.

With current imaging technology, most neural-tube defects are detected with sonography, and targeted sonography is the diagnostic test of choice (Dashe, 2006). Pregnant women now have the option of neural-tube defect screening with either MSAFP or sonography (American College of Obstetricians and Gynecologists, 2016c). Although level II is used as a synonym for *targeted sonography*, the former might best be removed from our lexicon. Namely, today's targeted sonography includes a much more comprehensive evaluation of fetal anatomy (Chap. 10, Fetal Anomaly Detection).

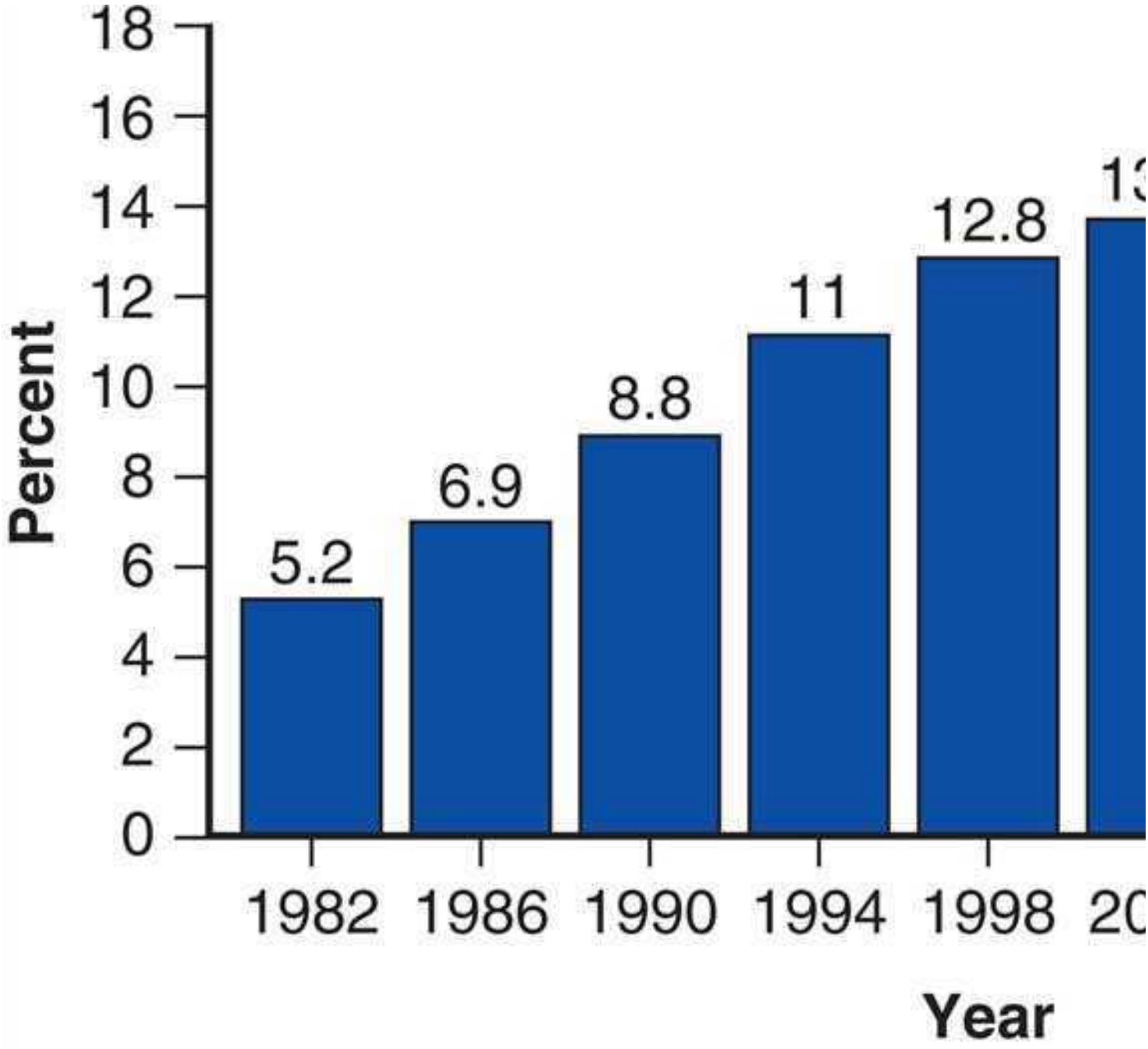
As MSAFP screening was being adopted, the designation "advanced maternal age" (AMA) became popular. A 1979 National Institutes of Health Consensus Development Conference recommended advising pregnant women who were 35 years and older about the possibility of amniocentesis for fetal karyotyping. The threshold was based on the greater risk for selected fetal chromosomal abnormalities with increasing maternal age and on the assumption that at that time, the loss rate attributable to amniocentesis was equivalent to the fetal Down syndrome risk at maternal age 35. *Notably, this is no longer the case, as discussed later* (Chorionic Villus Sampling).

Serum aneuploidy screening soon became available for women who would be younger than 35 at delivery. In 1984, Merkatz and colleagues reported that MSAFP levels were *lower* in pregnancies with trisomies 21 and 18 at 15 to 21 weeks' gestation. Maternal age was incorporated into the calculation, such that a specific risk

could be assigned (DiMaio, 1987; New England Regional Genetics Group, 1989). The MSAFP screen detected approximately 25 percent of cases of fetal trisomy 21 when the threshold ratio for a positive result was set at 1:270. This ratio reflects the approximate second-trimester risk for Down syndrome at maternal age 35. This trisomy 21 risk threshold and the associated 5-percent false-positive rate became standards that remain in use in some laboratories today.

For more than a decade after its introduction, serum aneuploidy screening was intended for women younger than 35, because it simply did not have sufficient sensitivity to be offered to women who had higher a priori risk. This is also no longer the case. And, because the prevalence of fetal aneuploidy rises sharply with maternal age, the positive-predictive value of all aneuploidy screening tests—whether analyte-based or cell-free DNA tests—is higher in women aged 35 years or older. Women 35 and older now make up more than 15 percent of deliveries in the United States (Fig. 14-1). At Parkland Hospital, this age group accounts for half of births with Down syndrome (Hussamy, 2017).

FIGURE 14-1
Trends in the percentage of births to women aged 35 to 44 years. (Data from the Centers for Disease Control and Prevention, 2015.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

SCREENING FOR ANEUPLOIDY

Aneuploidy is the presence of one or more extra chromosomes, usually resulting in trisomy, or loss of a chromosome—monosomy. Data from population-based registries that include births, fetal deaths, and pregnancy terminations indicate an overall prevalence of 4 such abnormalities per 1000 births (Wellesley, 2012).

Aneuploidy accounts for more than 50 percent of first-trimester abortions, about 20 percent of second-trimester losses, and 6 to 8 percent of stillbirths and early-childhood deaths (Reddy, 2012; Stevenson, 2004; Wou, 2016). Of recognized pregnancies with chromosomal abnormalities, trisomy 21 composes approximately half of cases; trisomy 18 accounts for 15 percent; trisomy 13, for 5 percent; and the sex chromosomal abnormalities—45,X, 47,XXX, 47,XXY, and 47,XYY—for approximately 12 percent (Wellesley, 2012).

The risk for fetal trisomy increases with maternal age, particularly after age 35 (Fig. 13-2). When counseling, a provider includes specific maternal-age-related aneuploidy risks (Tables 14-1 and 14-2). Other important fetal aneuploidy risk factors include a numerical chromosomal abnormality or structural chromosomal rearrangement in the woman or her partner—such as balanced translocation—or a prior pregnancy with autosomal trisomy or triploidy.

TABLE 14-1

Maternal Age-Related Risk for Down Syndrome and Any Aneuploidy at Midtrimester and at Term in Singleton Pregnancies

	Down Syndrome		Any Aneuploidy	
Age	**Midtrimester**	**Term**	**Midtrimester**	**Term**
35	1/250	1/385	1/132	1/204
36	1/192	1/303	1/105	1/167
37	1/149	1/227	1/83	1/130
38	1/115	1/175	1/65	1/103
39	1/89	1/137	1/53	1/81
40	1/69	1/106	1/40	1/63
41	1/53	1/81	1/31	1/50
42	1/41	1/64	1/25	1/39
43	1/31	1/50	1/19	1/30
44	1/25	1/38	1/15	1/24
45	1/19	1/30	1/12	1/19

Data from Hook EB, Cross PK, Schreinemachers DM: Chromosomal abnormality rates at amniocentesis and in live-born infants, JAMA. 1983 Apr 15;249(15):2034–2038.

TABLE 14-2

Maternal Age-Related Risk for Down Syndrome and Any Aneuploidy at Midtrimester and at Term in Dizygotic Twin Pregnancies[a]

	Down Syndrome		Any Aneuploidy	
Age	**Midtrimester**	**Term**	**Midtrimester**	**Term**
32	1/256	1/409	1/149	1/171
33	1/206	1/319	1/116	1/151
34	1/160	1/257	1/91	1/126
35	1/125	1/199	1/71	1/101
36	1/98	1/153	1/56	1/82
37	1/77	1/118	1/44	1/67
38	1/60	1/92	1/35	1/54
39	1/47	1/72	1/27	1/44
40	1/37	1/56	1/21	1/35
41	1/29	1/44	1/17	1/28
42	1/23	1/33	1/13	1/22

[a]Risk applies to one or both fetuses.

Data from Meyers C, Adam R, Dungan J, et al: Aneuploidy in twin gestations: when is maternal age advanced? Obstet Gynecol. 1997 Feb;89(2):248–251.

Broadly speaking, there are two types of aneuploidy screening tests, those that are traditional or analyte-based and those that are cell-free DNA-based. All pregnant women should be offered aneuploidy screening or diagnostic testing early in pregnancy (American College of Obstetricians and Gynecologists, 2016c). Considerations prior to screening are as follows:

1. *Has the patient elected screening?* At least 20 percent of women elect not to receive aneuploidy screening, even when financial barriers are removed. Fewer than 40 percent of women with a positive screening result elect prenatal diagnosis (Dar, 2014; Kuppermann, 2014).

2. *Would the patient prefer prenatal diagnosis?* Diagnostic testing is safe and effective, and chromosomal microarray analysis provides information about genetic conditions that screening tests and karyotyping alone currently do not (American College of Obstetricians and Gynecologists, 2016b). This is discussed further in Prenatal Diagnostic Procedures and Preimplantation Testing and in Chapter 13 (Chromosomal Microarray Analysis).

3. *Is this a multifetal gestation?* All traditional (analyte-based) aneuploidy screening tests are significantly less effective in multifetal gestations, and cell-free DNA screening is not currently recommended with multifetal gestations (Cell-Free DNA for Secondary Screening).

4. *What method will be used for neural-tube defect screening?* Whenever a patient elects an aneuploidy screening test that does not include second-trimester serum analytes, screening for neural-tube defects should be performed separately, either with MSAFP assessment or with sonography (American College of Obstetricians and Gynecologists, 2016c).

5. *Does the fetus have a major anomaly?* If so, diagnostic testing is recommended rather than screening.

The American College of Obstetricians and Gynecologists (2016c) has affirmed that screening for aneuploidy should be an informed patient choice, with an underlying foundation of shared decision making that fits her clinical circumstances, values, interests, and goals. Elements of counseling prior to aneuploidy screening are listed in Table 14-3.

TABLE 14-3

Aneuploidy Screening Counseling Elements

1. **All pregnant women have 3 options: screening, diagnostic testing, and no screening or testing.**
   The purpose of a screening test is to provide information, not to dictate a course of action.
   Diagnostic testing is safe and effective and provides information that screening does not.
2. **The difference between a screening test and a diagnostic test.**
   Screening evaluates whether the pregnancy is at increased risk and estimates degree of risk.
   Detection rate, false-negative rate, and false-positive rate are provided.
   Cell-free DNA screening does not always provide a result.
   Irreversible management decisions should not be based on screening test results.
   With a positive screening result, a diagnostic test is recommended if the patient wants to know whether the fetus is affected.
3. **Basic information is provided about each condition covered by the screening test (prevalence, associated abnormalities, prognosis), and screening test limitations.**
   A benefit of diagnosis includes earlier identification of associated abnormalities.
   In case of trisomy 18 or 13, diagnosis may affect pregnancy management if complications arise such as growth restriction or nonreassuring fetal heart rate.
   With sex chromosome aneuploidies, phenotypic expression varies widely. Several are so mild they would otherwise not be diagnosed.
4. **The patient's a priori risk for fetal aneuploidy may affect her screening test options or election.**
   Age-related risk information may be found in reference tables.
   If a patient has had a prior fetus with autosomal trisomy, robertsonian translocation, or other chromosomal abnormality, additional evaluation and counseling are suggested.

Modified with permission from Dashe JS: Aneuploidy screening in pregnancy, Obstet Gynecol. 2016 Jul;128(1):181–194.

Statistical Considerations

Aneuploidy screening can be challenging because the test characteristics of each option may vary with maternal age and with whether the test is analyte-based or cell-free DNA-based.

The test sensitivity is the detection rate—that is, the proportion of aneuploid fetuses identified by the screening test. Its converse, the false-negative rate, is the percentage of cases that the test is expected to miss. A first-trimester screening test with a sensitivity of 80 percent is expected to miss 1 in 5 cases. The sensitivity of screening tests for Down syndrome has increased steadily during the past 30 years, from just 25 percent with serum AFP alone to more than 90 percent with integrated or sequential screening.

Another key characteristic is the false-positive rate, the percentage of unaffected pregnancies that will "falsely" screen positive. This approximates 5 percent for first-trimester screening, quadruple-marker screening, or integrated screening options (Baer, 2015; Kazerouni, 2011; Malone, 2005b; Norton, 2015). The converse of false-positive rate is specificity— analyte-based screens will be reassuring in approximately 95 percent of unaffected pregnancies. Although test sensitivity has improved, the false-positive rate has been held constant for many different aneuploidy screening tests (Table 14-4). Both statistics are relevant for counseling. An additional consideration is that with all analyte-based screening tests, women 35 and older have higher rates of positive results (Kazerouni, 2011; Malone, 2005b).

TABLE 14-4

Characteristics of Screening Tests for Trisomy 21 in Singletons

Screening Test	Detection Rate	False-Positive Rate	Positive-Predictive Value[a]
Quadruple screen:			
AFP, hCG, estriol, inhibin	80–82%	5%	3%
First-trimester screen:			
NT, hCG, PAPP-A	80–84%	5%	3–4%
First-trimester NT alone	64–70%	5%	
Integrated screening	94–96%	5%	5%
Sequential screening:			
Stepwise	92%	5.1%	5%
Contingent	91%	4.5%	5%
Cell-free DNA screening:			
Positive result	99%	0.1%	Table 14-5
Low fetal fraction or no result	—	4–8%	4%

[a]The positive-predictive value represents the overall population studied and cannot be applied to any individual patient.

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; NT = nuchal translucency; PAPP-A = pregnancy-associated plasma protein A.

Data from Baer, 2015; Gil, 2015; Malone, 2005b; Norton, 2015; Pergament, 2014; Quezada, 2015; Dashe, 2016.

Importantly, neither sensitivity nor false-positive rate conveys individual risk. The statistic that patients and providers usually consider to be the test result is the positive-predictive value, which is the proportion of those with a positive screening result who actually have an aneuploid fetus. It may be expressed as a 1:X ratio or as a percentage. The positive-predictive value is directly affected by disease prevalence, so it is much higher for women aged 35 years and older than for younger women (Table 14-5). Positive-predictive values can also be reported for cohorts of pregnancies. For example, the positive-predictive value reported in a research trial is the proportion of women with positive screening results who have affected fetuses (see Table 14-4). Negative-predictive value is the proportion of those with a negative screening test result who have unaffected (euploid) fetuses. Because the prevalence of aneuploidy is so low, the negative-predictive value of all aneuploidy screening tests generally exceeds 99 percent (Gil, 2015; Norton, 2015).

TABLE 14-5

Positive-Predictive Value of Cell-Free DNA Screening for Autosomal Trisomies and Selected Sex Chromosome Abnormalities, According to Maternal Age

Maternal Age	Trisomy 21	Trisomy 18	Trisomy 13	45,X	47,XXY
20	48%	14%	6%	41%	29%
25	51%	15%	7%	41%	29%
30	61%	21%	10%	41%	29%
35	79%	39%	21%	41%	30%
40	93%	69%	50%	41%	52%
45	98%	90%	NA	41%	77%

NA = not available; NIPT = non-invasive prenatal test.

Positive-predictive values were obtained using the NIPT/Cell Free DNA Screening Predictive Value Calculator from the Perinatal Quality Foundation, 2017.

Calculations are based on prevalence at 16 weeks' gestation using sensitivities and specificities from Gil, 2015.

Traditional Aneuploidy Screening Tests

These screening tests have multiple markers or analytes and are also called conventional or traditional to differentiate them from cell-free DNA-based screening. There are three categories: first-trimester screens, second-trimester screens, and combinations of first- and second-trimester screens. If the test has a first-trimester component, it almost always includes a measurement of the sonographic nuchal translucency, which is discussed in the next section.

Each maternal serum analyte is measured as a concentration—for example, nanograms per milliliter of AFP. The concentration is converted to a multiple of the median (MoM) by adjusting for maternal age, maternal weight, and gestational age. The nuchal translucency measurement increases with crown-rump length (CRL), and thus its value is adjusted for CRL and also reported as an MoM. The AFP analyte is further adjusted for maternal race and ethnicity and for presence of diabetes, which all affect the calculation of neural-tube defect risk rather than of aneuploidy risk (Greene, 1988; Huttly, 2004). Reporting these results as an MoM of the unaffected population normalizes the distribution of analyte levels and permits comparison of results from different laboratories and populations.

The analyte-based aneuploidy screening result is based on a composite likelihood ratio, and the maternal age-related risk is multiplied by this ratio. This principle similarly applies to modification of fetal Down syndrome risk by selected sonographic markers, which are discussed later in Sonographic Screening. Each woman is provided with a specific risk for trisomy 21 and for trisomy 18—or in the first trimester, for trisomy 18 or 13 in some cases. The result is expressed as a ratio that represents the positive-predictive value.

Importantly, each screening test also has a predetermined value at which or above which it is deemed "positive" or abnormal. For second-trimester tests, this threshold has traditionally been set at the risk for fetal Down syndrome in a woman aged 35 years—approximately 1 in 270 in the second trimester (see Table 14-1). The threshold selected for a positive screen reflects the laboratory requirement but is somewhat problematic, as it may bear no relationship to patient preference. However, a positive screening result may affect whether the patient is deemed "high risk," receives formal genetic counseling, and is offered diagnostic testing with chorionic villus sampling or amniocentesis. Thus, it behooves the provider to discuss the patient's preferences prior to screening.

First-Trimester Aneuploidy Screening

Also called combined first-trimester screening, this test combines two maternal serum analytes, human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein A (PAPP-A), with the sonographic measurement of the nuchal translucency (NT). It is performed between 11 and 14 weeks' gestation. In cases of fetal Down syndrome, the first-trimester serum free β-hCG level is higher and the PAPP-A level is lower. With trisomy 18 and trisomy 13, levels of both analytes are lower (Cuckle, 2000; Malone, 2005b).

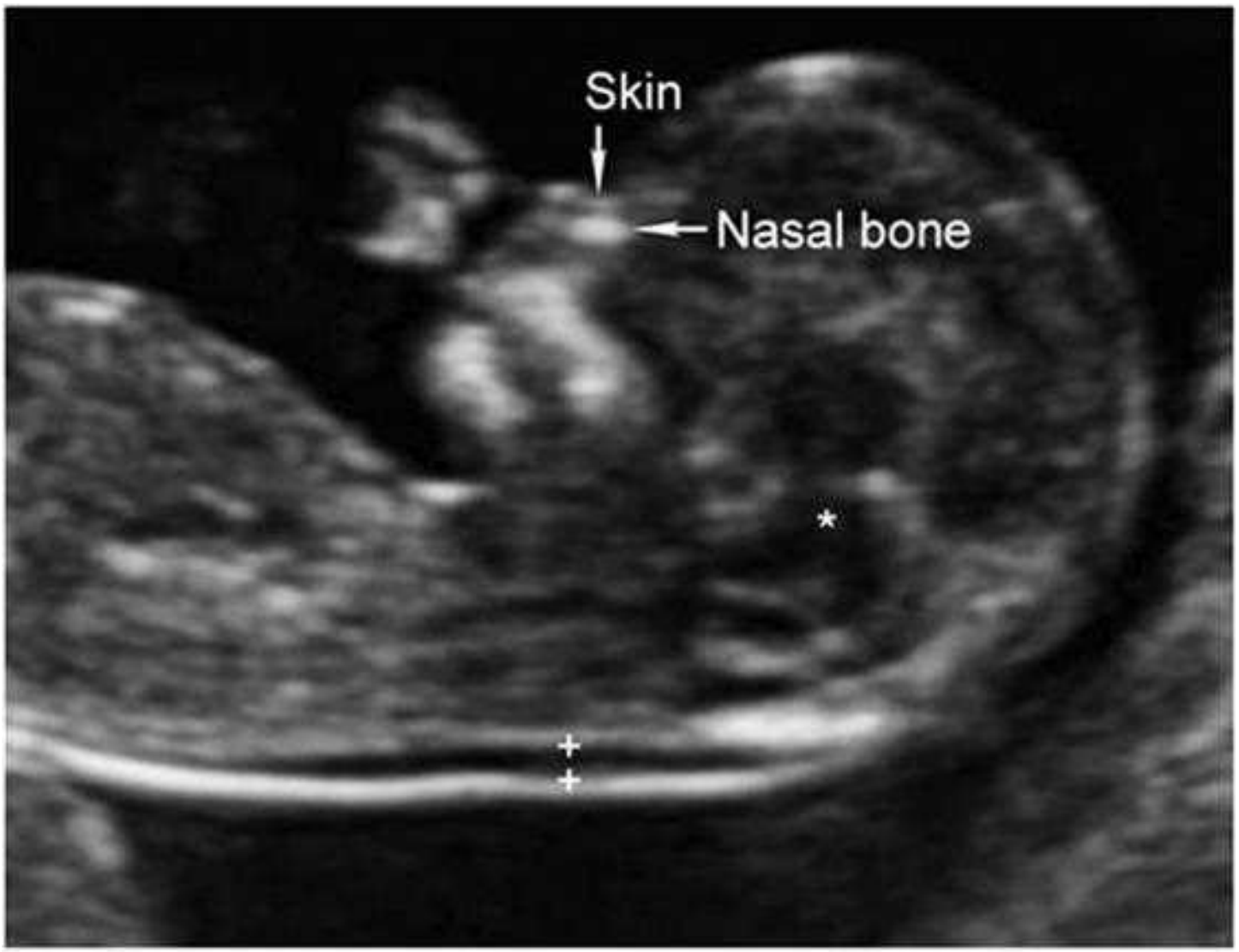
Nuchal Translucency

This is the maximum thickness of the subcutaneous translucent area between the skin and soft tissue overlying the fetal spine at the back of the neck (Fig. 14-2). An increased NT thickness is not a fetal abnormality but rather is a marker that confers increased risk. It is measured in the sagittal plane and is valid when the CRL value lies between 38 to 45 mm and 84 mm, with the lower limit varying according to the laboratory. Specific criteria for NT measurement are listed in Table 10-4. Whenever possible, it is helpful to differentiate increased NT from cystic hygroma, which is a venolymphatic malformation that appears as a septated hypoechoic space behind the neck, extending along the length of the back (Fig. 10-22). Cystic hygroma confers a fivefold increased aneuploidy risk when identified in the first trimester (Malone, 2005a).

FIGURE 14-2

Sagittal image of a normal, 12-week fetus demonstrating correct caliper placement (+) for nuchal translucency measurement. The fetal nasal bone and overlying skin are indicated. The nasal tip and the 3rd and 4th ventricles (*asterisk*), which are other landmarks that should be visible in the nasal bone image, are also shown. (Used

with permission from Dr. Michael Zaretsky.)



In addition to aneuploidy, an increased NT thickness is associated with other genetic syndromes and various birth defects, especially fetal cardiac anomalies (Simpson, 2007). And, if the NT measurement reaches 3 mm or more, the aneuploidy risk is unlikely to normalize using serum analyte assessment (Comstock, 2006). Because of this, if the NT measurement is at least 3 mm or exceeds the 99th percentile, the patient should receive counseling and be offered targeted sonography with fetal echocardiography. In addition, she should be offered cell-free DNA screening and prenatal diagnosis (American College of Obstetricians and Gynecologists, 2016c).

The NT must be imaged and measured with a high degree of precision for aneuploidy detection to be accurate. This has led to standardized training, certification, and ongoing quality review programs. In the United States, training, credentialing, and monitoring are available through the Nuchal Translucency Quality Review program of the Perinatal Quality Foundation and through the Fetal Medicine Foundation.

Efficacy of First-Trimester Screening

Before first-trimester screening became widely adopted, four large prospective trials were conducted, together including more than 100,000 pregnancies (Reddy, 2006). When the false-positive rate was set at 5 percent, the overall rate for trisomy 21 detection was 84 percent, comparable to quadruple-marker screening (see Table 14-4). The detection rate is approximately 5 percent higher if performed at 11 weeks' compared with 13 weeks' gestation, and slightly lower—80 to 82 percent—when cases with cystic hygroma are analyzed separately (Malone, 2005a). In a recent multicenter trial, first-trimester screening detected approximately 80 percent of fetuses with trisomy 21, 80 percent with trisomy 18, and 50 percent with trisomy 13 (Norton, 2015).

As an isolated marker, NT detects approximately two thirds of fetuses with Down syndrome, with a false-positive rate of 5 percent (Malone, 2005b). However, NT is generally used as an isolated marker only in screening for multifetal gestations, in which serum screening is less accurate or may not be available. The NT distribution is similar in twins and singletons (Cleary-Goldman, 2005). In twin pregnancies, serum free β-hCG and PAPP-A levels are approximately double the singleton values (Vink, 2012). Even with specific curves, a normal dichorionic cotwin will tend to normalize screening results, and thus, the aneuploidy detection rate is at least 15-percent lower (Bush, 2005).

Maternal age affects the performance of first-trimester aneuploidy screening. Prospective trials have demonstrated Down syndrome detection rates of 67 to 75 percent in women younger than 35 years at delivery, which are 10 percent lower than the overall detection rates in these studies (Malone, 2005b; Wapner, 2003). Among women older than 35 at delivery, Down syndrome detection reached 90 to 95 percent, albeit at a higher false-positive rate of 15 to 22 percent.

Unexplained Abnormalities of First-Trimester Analytes

There is a significant association between serum PAPP-A levels below the 5th percentile and preterm birth, growth restriction, preeclampsia, and fetal demise (Cignini, 2016; Dugoff, 2004; Jelliffe-Pawlowski, 2015). Similarly, low levels of free β-hCG have been associated with fetal demise (Goetzl, 2004). The sensitivity and positive-predictive values of isolated markers are generally too low to make them clinically useful as screening tests.

There has been renewed interest in low-dose aspirin for prevention of early preeclampsia in women identified as at risk based on mean arterial pressure, uterine artery Doppler values, and PAPP-A levels. However, these observations are preliminary (Park, 2015).

Second-Trimester Aneuploidy Screening

Currently, the only second-trimester multiple marker test widely used in the United States is the quadruple marker or “quad” screening test. It is performed from 15 to 21 weeks’ gestation, and inclusive gestational age ranges vary according to individual laboratories. Pregnancies with fetal Down syndrome are characterized by lower maternal serum AFP, higher hCG, lower unconjugated estriol, and higher dimeric inhibin levels. When the quad screen was initially described, the Down syndrome detection rate approximated 70 percent. But, by the early 2000s, the reported detection rate in two large prospective trials had improved to 81 to 83 percent, with a 5-percent screen-positive rate (Malone, 2005b; Wald, 1996, 2003). The improved detection rate is attributable, at least in part, to accurate gestational age assessment with sonography. In a review of more than 500,000 pregnancies receiving quadruple-marker screening through the statewide California Prenatal Screening Program, trisomy 21 detection was 78 percent with sonographic gestational age assessment but only 67 percent when the screen was calculated based on last menstrual period alone (Kazerouni, 2011). As with first-trimester screening, aneuploidy detection rates are lower in younger women and higher in women older than 35 years at delivery. If second-trimester serum screening is used in twin pregnancies, aneuploidy detection rates are significantly lower (Vink, 2012). With trisomy 18, the levels of the first three analytes are all decreased, and inhibin is not part of the calculation. Trisomy 18 detection is similar to that for Down syndrome, with a false-positive rate of only 0.5 percent (Benn, 1999).

Although the quadruple-marker screening test is used to screen for Down syndrome and trisomy 18, pregnancies with *other* chromosomal abnormalities may be identified as well. The California Prenatal Screening Program found that the quadruple-marker screen result was abnormal in 96 percent of those with triploidy, in 75 percent with Turner syndrome (45,X), in 44 percent with trisomy 13, and in more than 40 percent of those with other major chromosomal abnormalities (Kazerouni, 2011). Although a specific risk for these aneuploidies cannot be provided based on the test result, the information may be relevant for women considering amniocentesis.

Quadruple-marker screening offers no benefit over first-trimester screening from the standpoint of trisomy 21 or trisomy 18 detection. As a stand-alone test, it is generally used if women do not begin care until the second trimester or if first-trimester screening is not available. In 2011, women who initiated prenatal care beyond the first trimester made up nearly 25 percent of pregnancies in the United States. As subsequently discussed, combining first- and second-trimester screening yields an even greater aneuploidy detection rate.

Maternal Serum AFP Elevation: Neural-Tube Defect Screening

All pregnant women are offered screening for fetal open neural-tube defects in the second trimester, either with MSAFP screening or with sonography (American College of Obstetricians and Gynecologists, 2016c). Measurement of the MSAFP concentration between 15 and 20 weeks’ gestation has been offered as part of routine prenatal care for more than 30 years. Because AFP is the major protein in fetal serum, analogous to albumin in a child or adult, the normal concentration gradient between fetal plasma and maternal serum is on the order of 50,000:1. Defects in fetal integument, such as neural-tube and ventral-wall defects, permit AFP to leak into the amnionic fluid, resulting in dramatically increased maternal serum levels. The AFP value rises by about 15 percent per week during the screening window (Knight, 1992). The MoM is generally recalculated if the first-trimester CRL or second-trimester biparietal diameter differs from the stated gestational age by more than 1 week.

Using an MSAFP level of 2.5 MoM as the upper limit of normal, the neural-tube defect detection rate is at least 90 percent for anencephaly and 80 percent for spina bifida, with a screen-positive rate of 3 to 5 percent (American College of Obstetricians and Gynecologists, 2016a; Milunsky, 2004). Higher screening threshold values are used in twin pregnancies (Cuckle, 1990).

Virtually all cases of anencephaly and many cases of spina bifida may be detected or suspected during a standard second-trimester sonographic examination (Dashe, 2006). Most centers now use targeted sonography as the primary method to evaluate elevated MSAFP levels and as the prenatal diagnostic test of choice for neural-tube defects (Chap. 10, Neural-Tube Defects). If targeted sonography is not available and myelomeningocele cannot be excluded, amniocentesis may be considered for measurement of amnionic fluid AFP and acetylcholinesterase levels. That said, we recommend additional imaging prior to establishing the diagnosis, with the understanding that other abnormalities or conditions can result in elevation of these amnionic fluid analytes (Table 14-6). Sonographic findings characteristic of fetal neural-tube defects are reviewed in Chapter 10 (Neural-Tube Defects). Fetal surgery for myelomeningocele is discussed in Chapter 16 (Open Fetal Surgery).

TABLE 14-6

Conditions Associated with an Elevated MSAFP Concentration

Underestimated gestational age
Multifetal gestation
Fetal death
Neural-tube defect
Gastroschisis
Omphalocele
Cystic hygroma
Esophageal or intestinal obstruction
Liver necrosis
Renal anomalies—polycystic kidneys, renal agenesis, congenital nephrosis, urinary tract obstruction
Cloacal exstrophy
Osteogenesis imperfecta
Sacrococcygeal teratoma
Congenital skin abnormality
Pilonidal cyst
Chorioangioma of placenta
Placenta intervillous thrombosis
Placental abruption
Oligohydramnios
Preeclampsia
Fetal-growth restriction
Maternal hepatoma or teratoma

MSAFP = maternal serum alpha-fetoprotein.

Unexplained Abnormalities of Second-Trimester Analytes

The positive-predictive value of an elevated MSAFP value is only 2 percent. Approximately 98 percent of pregnancies with an MSAFP level exceeding 2.5 MoM have an etiology other than a neural-tube defect. Thus, counseling is indicated not only to inform the patient about the benefits and limitations of targeted sonography for the diagnosis of neural-tube defects but also to review the numerous other conditions. Some of these include fetal anomalies, placental abnormalities, and adverse outcomes associated with MSAFP level elevation (see Table 14-6). The likelihood of one of these abnormalities or of an adverse pregnancy outcome in the absence of a recognized abnormality rises in proportion to the AFP level. Adverse outcomes include fetal-growth restriction, preeclampsia, preterm birth, fetal demise, and stillbirth. More than 40 percent of pregnancies may be abnormal if the MSAFP level is greater than 7 MoM (Reichler, 1994).

Second-trimester elevation of either hCG or dimeric inhibin alpha levels also shows significant association with adverse pregnancy outcomes. The outcomes reported are similar to those associated with MSAFP level elevation. Moreover, the likelihood of adverse outcome is augmented when levels of several markers are elevated (Dugoff, 2005).

Many of these complications are assumed to result from placental damage or dysfunction. However, the sensitivity and positive-predictive values of these markers are considered too low to be useful for screening or management. No specific program of maternal or fetal surveillance has been found to favorably affect pregnancy outcomes (Dugoff, 2010). At Parkland Hospital, prenatal care for these women is not altered unless a specific complication arises. Despite the extensive list of possible adverse outcomes, it is reassuring that most women with unexplained elevation of these analytes have normal outcomes.

Low Maternal Serum Estriol Level

A maternal serum estriol level less than 0.25 MoM has been associated with two uncommon but important conditions. The first, *Smith-Lemli-Opitz syndrome*, is an autosomal recessive condition resulting from mutations in the 7-dehydrocholesterol reductase gene. It is characterized by abnormalities of the central nervous system, heart, kidney, and extremities; with ambiguous genitalia; and with fetal-growth restriction. For this reason, the Society for Maternal-Fetal Medicine has recommended that sonographic evaluation be performed if an unconjugated estriol level is <0.25 MoM (Dugoff, 2010). If abnormalities are identified, an elevated amnionic fluid 7-dehydrocholesterol level can confirm the diagnosis.

The second condition is *steroid sulfatase deficiency*, also known as *X-linked ichthyosis*. It is typically an isolated condition, but it may also occur in the setting of a contiguous gene deletion syndrome (Chap. 13, Abnormalities of Chromosome Structure). In such cases, it may be associated with Kallmann syndrome, chondrodysplasia punctata, and/or mental retardation (Langlois, 2009). If the estriol level is <0.25 MoM and the fetus appears to be male, chromosomal microarray analysis or fluorescence in situ hybridization to assess the steroid sulfatase locus on the X-chromosome may be considered.

Integrated and Sequential Screening

As shown in Table 14-4, if first-trimester screening is combined with second-trimester screening, aneuploidy detection is significantly improved. Combined screening test options require coordination between the provider and laboratory. Specifically, if a second sample is required, it is obtained during the appropriate gestational

age window, sent to the same laboratory, and linked to the first-trimester results. The first- and second-trimester components cannot be performed independently because if either component yields positive results, then providing accurate risk assessment would be problematic.

Three types of screening strategies are available:

1. *Integrated screening* combines results of first- and second-trimester tests. This includes a combined measurement of fetal NT and serum analyte levels at 11 to 14 weeks' gestation plus quadruple markers at approximately 15 to 21 weeks. An aneuploidy risk is then calculated from these seven parameters. As expected, integrated screening has the highest Down syndrome detection rate—94 to 96 percent, with a false-positive rate of 5 percent (see Table 14-4). If NT measurement is not available, then s*erum integrated screening* includes all six serum markers to calculate risk. This screening, however, is less effective, and Down syndrome detection rates are 85 to 88 percent (Malone, 2005b).

2. *Sequential screening* involves performing first-trimester screening and informing the patient of the results. This is coupled with the understanding that if the calculated risk value lies above a specified threshold, she will receive counseling and will be offered diagnostic testing. There are two testing strategies in this category:

- With *stepwise sequential screening*, women with first-trimester screen results that confer risk for Down syndrome above a particular threshold are offered invasive testing, and the remaining women receive second-trimester screening. Using data from the First- and Second-Trimester Evaluation of Risk (FaSTER) trial, when the first-trimester threshold is set at approximately 1:30, and the overall threshold is set at 1:270, stepwise sequential screening resulted in a 92-percent detection rate of Down syndrome pregnancies, with a false-positive rate of 5 percent (see Table 14-4) (Cuckle, 2008).

- With *contingent sequential screening*, women are divided into high-, moderate-, and low-risk groups. Those at highest risk for Down syndrome—for example, risk >1:30, are counseled and offered invasive testing. Women at moderate risk, between 1:30 and 1:1500, undergo second-trimester screening, whereas those at lowest risk of <1:1500 receive negative screening test results and have no further testing (Cuckle, 2008). Using this strategy, more than 75 percent of those screened are provided with reassuring results almost immediately, while still maintaining a high detection rate of about 91 percent, with a 5-percent false-positive rate (see Table 14-4). This option is also more cost effective because a second-trimester test is obviated in most patients.

In a population-based review of 450,000 pregnancies from the California Prenatal Screening Program, integrated screening detected 94 percent of trisomy 21 fetuses and 93 percent with trisomy 18 (Baer, 2015). Additionally, the screening result was abnormal in 93 percent of cases of trisomy 13, in 91 percent with triploidy, and in 80 percent with Turner syndrome. Women considering options of integrated screening and cell-free DNA screening may find this information helpful.

Cell-Free DNA Screening

This was introduced in 2011 and has completely changed the prenatal screening paradigm. The test works by identifying DNA fragments that are derived primarily from apoptotic trophoblasts, which are placental cells undergoing programmed cell death. Thus, the term cell-free *fetal* DNA is somewhat of a misnomer. Screening is not gestational-age dependent and can be performed at any time after 9 to 10 weeks' gestation. Results are available in 7 to 10 days (American College of Obstetricians and Gynecologists, 2017c). Three types of assays are currently available: whole-genome sequencing, which is also called massively parallel or shotgun sequencing; chromosome selective or targeted sequencing; and analysis of single nucleotide polymorphisms.

The screening performance of cell-free DNA is excellent. In a metaanalysis of 37 studies of largely high-risk pregnancies, the pooled sensitivity to detect Down syndrome was 99 percent, and for trisomies 18 and 13, 96 percent and 91 percent, respectively. For each of these autosomal trisomies, the specificity was 99.9 percent. Thus, most unaffected pregnancies received a normal screening result. Cell-free DNA also detects 90 percent with Turner syndrome (45,X) and 93 percent with sex chromosome aneuploidies other than 45,X (Gil, 2015). The false-positive rate is cumulative for each aneuploidy for which screening is performed, but it is usually only 0.5 to 1 percent. As a result, cell-free DNA screening is recommended as a screening option in those at increased risk for fetal autosomal trisomy (American College of Obstetricians and Gynecologists, 2017c; Society for Maternal-Fetal Medicine, 2015). This includes the following categories:

1. Women who will be 35 years or older at delivery
2. A positive first- or second-trimester analyte-based screening test
3. Sonogram with a minor aneuploidy marker
4. Prior pregnancy with autosomal trisomy
5. Known carriage (patient or partner) of a balanced robertsonian translocation involving chromosome 21 or 13.

Cell-Free DNA for Secondary Screening

If cell-free DNA screening is performed as a *secondary screen* following a positive first- or second-trimester analyte-based test result, a normal result is not quite as reassuring. The residual risk for chromosomal abnormality is estimated to be 2 percent (Norton, 2014). Compared with amniocentesis, use of cell-free DNA screening after an initial abnormal analyte-based test result is estimated to yield a 20-percent reduction in aneuploidy diagnoses. This takes into consideration false-negative diagnoses and aneuploidies not detectable with cell-free DNA screening (Davis, 2014; Norton, 2014). In addition, definitive diagnosis may be delayed, potentially affecting management. Concurrent or parallel screening is not recommended, and if an aneuploidy screening test of any type yields a negative result, additional screening is not indicated (American College of Obstetricians and Gynecologists, 2016b, 2017c).

The association between increased NT values and fetal structural and genetic abnormalities has raised questions about the role of a NT measurements following cell-free DNA screening. The College (2016b) has stated that NT measurement is not necessary at the time of cell-free DNA screening but that sonography may help to

confirm fetal number and viability and to assign gestational age. The Society for Maternal-Fetal Medicine (2015) states that after a negative cell-free DNA screening test result, the additional clinical utility of NT measurement to detect other chromosomal or structural abnormalities is unknown but appears to be limited.

Cell-Free DNA Screening in Low-Risk Pregnancies

Most studies of cell-free DNA have been conducted in high-risk pregnancies. Pragmatically, chromosomal abnormalities are individually so rare that even large studies of low-risk pregnancies contain few affected cases. Available data suggest that the high sensitivity and specificity for Down syndrome detection are preserved in low-risk pregnancies (Norton, 2015; Pergament, 2014; Zhang, 2015). Importantly, the positive-predictive value of cell-free DNA screening still depends greatly on maternal age and the specific aneuploidy in question (see Table 14-5). For a woman in her early 20s, the positive-predictive value is approximately 50 percent for fetal trisomy 21, 15 percent for trisomy 18, and <10 percent for trisomy 13. Hence, decisions for irreversible medical intervention should not be based on the results of this or other screening test alone.

Cell-Free DNA Screening Limitations

Important caveats are considered with selection of cell-free DNA aneuploidy screening. Because the cell-free DNA that is analyzed is maternal and placental, results may not reflect the fetal DNA complement but rather may indicate confined placental mosaicism, early demise of an aneuploid co- twin, maternal mosaicism, or even occult maternal malignancy (Bianchi, 2015; Curnow, 2015; Grati, 2014; Wang, 2014). In addition, if a twin pregnancy is identified sonographically, cell-free DNA screening is not currently recommended because of limited evidence regarding efficacy.

Another limitation is that cell-free DNA testing does not yield a result in approximately 4 to 8 percent of screened pregnancies, due to assay failure, high assay variance, or low fetal fraction (Norton, 2012; Pergament, 2014; Quezada, 2015). Most cell-free DNA is maternal. The fetal fraction is the proportion derived from the placenta and generally is about 10 percent of the total. A low fetal fraction is usually defined as <4 percent of the total and confers significantly higher risk for fetal aneuploidy (Ashoor, 2013; Norton, 2015; Pergament, 2014). Women with a low fetal fraction or “no-call” results have fetal aneuploidy rates as high as 4 percent, a percentage comparable to the average predictive value conferred by a positive first-trimester screening test result (see Table 14-4). The fetal fraction is not related to maternal age or analyte-based screening test results. However, it is lower earlier in pregnancy and appears to be reduced in women of greater weight (Ashoor, 2013).

Because of the increased risk for fetal aneuploidy in cases not generating a cell-free DNA screening result (no-call result), genetic counseling is indicated, and amniocentesis should be offered. If the patient elects repeat screening, the risk for screen failure may exceed 40 percent (Dar, 2014; Quezada, 2015). Targeted sonography is recommended but is not a substitute for amniocentesis, because it is unclear what the residual risk would be with normal sonogram findings. (American College of Obstetricians and Gynecologists, 2016b, 2017c). Pretest counseling should include the possibility of a low fetal fraction or no-call result and its clinical significance.

Comparison with Analyte-Based Screening

Cell-free DNA screening has obvious advantages, but it is not simply a “better” test—because no screening test is superior for all test characteristics (American College of Obstetricians and Gynecologists, 2016c). Compared with analyte-based tests, benefits of cell-free DNA screening in women 35 years and older include the lower likelihood of a false-positive result, its higher positive-predictive value, and the fact that isolated minor aneuploidy markers are generally not a concern (Sonographic Screening).

But, analyte-based tests are frequently positive with a large range of chromosomal abnormalities, whereas cell-free DNA screens are specific for individual aneuploidies (Baer, 2015; Kazerouni, 2011). Women younger than 35 are at lower risk for the specific autosomal trisomies for which cell-free DNA screening is typically performed. Thus, if the goal is to select a screening test that will identify the highest proportion of fetuses with any chromosomal abnormality, the yield may be comparable or even slightly higher with integrated or sequential screening than with current cell-free DNA screening (Baer, 2015; Norton, 2014).

Sonographic Screening

Sonography can augment aneuploidy screening by providing accurate gestational age assessment, by detecting multifetal gestations, and by identifying major structural abnormalities and minor sonographic markers. As shown in Table 14-7, with rare exceptions, the aneuploidy risk associated with any major abnormality is high enough to warrant offering prenatal diagnosis. Generally, chromosomal microarray analysis is recommended as the first-line test. Importantly, a fetus with one abnormality may have others that are less likely to be detected sonographically but that greatly affect the prognosis. Aneuploidy screening—including cell-free DNA—is not recommended if a major abnormality has been identified. The fetal risk cannot be normalized with a normal screening result, not merely because screening results can be falsely negative, but also because major anomalies confer risk for genetic syndromes not identified through screening tests.

TABLE 14-7

Aneuploidy Risk Associated with Selected Major Fetal Anomalies

Abnormality	Birth Prevalence	Aneuploidy Risk (%)	Common Aneuploidies[a]
Cystic hygroma	1/5000	50–70	45,X; 21; 18; 13; triploidy
Nonimmune hydrops	1/1500–4000	10–20	21, 18, 13, 45X, triploidy
Ventriculomegaly	1/1000–2000	5–25	13, 18, 21, triploidy
Holoprosencephaly	1/10,000–15,000	30–40	13, 18, 22, triploidy
Dandy-Walker malformation	1/12,000	40	18, 13, 21, triploidy
Cleft lip/palate	1/1000	5–15	18, 13
Cardiac defects	5–8/1000	10–30	21; 18; 13; 45,X; 22q11.2 microdeletion
Diaphragmatic hernia	1/3000–4000	5–15	18, 13, 21
Esophageal atresia	1/4000	10	18, 21
Duodenal atresia	1/10,000	30	21
Gastroschisis	1/2000–4000	No increase	
Omphalocele	1/4000	30–50	18, 13, 21, triploidy
Clubfoot	1/1000	5–30	18, 13

[a]Numbers indicate autosomal trisomies except where indicated. For example, 45,X indicates Turner syndrome.

Data from Best, 2012; Canfield, 2006; Colvin, 2005; Cragan, 2009; Dolk, 2010; Ecker, 2000; Gallot, 2007; Long, 2006; Orioli, 2010; Pedersen, 2012; Sharma, 2011; Solomon, 2010; Walker, 2001.

If a major abnormality is identified, targeted sonography is indicated. Sonography is not an alternative to prenatal diagnosis, but the aneuploidy risk is further increased if additional findings are identified. An earlier study reported that only 25 to 30 percent of second-trimester fetuses with Down syndrome had a major malformation that could be identified sonographically (Vintzileos, 1995). When both major anomalies and minor aneuploidy markers are considered, it is estimated that 50 to 60 percent of Down syndrome pregnancies can be detected sonographically (American College of Obstetricians and Gynecologists, 2016c). Fortunately, most fetuses with aneuploidy that is likely to be lethal in utero—such as trisomy 18 and 13 and triploidy—usually have sonographic abnormalities that can be seen by the second trimester.

Second-Trimester Markers—"Soft Signs"

For three decades, investigators have recognized that the sonographic detection of aneuploidy, particularly Down syndrome, may be improved by minor markers that are collectively referred to as "soft signs." Minor markers are normal variants rather than fetal abnormalities, and in the absence of aneuploidy or an associated abnormality, they do not significantly affect prognosis. They are present in at least 10 percent of unaffected pregnancies (Bromley, 2002; Nyberg, 2003). Examples of these sonographic findings are listed in Table 14-8 and depicted in Figure 14-3. Findings are generally useful from 15 to 20 or 22 weeks' gestation. Six of these markers have been the focus of sonographic studies, in which likelihood ratios have been derived that allow a numerical aneuploidy risk to be calculated (Table 14-9). The risk rises steeply with the number of markers identified. Alternatively, absence of a minor marker has been used to reduce the calculated risk (Agathokleous, 2013). This should be done systematically, following a protocol that specifies the markers included in a model, the definition for what constitutes a finding, and positive- and negative-likelihood ratios (Reddy, 2014).

TABLE 14-8

Second-Trimester Sonographic Markers or "Soft Signs" Associated with Fetal Trisomy 21[a]

Aberrant right subclavian artery
Brachycephaly or shortened frontal lobe
Clinodactyly (hypoplasia of the 5th digit middle phalanx)
Echogenic bowel
Flat facies
Echogenic intracardiac focus
Nasal bone absence or hypoplasia
Nuchal fold thickening
Renal pelvis dilation (mild)
"Sandal gap" between first and second toes
Shortened ear length
Single transverse palmar crease
Single umbilical artery
Short femur
Short humerus
Widened iliac angle

[a]Listed alphabetically.

TABLE 14-9

Likelihood Ratios and False-Positive Rates for Isolated Second-Trimester Markers Used in Down Syndrome Screening Protocols

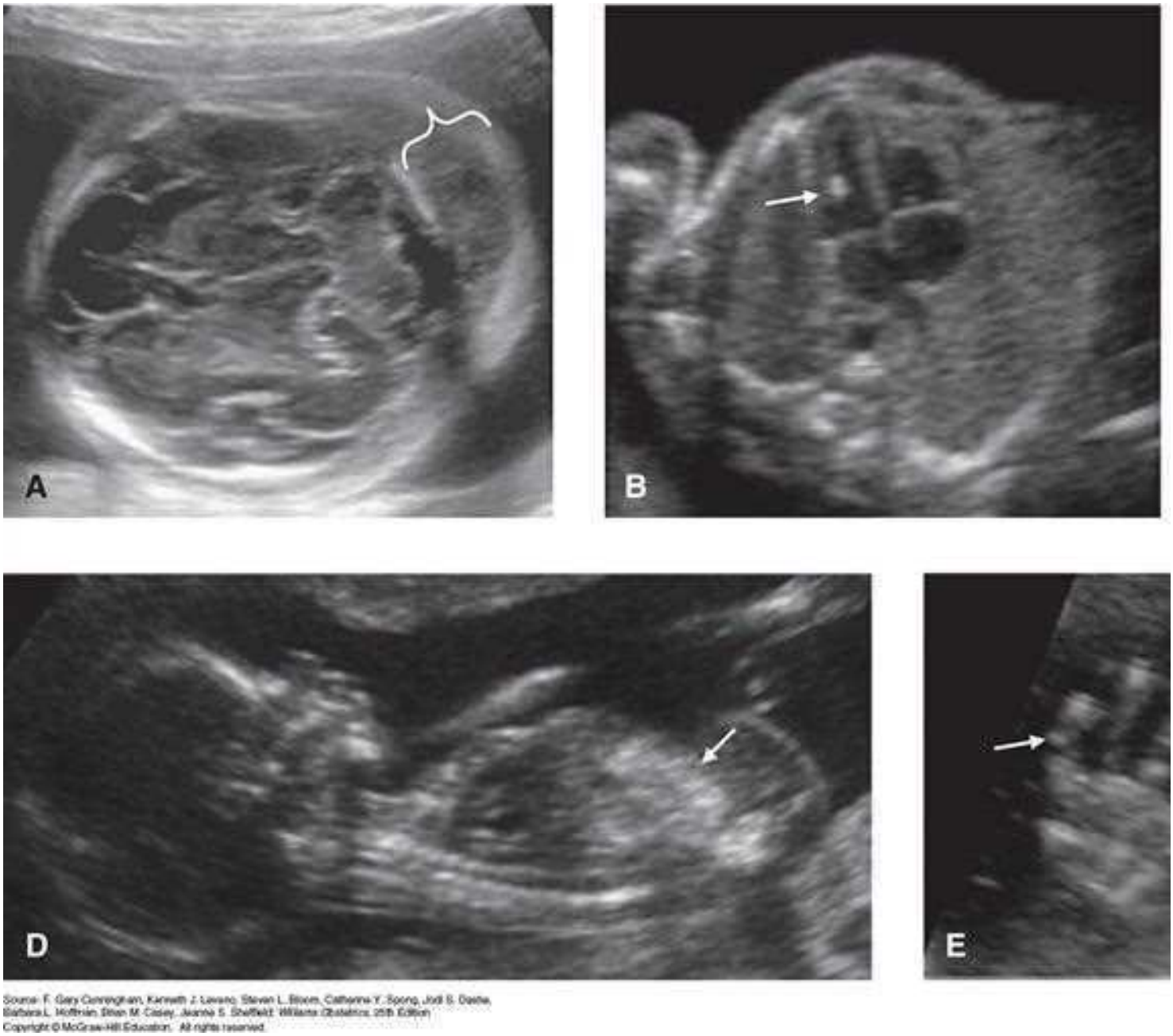
Sonographic Marker	Likelihood Ratio	Prevalence in Unaffected Fetuses (%)
Nuchal skinfold thickening	11–17	0.5
Renal pelvis dilation	1.5–1.9	2.0–2.2
Echogenic intracardiac focus	1.4–2.8	3.8–3.9[a]
Echogenic bowel	6.1–6.7	0.5–0.7
Short femur	1.2–2.7	3.7–3.9
Short humerus	5.1–7.5	0.4
Any one marker	1.9–2.0	10.0–11.3
Two markers	6.2–9.7	1.6–2.0
Three or more	80–115	0.1–0.3

[a]Higher in Asian individuals.

Data from Bromley, 2002; Nyberg, 2001; Smith-Bindman, 2001.

FIGURE 14-3

Minor sonographic markers that are associated with increased risk for fetal Down syndrome. **A.** Nuchal skinfold thickening (*bracket*). **B.** Echogenic intracardiac focus (*arrow*). **C.** Mild renal pelvis dilatation (pyelectasis) (*arrows*). **D.** Echogenic bowel (*arrow*). **E.** Clinodactyly—hypoplasia of the 5th finger middle phalanx creates an inward curvature (*arrow*). **F.** "Sandal-gap" (*arrow*).



The *nuchal skinfold* is measured in the transcerebellar view of the fetal head, from the outer edge of the skull to the outer border of the skin (see Fig. 14-3A). A measurement ≥6 mm is typically considered abnormal (Benacerraf, 1985). This finding is present in approximately 1 per 200 pregnancies and confers a more than tenfold risk for Down syndrome (Bromley, 2002; Nyberg, 2001; Smith-Bindman, 2001).

An *echogenic intracardiac focus* is a focal papillary muscle calcification that is neither a structural nor functional cardiac abnormality. It is usually left-sided (see Fig. 14-3B). Such a focus is present in approximately 4 percent of fetuses, but it may be found in up to 30 percent of Asian individuals (Shipp, 2000). As an isolated finding, this approximately doubles the risk for fetal Down syndrome (see Table 14-9). Bilateral echogenic foci are associated with trisomy 13 (Nyberg, 2001).

Mild *renal pelvis dilatation* is usually transient or physiological and does not represent an underlying abnormality (Chap. 10, Renal Pelvis Dilatation). The renal pelves are measured in a transverse image of the kidneys, anterior-to-posterior, with calipers placed at the inner borders of the fluid collection (see Fig. 14-3C). A measurement ≥4 mm is found in about 2 percent of fetuses and approximately doubles the risk for Down syndrome. The degree of pelvic dilatation beyond 4 mm correlates with the likelihood of an underlying renal abnormality, and additional evaluation is generally performed at approximately 32 weeks.

Echogenic fetal bowel is defined as bowel that appears as bright as fetal bone (see Fig. 14-3D). It is identified in approximately 0.5 percent of pregnancies and most commonly represents small amounts of swallowed blood, frequently in the setting of maternal serum AFP level elevation. Although typically associated with normal outcomes, it raises the risk for Down syndrome approximately sixfold. Echogenic bowel has also been associated with fetal cytomegalovirus infection and cystic fibrosis—representing inspissated meconium in the latter.

The femur and humerus are slightly shorter in Down syndrome fetuses. The femur is considered “short” for Down syndrome screening if it measures below the 2.5th percentile or is shortened to ≤90 percent of that expected based on the measured biparietal diameter (American College of Obstetricians and Gynecologists, 2016c; Benacerraf, 1987). As an isolated finding in an otherwise low-risk pregnancy, it is generally not considered to pose great enough risk to warrant counseling

modification. Similarly, a humerus shortened to ≤89 percent of that expected, based on a given biparietal diameter, has also been associated with an elevated risk for Down syndrome.

If an isolated minor marker is identified in a woman who has not yet received aneuploidy screening, screening should be offered, and a minor marker is considered an indication to offer cell-free DNA screening (American College of Obstetricians and Gynecologists, 2016c). If cell-free DNA screening has already been performed, the association between isolated minor markers and aneuploidy risk is no longer considered relevant (Reddy, 2014). And, if the cell-free DNA screening result is negative, the fetal aneuploidy risk is not modified by the marker. Conversely, if a cell-free DNA screening result is positive, the absence of minor markers is not considered reassuring.

First-Trimester Sonographic Findings

Unlike second-trimester soft signs, which may be readily visible during standard sonography, first-trimester findings associated with aneuploidy require specialized training. The fetal NT measurement has gained widespread use for aneuploidy screening. Other first-trimester sonographic findings are not routinely used in the United States but may be available in specialized centers. The Perinatal Quality Foundation's Nuchal Translucency Quality Review Program offers an education program in first-trimester nasal bone assessment (see Fig. 14-2). The Fetal Medicine Foundation also provides online instruction and certification in first-trimester assessment of nasal bone, ductus venosus flow, and tricuspid flow.

Other benefits of first-trimester sonography in women who elect aneuploidy screening include accurate assessment of gestational age and early detection of multifetal gestation or fetal demise. As discussed in Chapter 10 (Second- and Third-Trimester Sonography), first-trimester sonography may identify selected major anomalies associated with aneuploidy, such as cystic hygroma.

CARRIER SCREENING FOR GENETIC DISORDERS

Three types of carrier screening may be offered: ethnicity-based screening, panethnic screening (performed regardless of ethnicity), and expanded carrier screening —which is a type of panethnic screening performed for a larger number of conditions, potentially 100 or more. The goal of screening is to provide individuals with meaningful information to guide pregnancy planning according to their values (American College of Obstetricians and Gynecologists, 2017a). Each type of screening has benefits, risks, and limitations. For example, so many disorders are included in expanded carrier screening panels that more than 50 percent of those screened may be identified to be carriers for at least 1 condition. This can cause anxiety for families and may pose challenges if genetic counseling resources are limited. Recognizing that each type of screening is an acceptable strategy, it is recommended that obstetrical providers develop a standard approach to offer one of these three types of carrier screening to pregnant women and couples considering pregnancy (American College of Obstetricians and Gynecologists, 2017a). All carrier screening is optional and should be an informed choice.

Couples with a personal or family history of a heritable genetic disorder should be offered genetic counseling. They are provided an estimated risk of having an affected newborn and given information concerning benefits and limitations of available prenatal testing options. Prenatal diagnosis may be available if the disease-causing mutation or mutations are known. The publicly funded Genetic Testing Registry website contains detailed information regarding more than 10,000 genetic conditions and 48,000 genetic tests (www.ncbi.nlm.nih.gov/gtr/). That said, many genetic disorders are characterized by a high degree of penetrance but variable expressivity. Thus, prediction of phenotype may not be possible, even when family members are affected. Common examples include neurofibromatosis, tuberous sclerosis, and Marfan syndrome. There are also conditions for which risk may be refined by detection of associated sonographic abnormalities or by gender determination if X-linked.

Ethnicity-based carrier screening is offered for certain autosomal recessive disorders that are found in greater frequency in specific racial or ethnic groups (Table 14-10). The *founder effect* occurs when an otherwise rare gene is found with greater frequency in a certain population and can be traced back to a single family member or small group of ancestors. This phenomenon may develop when generations of individuals procreate only within their own groups because of religious or ethnic prohibitions or geographical isolation. Because it is becoming increasingly difficult to assign a single ethnicity, a panethnic screening panel is another option.

TABLE 14-10

Autosomal Recessive Diseases Found with Increased Frequency in Certain Ethnic Groups

Disease	Heritage of Groups at Increased Risk
Sickle hemoglobinopathies	African, Mediterranean, Middle Eastern, Indian
α-Thalassemia	African, Mediterranean, Middle Eastern, West Indian, Southeast Asian
β-Thalassemia	African, Mediterranean, Middle Eastern, Indian, Southeast Asian
Inborn errors of metabolism:	Ashkenazi Jewish
Tay-Sachs disease Canavan disease Familial dysautonomia Bloom syndrome Familial hyperinsulinism Fanconi anemia Gaucher disease Glycogen storage disease type I Joubert syndrome Maple syrup urine disease Mucolipidosis type IV Niemann-Pick disease Usher syndrome	Tay-Sachs is also more common in groups with French-Canadian and Cajun heritage

The American College of Obstetricians and Gynecologists (2017a) has developed the following criteria for expanded carrier screening panels:

1. Conditions included in the panel should have a carrier frequency of at least 1:100, which correlates with a population frequency, at minimum, of 1:40,000.
2. Conditions should have a well-defined phenotype, detrimental effect on quality of life, cognitive or physical impairment, early onset, or require surgical or medical intervention.
3. Conditions primarily associated with disease of adult onset are not recommended for inclusion.
4. If an individual is at increased risk for a specific condition, such as Tay-Sachs disease or β-thalassemia, the provider should consider that the test included in the panel may not be the most sensitive one for that condition.

Cystic Fibrosis

This disorder is caused by a mutation in the *cystic fibrosis conductance transmembrane regulator (CFTR)* gene, which is located on the long arm of chromosome 7 and encodes a chloride-channel protein. Although the most common CFTR gene mutation associated with classic cystic fibrosis (CF) is the Δ*F508* mutation, more than 2000 mutations have been identified (Cystic Fibrosis Mutation Database, 2016). CF may develop from either *homozygosity* or *compound heterozygosity* for mutations in the CFTR gene. In other words, one mutation must be present in each copy of the gene, but they need not be the same mutation. As expected, this results in a tremendous range of clinical disease severity. Median survival is approximately 37 years, but approximately 15 percent have milder disease and can survive for decades longer. Care for the pregnant woman with CF is discussed in Chapter 51 (Pathophysiology).

The American College of Obstetricians and Gynecologists (2017a,b) recommends that all patients who are considering pregnancy or who are already pregnant should be offered carrier screening for CF, regardless of ethnicity.

The current recommended screening panel contains 23 panethnic CF gene mutations, selected because they are present in at least 0.1 percent of patients with classic CF (American College of Obstetricians and Gynecologists, 2017b). The CF carrier frequency approximates 1 in 25 in non-Hispanic white Americans and those of Ashkenazi Jewish descent, who are from Eastern Europe. Thus, the incidence of CF in a child born to a non-Hispanic white couple approximates $¼ \times {}^{1}/_{25} \times {}^{1}/_{25}$, or 1:2500. As shown in Table 14-11, both CF incidence and the sensitivity of the screening test are lower for other ethnicities.

TABLE 14-11

Cystic Fibrosis Detection and Carrier Rates before and after Testing

Racial or Ethnic Group	Detection (%)	Carrier Risk before Test	Carrier Risk after Negative Test
Ashkenazi Jewish	94.0	1/24	1 in 384
Caucasian	88.3	1/25	1 in 206
Hispanic American	71.7	1/58	1 in 203
African American	64.5	1/61	1 in 171
Asian American	48.9	1/94	1 in 183

Data from American College of Medical Genetics, 2006.

Although a negative screening test result does not preclude the possibility of carrying a less-common mutation, it reduces the risk substantively from the background rate. If both parents are carriers, chorionic villus sampling or amniocentesis can help determine whether the fetus has inherited one or both of the parental mutations. Counseling following identification of two disease-causing mutations is challenging, because phenotype prediction is reasonably accurate only for pancreatic disease, and then only for well-characterized mutations. Prognosis is most heavily affected by the degree of pulmonary disease, which varies considerably even among individuals with the most common genotype associated with classic disease, that is, those homozygous for the Δ*F508* mutation. This likely reflects the effect of genetic modifiers on protein function, which may further vary depending on the CFTR mutation and on exposure and susceptibility to environmental factors (Cutting, 2005; Drumm, 2005).

Spinal Muscular Atrophy

This autosomal recessive disorder results in spinal cord motor neuron degeneration that leads to skeletal muscle atrophy and generalized weakness. There is currently no effective treatment. The prevalence of spinal muscular atrophy (SMA) is 1 in 6,000 to 10,000 live births. Types I, II, III, and IV are caused by mutations in the *survival motor neuron (SMN1)* gene, which is located on the long arm of chromosome 5 (5q13.2) and encodes the SMN protein. Types I and II account for 80 percent of cases and are both lethal (American College of Obstetricians and Gynecologists, 2017b). SMA type I, known as Werdnig-Hoffmann, is the most severe. Disease onset is within the first 6 months, and affected children die of respiratory failure by age 2 years. Type II generally has onset before age 2 years, and the age at death can range from 2 years to the third decade of life. Type III also presents before age 2 years, with disease severity that is milder and more variable. Type IV does not present until adulthood.

The American College of Obstetricians and Gynecologists (2017b) recommends that carrier screening for SMA be offered to all women who are considering pregnancy or are currently pregnant. The SMA carrier frequency approximates 1:35 in those of non-Hispanic white (caucasian) ethnicity, 1:41 in Ashkenazi Jews, 1:53 in Asians, 1:66 in African Americans, and 1:117 in those of Hispanic white ethnicity (Hendrickson, 2009). Carrier detection rates range from 90 to 95 percent for each race/ethnicity except African Americans, in whom it just exceeds 70 percent. Approximately 2 percent of individuals with *SMN1* mutations are not identified with carrier screening. In addition, although there is usually one copy of the *SMN1* gene on each chromosome, approximately 3 to 4 percent of individuals have two copies of this gene on one chromosome and no copies on the other. These individuals are carriers for the disease. African Americans are more likely to have this genetic variation, which explains the lower sensitivity of screening in this group. The American College of Obstetricians and Gynecologists (2017b) recommends that prior to screening for SMA, providers counsel about its potential spectrum of severity, carrier frequency, and its detection rate. Posttest counseling should include the residual risk after a negative screening result, which differs according to the patient's ethnicity and also according to the number of *SMN1* copies detected. Most unaffected individuals have two copies, but a small percentage has three copies and is at even lower risk. If the patient or her partner has a family history of SMA, or if carrier screening is positive, genetic counseling is recommended.

Sickle Hemoglobinopathies

These include sickle-cell anemia, sickle-cell hemoglobin C disease, and sickle-cell β-thalassemia. Their pathophysiology and inheritance are discussed in detail in Chapter 56 (Polycythemias).

African and African-American patients are at increased risk to carry hemoglobin S and other hemoglobinopathies and should be offered preconceptional or prenatal screening. Of African Americans, 1 in 12 has sickle-cell trait, 1 in 40 carries hemoglobin C, and 1 in 40 carries the trait for β-thalassemia. Hemoglobin S is also more common among individuals of Mediterranean, Middle Eastern, and Asian Indian descent (Davies, 2000). The American College of Obstetricians and Gynecologists (2015) recommends that patients of African descent be offered hemoglobin electrophoresis. If a couple is at risk to have a child with a sickle hemoglobinopathy, genetic counseling should be offered. Prenatal diagnosis can be performed with either chorionic villus sampling or amniocentesis.

Thalassemias

These syndromes are the most common single-gene disorders worldwide, and up to 200 million people carry a gene for one of these hemoglobinopathies (Chap. 56, Thalassemia Syndromes). Some individuals with thalassemia have microcytic anemia secondary to decreased synthesis of either α- or β-hemoglobin chains. In

general, *deletions* of α-globin chains cause α-thalassemia, whereas *mutations* in β-globin chains cause β-thalassemia. Less commonly, an α-globin chain mutation also causes α-thalassemia.

Alpha-Thalassemia

The number of α-globin genes that are deleted may range from one to all four. If two α-globin genes are deleted, both may be deleted from the same chromosome—*cis* configuration (αα/––), or one may be deleted from each chromosome—*trans* configuration (α–/α–). Alpha-thalassemia trait is common among individuals of African, Mediterranean, Middle Eastern, West Indian, and Southeast Asian descent and results in mild anemia. The *cis* configuration is more prevalent among Southeast Asians, whereas those of African descent are more likely to inherit the *trans* configuration. Clinically, when both parents carry *cis* deletions, offspring are at risk for an absence of α-hemoglobin, called Hb Barts disease. This typically leads to hydrops and fetal loss as discussed in Chapter 15 (Hydrops Fetalis).

Detection of α-thalassemia or α-thalassemia trait is based on molecular genetic testing and is not detectable using hemoglobin electrophoresis. Because of this, routine carrier screening is not offered. If there is microcytic anemia in the absence of iron deficiency and the hemoglobin electrophoresis is normal, then testing for α-thalassemia can be considered, particularly among individuals of Southeast Asian descent (American College of Obstetricians and Gynecologists, 2015).

Beta-Thalassemia

Mutations in β-globin genes may cause reduced or absent production of β-globin chains. If the mutation affects one gene, it results in β-thalassemia minor. If both copies are affected, the result is either β-thalassemia major—termed Cooley anemia—or β-thalassemia intermedia. Because of reduced production of hemoglobin A among carriers, electrophoresis demonstrates elevated levels of hemoglobins that do not contain β-chains. These include hemoglobins F and A_2.

β-Thalassemia minor is more common among individuals of African, Mediterranean, and Southeast Asian descent. The American College of Obstetricians and Gynecologists (2015) recommends that they be offered carrier screening with hemoglobin electrophoresis, particularly if found to have microcytic anemia in the absence of iron deficiency. Hemoglobin A_2 levels exceeding 3.5 percent confirm the diagnosis. Other ethnicities at increased risk include those of Middle Eastern, West Indian, and Hispanic descent.

Tay-Sachs Disease

This autosomal recessive lysosomal-storage disease is characterized by absence of the hexosaminidase A enzyme. This leads to accumulation of GM2 gangliosides in the central nervous system, progressive neurodegeneration, and death in early childhood. Affected individuals have almost complete absence of the enzyme, whereas carriers are asymptomatic but have less than 55-percent hexosaminidase A activity. The carrier frequency of Tay-Sachs disease in Jewish individuals of Eastern European (Ashkenazi) descent approximates 1 in 30, but it is much lower, only about 1 in 300, in the general population. Other groups at greater risk for Tay-Sachs disease include those of French-Canadian and Cajun descent. An international Tay-Sachs carrier-screening campaign was initiated in the 1970s and met with unprecedented success in the Ashkenazi Jewish population. The incidence of Tay-Sachs disease subsequently declined more than 90 percent (Kaback, 1993). Most cases of Tay-Sachs disease now occur in non-Jewish individuals.

The American College of Obstetricians and Gynecologists (2017b) has the following screening recommendations for Tay-Sachs disease:

1. Screening should be offered before pregnancy if both members of a couple are of Ashkenazi Jewish, French-Canadian, or Cajun descent, or if there is a family history of Tay-Sachs disease.
2. When only one member of the couple is of one of the above ethnicities, the high-risk partner may be screened first, and if found to be a carrier, the other partner also should be offered screening. If there is a family history of Tay-Sachs disease, an expanded carrier screening panel may not be the best approach unless the familial mutation is included in the panel.
3. Molecular testing (DNA-based mutation analysis) is highly effective in Ashkenazi Jewish individuals and other high-risk groups, but the detection rate in low-risk groups is more limited.
4. Biochemical analysis of the hexosaminidase A serum level has a sensitivity of 98 percent and is the test that should be performed in individuals from low-risk ethnicities. *Leukocyte testing* must be used if the woman is already pregnant or taking oral contraceptives.
5. If both partners are found to be carriers of Tay-Sachs disease, genetic counseling and prenatal diagnosis should be offered. Hexosaminidase activity may be measured from chorionic villus sampling or amniocentesis specimens.

Other Recessive Diseases in Ashkenazi Jewish Individuals

The carrier rate among individuals of Eastern European (Ashkenazi) Jewish descent approximates 1 in 30 for Tay-Sachs disease, 1 in 40 for Canavan disease, and 1 in 32 for familial dysautonomia. Fortunately, the detection rate of screening tests for each is at least 98 percent in this population. Because of their relatively high prevalence and consistently severe and predictable phenotype, the American College of Obstetricians and Gynecologists (2017b) recommends that carrier screening for these three conditions be offered to Ashkenazi Jewish individuals, either before conception or during early pregnancy. This is in addition to carrier screening for cystic fibrosis and spinal muscular atrophy, which are offered to all women who are considering pregnancy or who are currently pregnant. Further, there are several other autosomal recessive conditions for which the College recommends that screening be considered (American College of Obstetricians and Gynecologists, 2017b). As of 2017, these include Bloom syndrome, familial hyperinsulinism, Fanconi anemia, Gaucher disease, glycogen storage disease type I (von Gierke disease), Joubert syndrome, maple syrup urine disease, mucolipidosis type IV, Niemann-Pick disease, and Usher syndrome. Gaucher disease differs from the other conditions listed in

that it is has a wide range in phenotype—from childhood illness to absence of symptoms throughout life. Also, effective treatment is available in the form of enzyme therapy.

PRENATAL DIAGNOSTIC PROCEDURES AND PREIMPLANTATION TESTING

Diagnostic procedures used in prenatal diagnosis include amniocentesis, chorionic villus sampling (CVS), and rarely fetal blood sampling. These enable characterization of an increasingly large number of genetic abnormalities before birth. Karyotype analysis has a diagnostic accuracy of more than 99 percent for aneuploidy and chromosomal abnormalities larger than 5 to 10 megabases. In the setting of a fetal structural abnormality, chromosomal microarray analysis (CMA) is recommended as the first-line genetic test performed, as it may detect clinically significant chromosomal abnormalities in approximately 6 percent of fetuses with normal standard karyotype (Callaway, 2013; de Wit, 2014). An exception would be if the structural abnormality strongly suggests a particular karyotype—such as endocardial cushion defect with trisomy 21 or holoprosencephaly with trisomy 13. In such cases, karyotyping with or without fluorescence in-situ hybridization (FISH) may be offered as the initial test (American College of Obstetricians and Gynecologists, 2016b). Among those without evidence of a fetal structural abnormality and with a normal karyotype, CMA has detected additional chromosomal abnormalities (pathogenic copy number variants) in approximately 1 percent. It is therefore made available whenever a prenatal diagnostic procedure is performed (American College of Obstetricians and Gynecologists, 2016b; Callaway, 2013). Types of CMA platforms and their benefits and limitations are reviewed in Chapter 13 (Chromosomal Microarray Analysis).

Ironically, improvements in aneuploidy screening tests, in particular the widespread use of cell-free DNA screening, have resulted in a dramatic drop in the number of prenatal diagnostic procedures. Larion and colleagues (2014) reported a 70-percent decline in CVS procedures and a nearly 50-percent drop in amniocentesis procedures following introduction of cell-free DNA screening in 2012. This further amplified the decrease in amniocentesis procedures that began following adoption of first-trimester screening (Warsof, 2015). In addition, because so many disorders can be diagnosed from amnionic fluid specimens, fetal blood sampling is now rarely, if ever, indicated for genetic diagnoses.

Amniocentesis

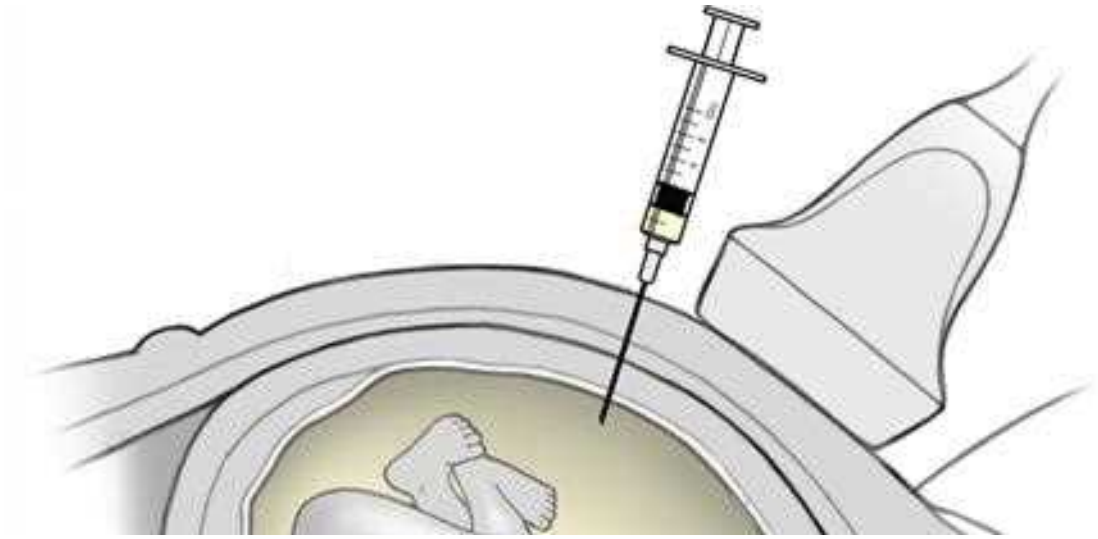
This is the most common prenatal diagnostic procedure. Transabdominal withdrawal of amnionic fluid is generally done between 15 and 20 weeks but may be performed at any point later in gestation. Indications include diagnosis of fetal genetic disorders, congenital infections, and alloimmunization, as well as assessment of fetal lung maturity. The most common types of prenatal diagnostic tests are CMA to assess copy-number gains or losses, karyotype analysis to test for aneuploidy, and FISH to identify gain or loss of specific chromosomes or chromosome regions (Chap. 13, Genetic Tests). Because amniocytes must be cultured before fetal karyotype can be assessed, the time needed for karyotyping is 7 to 10 days. In contrast, FISH studies are usually completed within 24 to 48 hours. CMA can often be performed directly on uncultured amniocytes with a turnaround time of only 3 to 5 days, and if amniocyte culture is required, turnaround time is 10 to 14 days (American College of Obstetricians and Gynecologists, 2016b).

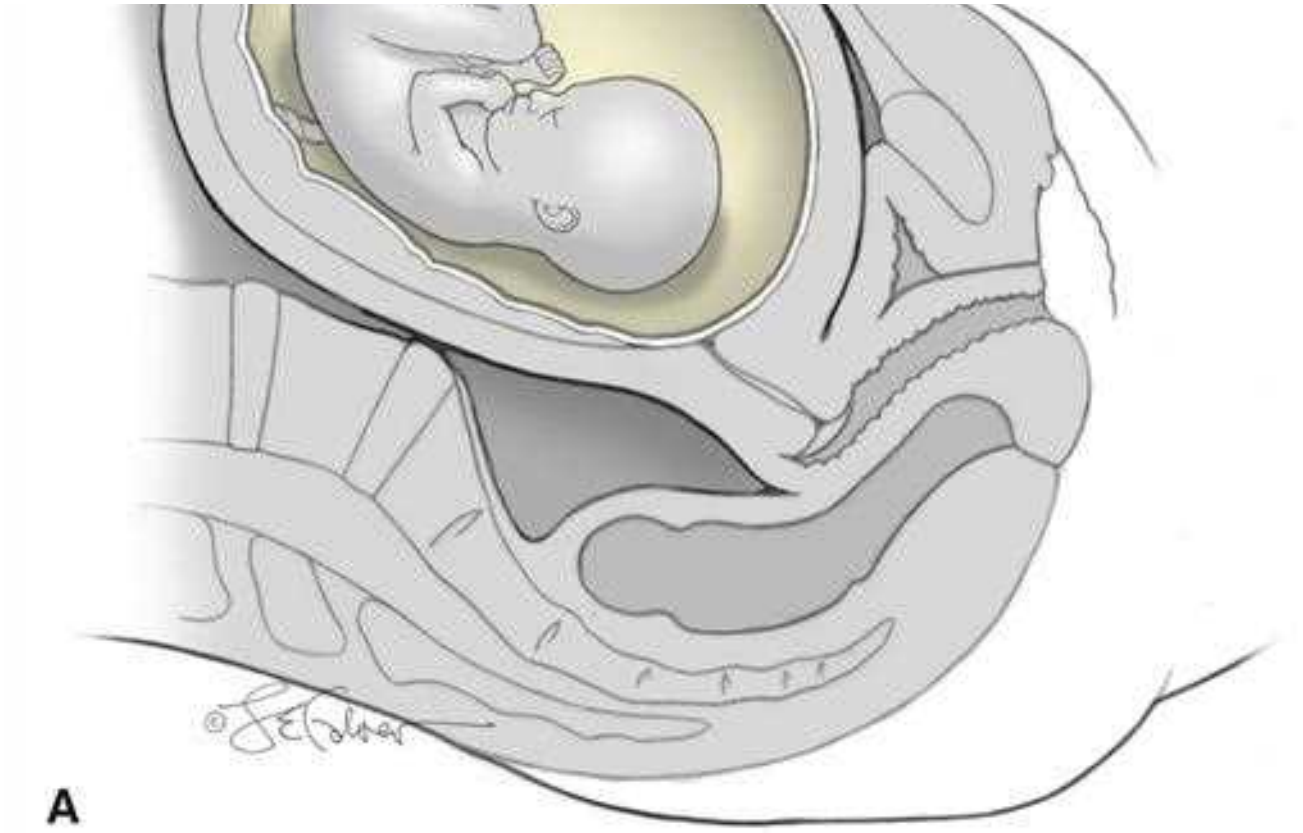
Technique

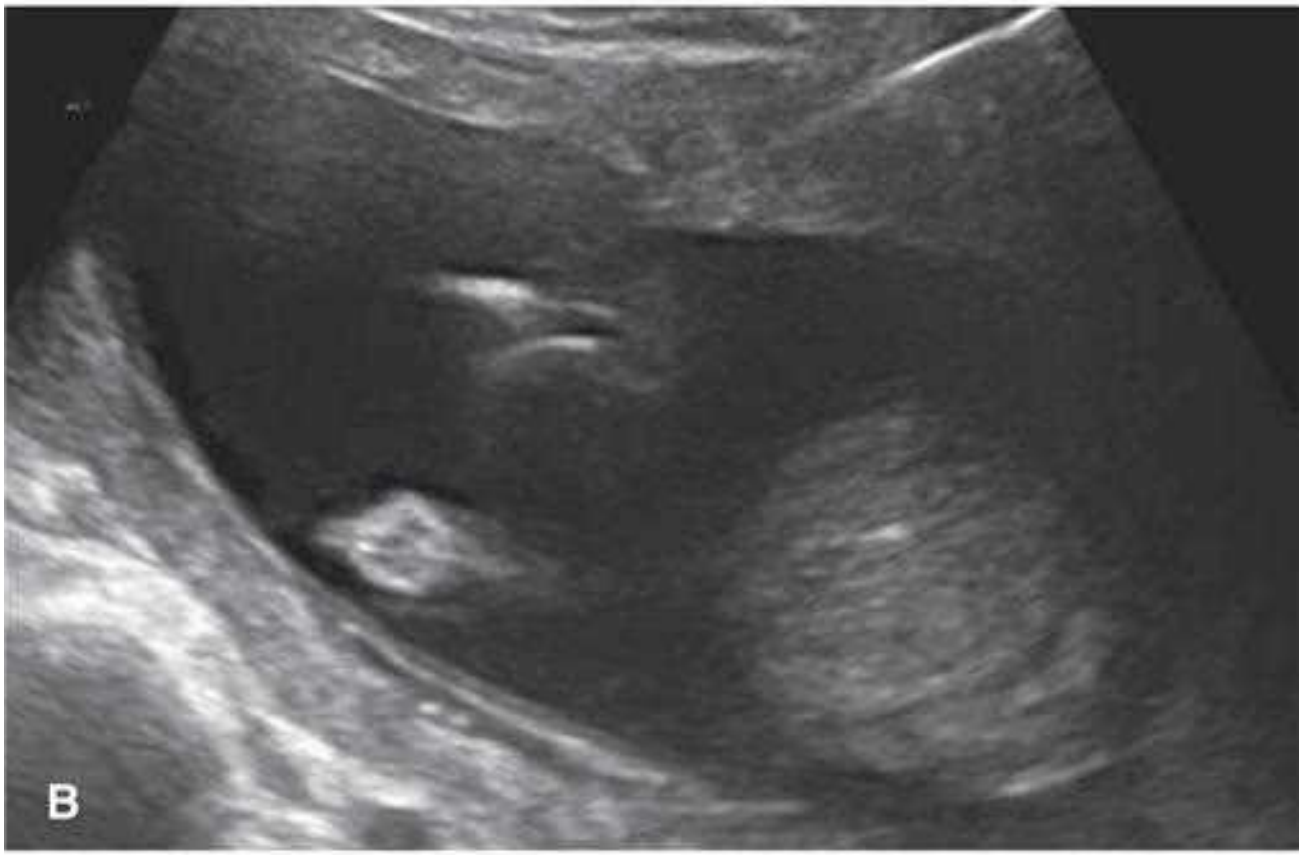
Amniocentesis is performed using aseptic technique, with a 20- or 22-gauge spinal needle and ultrasound guidance (Fig. 14-4). A standard spinal needle is 9 cm long, and depending on patient habitus, a longer needle may be required. Measurement of the sonographic distance from skin to amnionic fluid pocket may aid needle selection. Sonography is used to identify a pocket of amnionic fluid that is close to the midline, being cognizant of uterine size and shape. The needle is inserted perpendicular to the skin and guided into the deepest portion of the fluid pocket, avoiding fetal parts and umbilical cord. Efforts are made to puncture the chorioamnion rather than to push or "tent" it away from the uterine wall. The amnion usually fuses with the adjacent chorion by 16 weeks' gestation, and the procedure is generally deferred until after chorioamnion fusion has occurred. Discomfort from the procedure is considered minor, and local anesthetic has not been found to be beneficial (Mujezinovic, 2011).

FIGURE 14-4

A. Amniocentesis. **B.** The amniocentesis needle is seen in the upper right portion of this sonogram. (Reproduced with permission from Mastrobattista JM, Espinoza J: Invasive prenatal diagnostic procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)







Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Following the procedure, the color and clarity of the fluid are documented. Amnionic fluid should be clear and colorless or pale yellow. Blood-tinged fluid is more frequent if there is transplacental passage of the needle. However, it generally clears with continued aspiration. The placenta implants along the anterior uterine wall in approximately half of pregnancies. In these cases, the placenta will be traversed by the needle approximately 60 percent of the time (Bombard, 1995). Needle

passage through the placenta is avoided when possible, although fortunately this has not been associated with greater pregnancy loss rates (Marthin, 1997). Dark brown or greenish fluid may represent a past episode of intraamnionic bleeding.

The volume of fluid generally needed for commonly performed analyses is shown in Table 14-12. Because the initial 1 to 2 mL of fluid aspirate may be contaminated with maternal cells, it is generally discarded. Approximately 20 to 30 mL of fluid is then collected for either fetal CMA or karyotyping before removing the needle. Sonography is used to observe the uterine puncture site for bleeding, and fetal cardiac motion is documented at the procedure's end. If the patient is Rh D-negative and unsensitized, anti-D immune globulin is administered following the procedure (Chap. 15, Prevention of Anti-D Alloimmunization).

TABLE 14-12

Selected Tests Performed on Amnionic Fluid and Typical Volume of Fluid Required

Test	Volume (mL)[a]
Fetal karyotype	20
Chromosomal microarray analysis	20
FISH[b]	10
Alpha-fetoprotein	2
PCR tests for cytomegalovirus, toxoplasmosis, or parvovirus	1–2 each test
Cytomegalovirus culture	2–3
Delta OD 450 (bilirubin analysis)	2–3
Genotype studies (alloimmunization)	20
Fetal lung maturity tests	10

[a]The volume of fluid needed for each test may vary according to individual laboratory specifications.

[b]Fluorescence in-situ hybridization (FISH) is typically performed for chromosomes 21, 18, 13, X, and Y.

PCR = polymerase chain reaction.

Multifetal Pregnancy

When performing the procedure in a diamnionic twin gestation, careful attention is paid to the location of each sac and the dividing membrane. Until recently, a small quantity of dilute indigo carmine dye was often injected before removing the needle from the first sac, with return of clear amnionic fluid anticipated following needle placement into the second sac. Because of widespread shortages of indigo carmine dye, most experienced providers offer amniocentesis in multifetal gestations when indicated, without dye injection. Methylene blue dye is contraindicated because it has been associated with jejunal atresia and neonatal methemoglobinemia (Cowett, 1976; van der Pol, 1992).

Complications

The procedure-related loss rate following midtrimester amniocentesis has decreased with improvements in imaging technology. Based on single-center studies and metaanalysis data, the amniocentesis procedure-related loss rate approximates 0.1 to 0.3 percent when performed by an experienced provider—about 1 per 500 procedures (Akolekar, 2015; American College of Obstetricians and Gynecologists, 2016b; Odibo, 2008). The loss rate may be doubled in women with class 3 obesity, which is a body mass index (BMI) >40 kg/m^2 (Harper, 2012). In twin pregnancies, Cahill and coworkers (2009) reported a loss rate of 1.8 percent attributable to amniocentesis.

The amniocentesis indication can influence loss rates, which can be greater with some fetal abnormalities, aneuploidies, and conditions such as hydrops. And, some losses are due to abnormal placental implantation or abruption, uterine abnormalities, or infection. Wenstrom and colleagues (1990) analyzed 66 fetal deaths following nearly 12,000 procedures and found that 12 percent were associated with preexisting intrauterine infection.

Other complications of amniocentesis include amnionic fluid leakage or transient vaginal spotting in 1 to 2 percent. Following leakage of amnionic fluid, which generally occurs within 48 hours of the procedure, fetal survival exceeds 90 percent (Borgida, 2000). Needle injuries to the fetus are rare. Amnionic fluid culture is successful in more than 99 percent of cases, although cells are less likely to grow if the fetus is abnormal (Persutte, 1995).

Early Amniocentesis

This describes amniocentesis performed between 11 and 14 weeks' gestation. The technique is the same as for traditional amniocentesis, but sac puncture may be more challenging due to lack of membrane fusion to the uterine wall. Less fluid is typically withdrawn—approximately 1 mL for each gestational week (Shulman,

1994; Sundberg, 1997).

Early amniocentesis is associated with significantly higher rates of procedure-related complications than other fetal procedures. These include development of talipes equinovarus (clubfoot), amnionic fluid leakage, and fetal loss (Canadian Early and Mid-Trimester Amniocentesis Trial, 1998; Philip, 2004). Given these risks, the American College of Obstetricians and Gynecologists (2016b) recommends that early amniocentesis not be performed.

Chorionic Villus Sampling

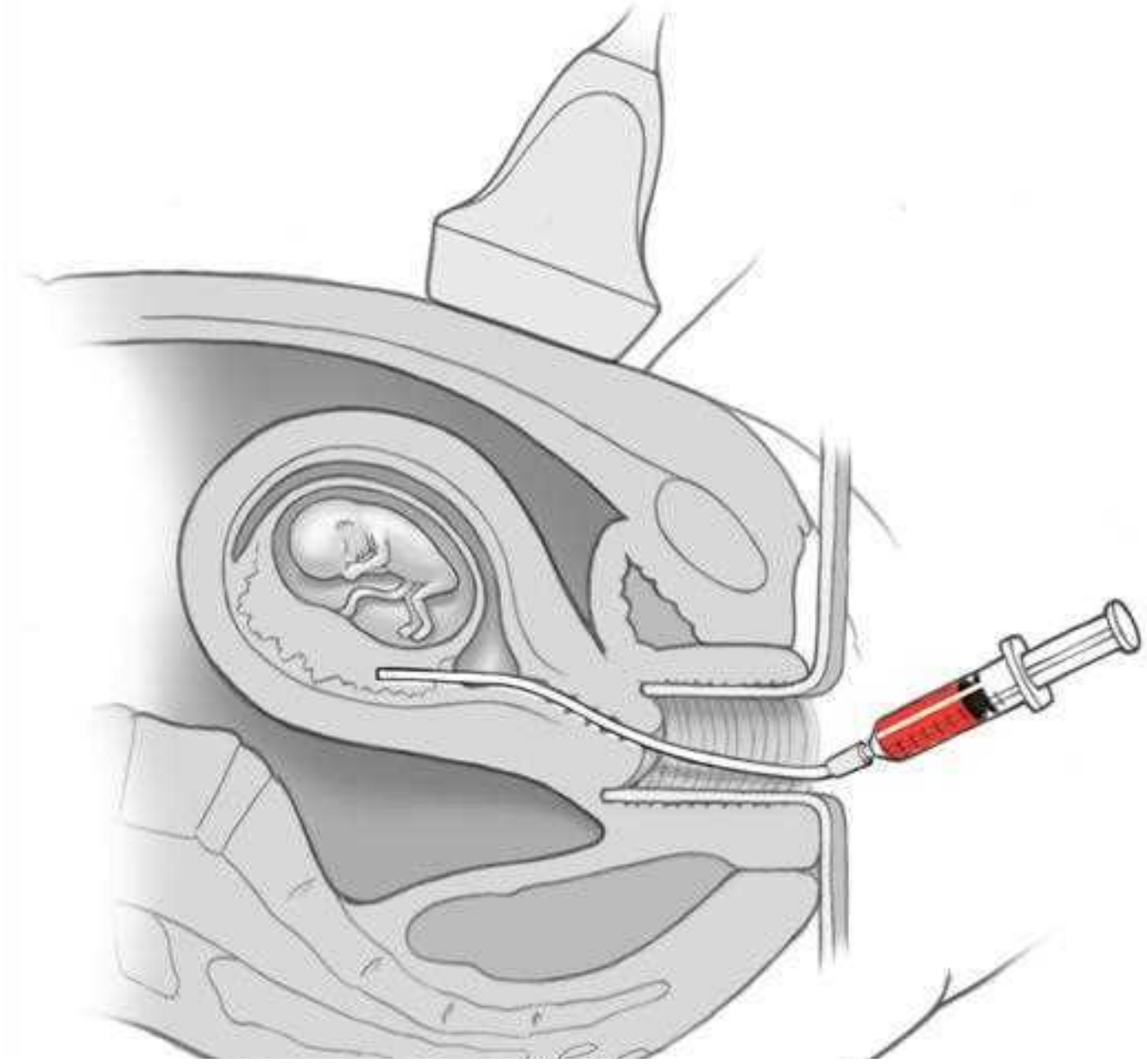
Biopsy of chorionic villi is typically performed between 10 and 13 weeks' gestation. As with amniocentesis, the specimen is generally sent for karyotyping or CMA. The primary advantage of villus biopsy is that results are available earlier in pregnancy, permitting more time for decision-making and safer pregnancy termination, if desired. Very few analyses specifically require either amnionic fluid or placental tissue.

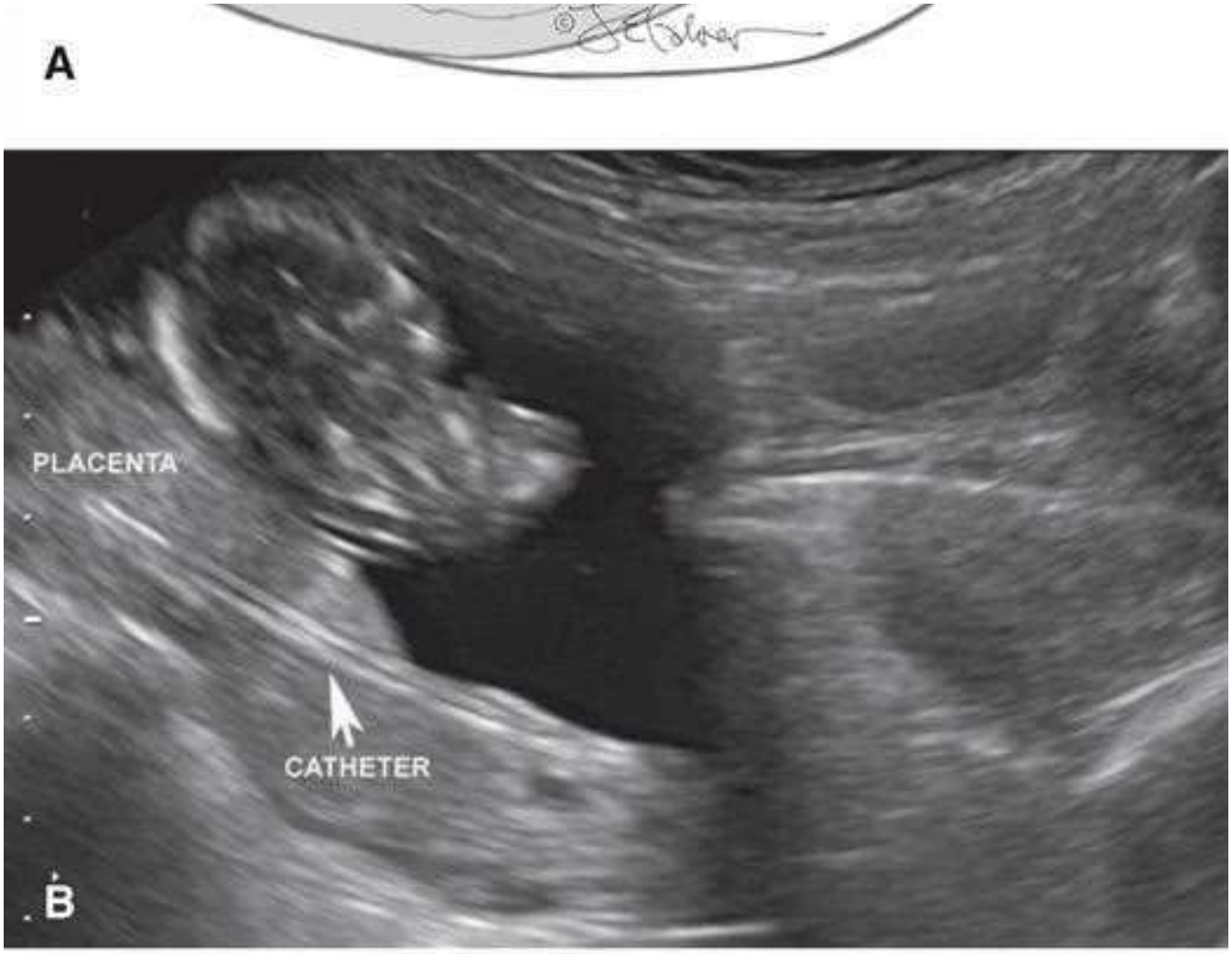
Technique

Chorionic villi may be obtained transcervically or transabdominally, using aseptic technique. Both approaches are considered equally safe and effective (American College of Obstetricians and Gynecologists, 2016b). Transcervical CVS is performed using a specifically designed catheter made from flexible polyethylene that contains a blunt-tipped, malleable stylet. Transabdominal sampling is performed using an 18- or 20-gauge spinal needle. With either technique, transabdominal sonography is used to guide the catheter or needle into the early placenta—*chorion frondosum*, followed by aspiration of villi into a syringe containing tissue culture media (Fig. 14-5).

FIGURE 14-5

A. Transcervical chorionic villus sampling. **B.** Catheter entering the placenta is marked and labeled. (Reproduced with permission from Mastrobattista JM, Espinoza J: Invasive prenatal diagnostic procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)





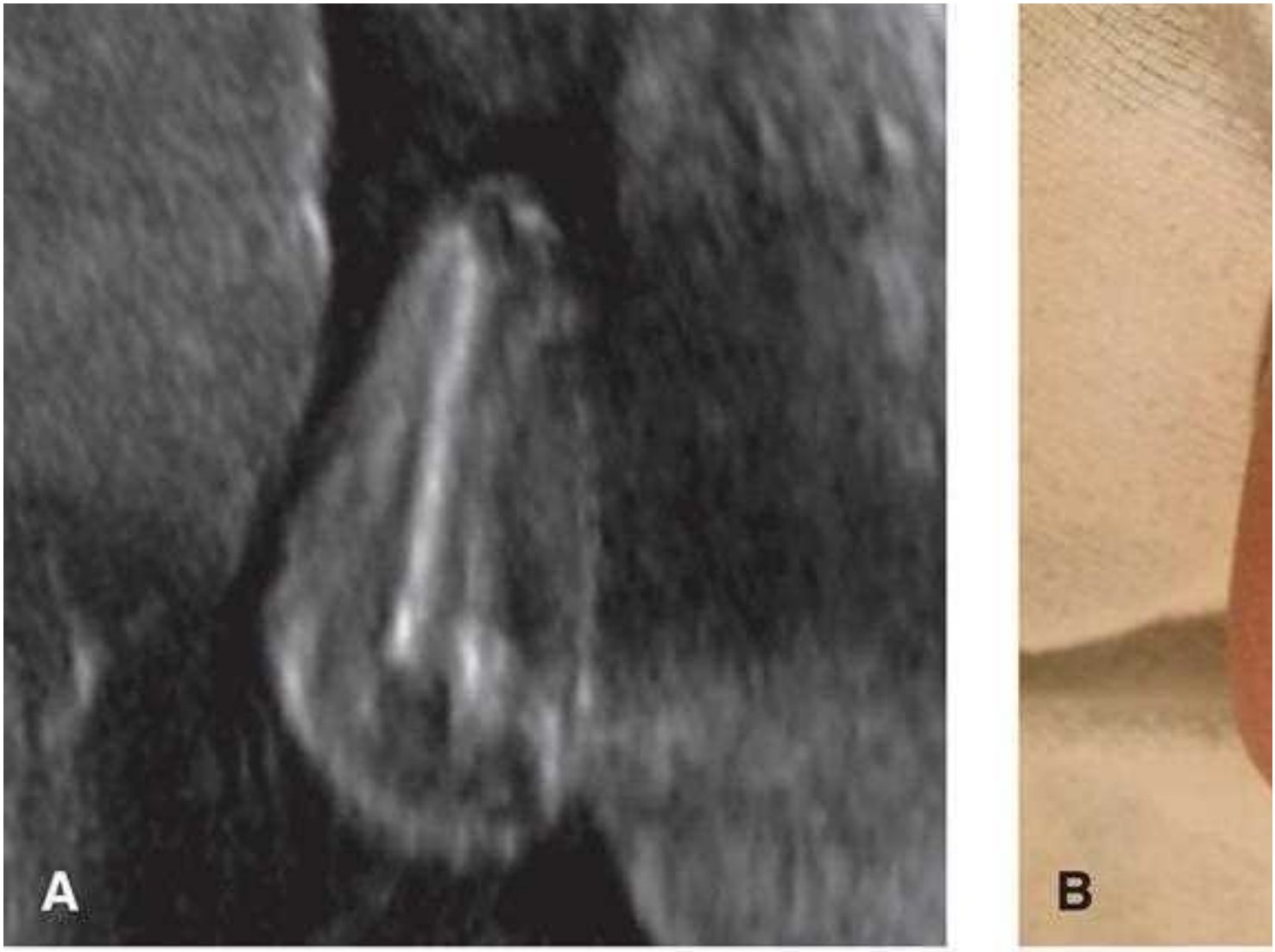
Relative contraindications include vaginal bleeding or spotting, active genital tract infection, extreme uterine ante- or retroflexion, or body habitus precluding adequate visualization. If the patient is Rh D-negative and unsensitized, anti-D immune globulin is administered following the procedure.

Complications

The *overall* loss rate following CVS is higher than that following midtrimester amniocentesis. This is because of background spontaneous losses, that is, losses that would have occurred between the first and second trimester in the absence of a fetal procedure. The procedure-related fetal loss rate is comparable with that of amniocentesis. Caughey and colleagues (2006) found that the overall loss rate following CVS was approximately 2 percent compared with less than 1 percent following amniocentesis. However, the adjusted procedure-related loss rate approximated 1 per 400 for either procedure. The indication for CVS will also affect the loss rate. For example, fetuses with increased NT thickness have a greater likelihood of demise. Finally, there is a learning curve associated with safe performance of CVS (Silver, 1990; Wijnberger, 2003).

An early problem with CVS was its association with *limb-reduction defects* and *oromandibular limb hypogenesis,* shown in Figure 14-6 (Firth, 1991, 1994; Hsieh, 1995). These were subsequently found to be associated with procedures performed at 7 weeks' gestation (Holmes, 1993). When performed at ≥10 weeks' gestation, the incidence of limb defects does not exceed the background population rate of about 1 per 1000 (Evans, 2005; Kuliev, 1996).

FIGURE 14-6
Oromandibular limb hypogenesis is characterized by transverse limb deficiency and absence or hypoplasia of the tongue or mandible. This is hypothesized to result from vascular disruption with subsequent loss of tissue. **A.** Sonogram obtained at 25 weeks' gestation demonstrates a fetal limb reduction defect involving the right hand. **B.** Photograph of the right extremity of the same newborn. Chorionic villus sampling was not performed in this pregnancy. (Used with permission from Dr. Jamie Morgan.)



Vaginal spotting is not uncommon following transcervical sampling, but it is self-limited and not associated with pregnancy loss. The incidence of infection is less than 0.5 percent (American College of Obstetricians and Gynecologists, 2016c).

A limitation of CVS is that chromosomal mosaicism is identified in up to 2 percent of specimens (Malvestiti, 2015). In most cases, the mosaicism reflects confined placental mosaicism rather than a true second cell line within the fetus. This is discussed in Chapter 13 (Chromosomal Mosaicism). Amniocentesis should be offered, and if the result is normal, the mosaicism is usually presumed to be confined to the placenta. Confined placental mosaicism has been associated with growth-restricted newborns (Baffero, 2012).

Fetal Blood Sampling

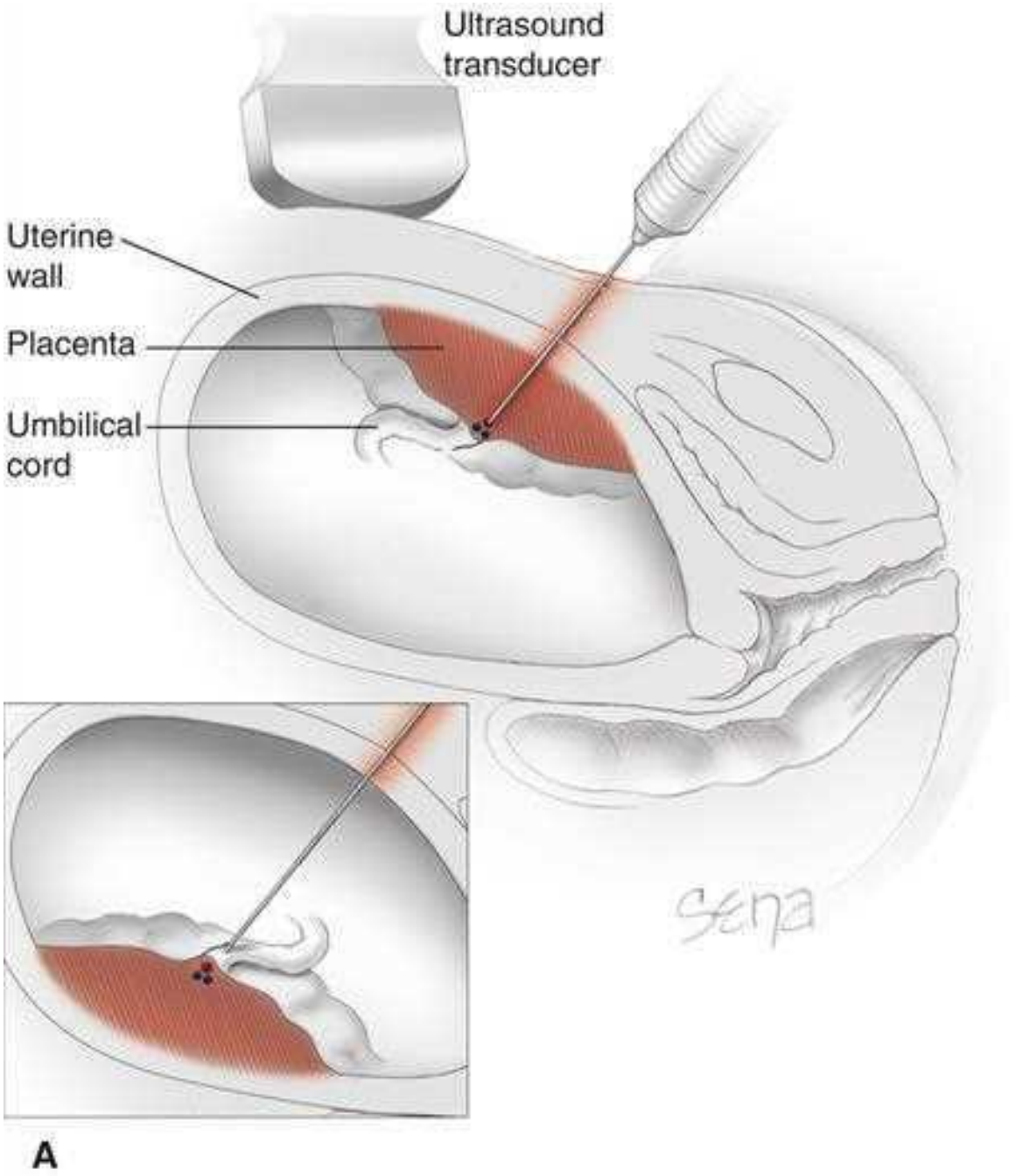
This procedure is also called cordocentesis or percutaneous umbilical blood sampling (PUBS). It was initially described for fetal transfusion of red blood cells in the setting of anemia from alloimmunization, and fetal anemia assessment remains the most common indication (Chap. 16, Surgical Therapy). Fetal blood sampling is also performed for assessment and treatment of platelet alloimmunization and for fetal karyotype determination, particularly in cases of mosaicism identified following amniocentesis or CVS. Fetal blood karyotyping can be accomplished within 24 to 48 hours. Thus, it is significantly quicker than the 7- to 10-day turnaround time with amniocentesis or CVS. Although fetal blood *can* be analyzed for virtually any test performed on neonatal blood, improvements in tests available with amniocentesis and CVS have eliminated the need for fetal venipuncture in most cases (Society for Maternal-Fetal Medicine, 2013).

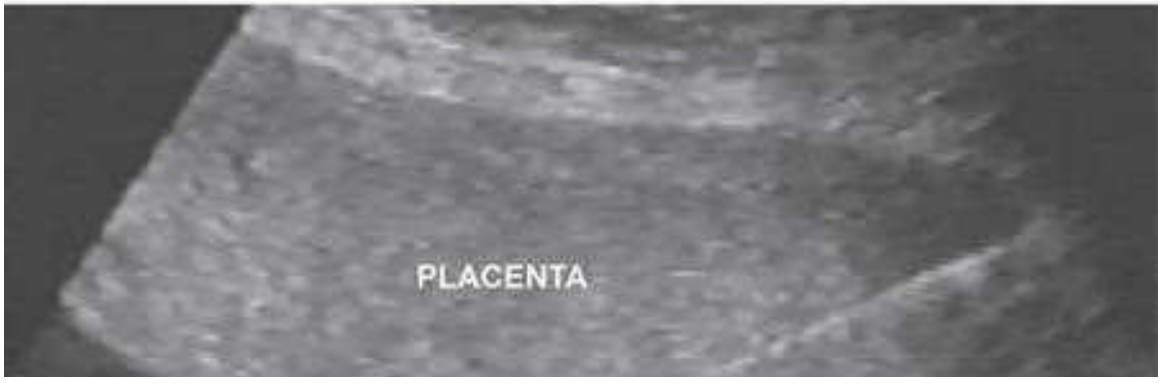
Technique

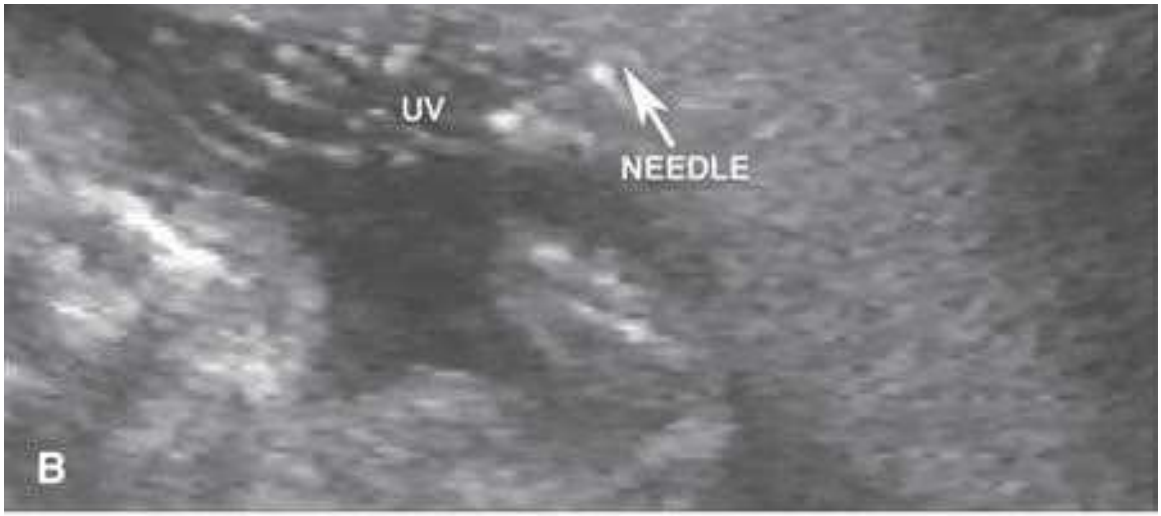
Under direct sonographic guidance, using aseptic technique, the operator introduces a 22- or 23-gauge spinal needle into the umbilical vein, and blood is slowly withdrawn into a heparinized syringe (Fig. 14-7). Adequate visualization of the needle is essential. As with amniocentesis, a longer needle may be required depending on patient habitus. Fetal blood sampling is often performed near the placental cord insertion site, where it may be easier to enter the cord if the placenta lies anteriorly. Alternatively, a free loop of cord may be punctured. Because fetal blood sampling requires more time than other fetal procedures, a local anesthetic may be administered. Prophylactic antibiotics are used at some centers, although no trials support this policy. Arterial puncture is avoided, because it may result in vasospasm and fetal bradycardia. After the needle is removed, fetal cardiac motion is documented, and the site is observed for bleeding.

FIGURE 14-7

Fetal blood sampling. **A.** Access to the umbilical vein varies depending on placental location and cord position. With an anterior placenta, the needle may traverse the placenta. Inset: With posterior placentation, the needle passes through amnionic fluid before penetrating the umbilical vein. Alternatively, a free loop of cord may be accessed. **B.** Sonogram shows an anterior placenta with transplacental needle passage into the umbilical vein (UV). (Reproduced with permission from Mastrobattista JM, Espinoza J: Invasive prenatal diagnostic procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)







Complications

The procedure-related fetal loss rate following fetal blood sampling approximates 1.4 percent (Ghidini, 1993; Tongsong, 2001). The actual loss rate varies according to the procedure indication and the fetal status. Other complications may include cord vessel bleeding in 20 to 30 percent of cases, fetal-maternal bleeding in approximately 40 percent of cases in which the placenta is traversed, and fetal bradycardia in 5 to 10 percent (Boupaijit, 2012; Society for Maternal-Fetal Medicine, 2013). Most complications are transitory, with complete recovery, but some result in fetal loss.

In one series of more than 2000 procedures comparing fetal blood sampling near the placental cord insertion site with puncture of a free loop, rates of procedure success, pregnancy loss, visible bleeding from the cord, and fetal bradycardia did not differ. Time to complete the procedure was significantly shorter if the cord was sampled at the placental insertion site than in a free loop—5 versus 7 minutes. However, sampling at the insertion site had a higher rate of maternal blood contamination (Tangshewinsirikul, 2011).

Preimplantation Genetic Testing

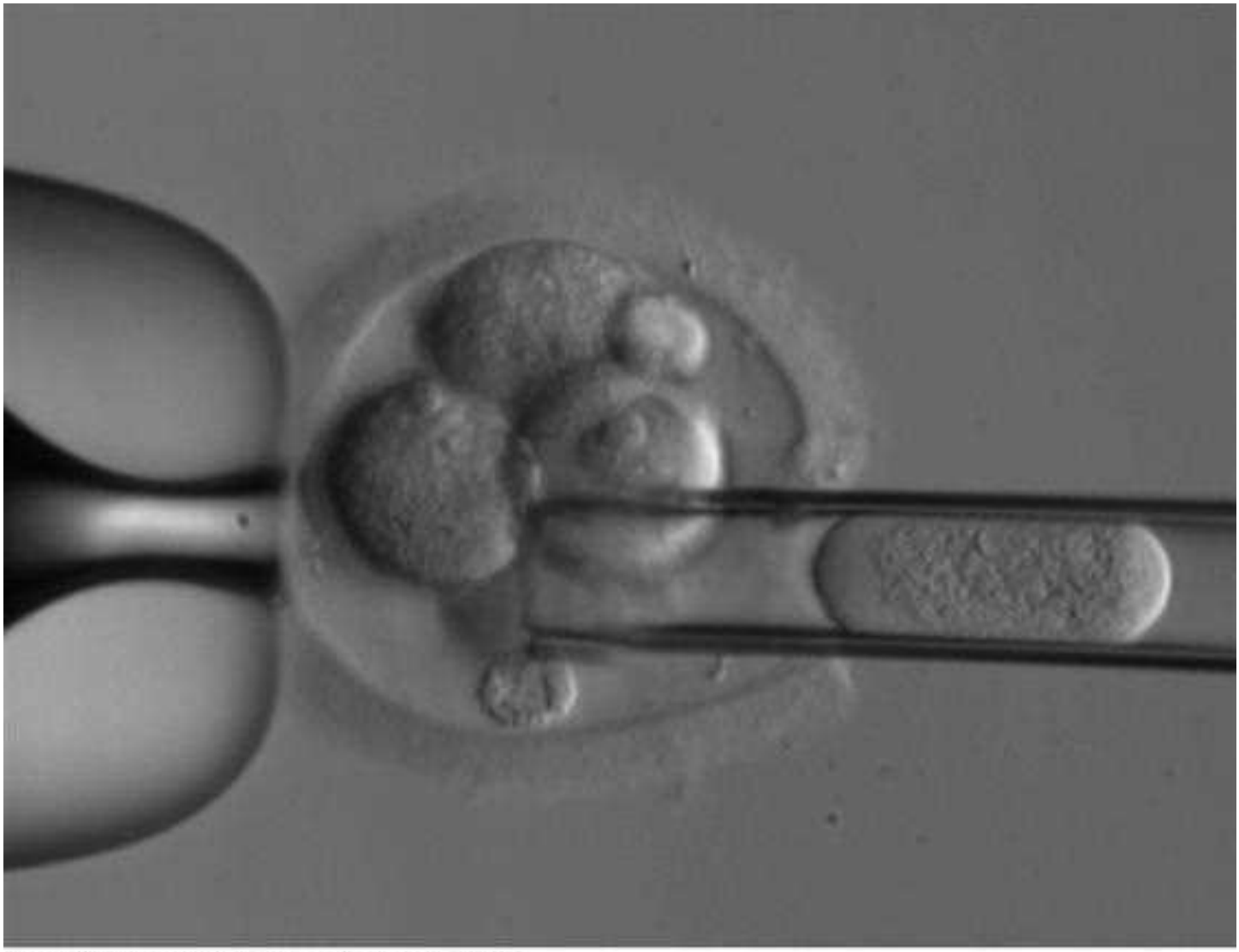
For couples undergoing in vitro fertilization (IVF), genetic testing performed on oocytes or embryos before implantation may provide valuable information regarding the chromosomal complement and single-gene disorders. There are two separate categories of testing—*preimplantation genetic diagnosis (PGD)* and *preimplantation genetic screening (PGS)*—each with different indications. Comprehensive genetic counseling is required before consideration of these procedures. There are three techniques that are used for both categories:

1. *Polar body analysis* is a technique used to infer whether a developing oocyte is affected by a maternally inherited genetic disorder. The first and second polar bodies are normally extruded from the developing oocyte following meiosis I and II, and their sampling should not affect fetal development. However, two separate micromanipulation procedures are required, and genetic abnormalities of paternal origin are not detected. This technique has been used to diagnose 146 mendelian disorders, and the reported accuracy exceeds 99 percent (Kuliev, 2011).

2. *Blastomere biopsy* is done at the 6- to 8-cell (cleavage) stage when an embryo is 3 days old. This allows both maternal and paternal genomes to be evaluated. One cell is typically removed through a hole made in the zona pellucida (Fig. 14-8). A limitation of using this technique for aneuploidy assessment is that because of mitotic nondisjunction, mosaicism of the blastomeres may not reflect the chromosomal complement of the developing embryo (American Society for Reproductive Medicine, 2008). In addition, the implantation rate of normal embryos is slightly lower following this technique.

3. *Trophectoderm biopsy* involves removal of 5 to 7 cells from a 5- to 6-day blastocyst. An advantage is that because the trophectoderm cells give rise to the trophoblast—the placenta—no cells are removed from the developing embryo. Disadvantageously, because the procedure is performed later in development, if genetic analysis cannot be performed rapidly, then cryopreservation and embryo transfer during a later IVF cycle may be required.

FIGURE 14-8
Blastomere biopsy. After a blastomere is selected, it is then drawn into the pipette. (Reproduced with permission from Doody KJ: Treatment of the infertile couple. Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Preimplantation Genetic Diagnosis

A genetic abnormality—rather than infertility—may be a reason for a couple to elect IVF. With a known carrier(s) of a specific genetic disease or a balanced chromosomal rearrangement, PGD may be performed to determine if an oocyte or embryo has the defect. Only embryos without the abnormality would be implanted.

This procedure has numerous applications. It is used to diagnose single-gene disorders such as cystic fibrosis, β-thalassemia, and hemophilia; to determine gender in X-linked diseases; to identify mutations such as *BRCA-1* that do not cause disease but confer significantly greater later cancer risk; and to match human leukocyte antigens for umbilical cord stem cell transplantation for a sibling (de Wert, 2007; Fragouli, 2007; Grewal, 2004; Rund, 2005; Xu, 2004).

Because typically only one or two cells are available for analysis and because rapid completion time is essential, this procedure is technically challenging. Risks include failure to amplify the genetic region of interest, selection of a cell that does not contain a nucleus, and maternal cell contamination. Infrequently, affected embryos thought to be normal are implanted, and unaffected embryos are misdiagnosed as abnormal and discarded. Because of this, the American Society for Reproductive Medicine (2008) encourages further prenatal diagnostic testing—either CVS or amniocentesis—to confirm PGD results.

Preimplantation Genetic Screening

This term is used for aneuploidy screening that is performed on oocytes or embryos before IVF transfer. Such screening is used with couples who are not known to have or carry a genetic abnormality. Although PGS has obvious theoretical advantages, it has faced challenges in practice.

Mosaicism is common in cleavage-stage embryo blastomeres. However, it may not be clinically significant because it often does not reflect the actual embryonic chromosomal complement. In addition, among women 35 years or older, pregnancy rates following PGS with FISH are significantly lower than rates observed following IVF without PGS (Mastenbroek, 2007, 2011). Because the number of chromosome pairs per cell nucleus that can be evaluated with FISH is limited, more recent efforts have focused on the use of chromosomal comprehensive screening with CMA (Dahdouh, 2015).

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CHAPTER 15: Fetal Disorders

General dropsy of the foetus is a rare condition in which the foetus and placenta are markedly oedematous. As the result of infiltration with serum the former may attain immense proportions and the latter may be increased to three or four times its normal size. Although a good deal has been written on the subject, no satisfactory explanation of the anomaly has as yet been arrived at.

—J. Whitridge Williams (1903)

INTRODUCTION

Little was written of fetal disorders in the first edition of this textbook. General dropsy described above is today known as *hydrops fetalis* (Hydrops Fetalis). Hydrops is perhaps the quintessential fetal disorder, as it can be a manifestation of severe illness from a wide variety of etiologies. Fetal disorders may be acquired—such as alloimmunization, they may be genetic—congenital adrenal hyperplasia or α4-thalassemia, or they may be sporadic developmental abnormalities—like many structural malformations. In this chapter, fetal anemia and thrombocytopenia as well as immune and nonimmune fetal hydrops are reviewed. Fetal structural malformations are reviewed in Chapter 10, genetic abnormalities in Chapters 13 and 14, and conditions amenable to medical and surgical fetal therapies in Chapter 16. Because congenital infections arise as a result of maternal infection or colonization, they are considered in Chapters 64 and 65.

FETAL ANEMIA

Of the many causes of fetal anemia, one of the most frequent is red cell alloimmunization, which results from transplacental passage of maternal antibodies that destroy fetal red cells. Alloimmunization leads to overproduction of immature fetal and neonatal red cells—*erythroblastosis fetalis*—a condition now referred to as *hemolytic disease of the fetus and newborn (HDFN).*

In addition, several congenital infections are also associated with fetal anemia, particularly parvovirus B19, discussed in Chapter 64 (Respiratory Viruses). In Southeast Asian populations, α4-thalassemia is a common cause of severe anemia and nonimmune hydrops. Fetomaternal hemorrhage occasionally creates severe fetal anemia and is discussed in Fetomaternal Hemorrhage. Rare causes of anemia include red cell production disorders—such as Blackfan-Diamond anemia and Fanconi anemia; red cell enzymopathies—glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency; red cell structural abnormalities—hereditary spherocytosis and elliptocytosis; and myeloproliferative disorders—leukemias. Anemia may be identified through fetal blood sampling, described in Chapter 14 (Fetal Blood Sampling), or by Doppler evaluation of the fetal middle cerebral artery (MCA) peak systolic velocity, described in Management of the Alloimmunized Pregnancy.

Progressive fetal anemia from any cause leads to heart failure, hydrops fetalis, and ultimately death. Fortunately, the prevalence and the course of this otherwise devastating disorder have been dramatically changed by prevention and treatment. Prevention of D alloimmunization is with *anti-D immune globulin*. Identification and treatment of fetal anemia is with MCA Doppler studies and intrauterine transfusions, respectively. Severely anemic fetuses transfused in utero have survival rates exceeding 90 percent, and even in cases of hydrops fetalis, survival rates approach 80 percent (Lindenberg, 2013; Zwiers, 2017).

Red Cell Alloimmunization

Currently, 33 different blood group systems and 339 red cell antigens are recognized by the International Society of Blood Transfusion (Storry, 2014). Although some of these are immunologically and genetically important, many are so rare as to be of little clinical significance. Any individual who lacks a specific red cell antigen may produce an antibody when exposed to that antigen. Such antibodies can prove harmful to that individual if she receives an incompatible blood transfusion. Accordingly, blood banks routinely screen for erythrocyte antigens. These antibodies may also be harmful to a mother's fetus during pregnancy. As noted, maternal antibodies formed against fetal erythrocyte antigens may cross the placenta to cause fetal red cell lysis and anemia.

Typically, a fetus inherits at least one red cell antigen from the father that is lacking in the mother. Thus, the mother may become sensitized if enough fetal erythrocytes reach her circulation to elicit an immune response. Even so, alloimmunization is uncommon for the following reasons: (1) low prevalence of incompatible red cell antigens; (2) insufficient transplacental passage of fetal antigens or maternal antibodies; (3) maternal-fetal ABO incompatibility, which leads to rapid clearance of fetal erythrocytes before they elicit an immune response; (4) variable antigenicity; and (5) variable maternal immune response to the antigen.

In population-based screening studies, the prevalence of red cell alloimmunization in pregnancy approximates 1 percent (Bollason, 2017; Koelewijn, 2008). Most cases of severe fetal anemia requiring antenatal transfusion are attributable to anti-D, anti-Kell, anti-c, or anti-E alloimmunization (de Haas, 2015).

Alloimmunization Detection

At the first prenatal visit, a blood type and antibody screen are routinely assessed, and unbound antibodies in maternal serum are detected by the *indirect Coombs test* (Chap. 9, Definitions). When the result is positive, the specific antibodies are identified, their immunoglobulin subtype is determined as either immunoglobulin G (IgG) or M (IgM), and the titer is quantified. Only IgG antibodies are a concern because IgM antibodies do not cross the placenta. Selected antibodies and their potential to cause fetal hemolytic anemia are listed in Table 15-1. The critical titer is the level at which significant fetal anemia could potentially develop. This may be

different for each antibody, is determined individually by each laboratory, and usually ranges between 1:8 and 1:32. If the critical titer for anti-D antibodies is 1:16, a titer ≥1:16 indicates the possibility of severe hemolytic disease. An important exception is Kell sensitization, which is discussed in Alloimmunization to Minor Antigens.

TABLE 15-1

Selected Red Cell Antigens and Their Relationship to Fetal Hemolytic Disease

Blood Group System	Antigens	Fetal Hemolysis Potential
CDE (Rh)	D, c	Severe disease risk
	E, Be^a, Ce, Cw, Cx, ce, Dw, Evans, e, G, Goa7, Hr, Hro, JAL, HOFM, LOCR, Riv, Rh29, Rh32, Rh42, Rh46, STEM, Tar	Severe disease infrequent, mild disease risk
Kell	K	Severe disease risk
	k, Kp^a, Kp^b, K11, K22 Ku, Js^a, Js^b, Ula	Severe disease infrequent, mild disease risk
Duffy	Fy^a	Severe disease infrequent, mild disease risk
	Fy^b	Not associated with fetal hemolytic disease
Kidd	Jk^a	Severe disease infrequent, mild disease risk
	Jk^b, Jk^3	Mild disease possible
MNS	M, N, S, s, U, Mt^a, Ena, Far, Hil, Hut, Mi^a, Mit, Mut, Mur, Mv, sD, Vw	Severe disease infrequent, mild disease risk
Colton	Co^a, Co^3	Severe disease infrequent, mild disease risk
Diego	Di^a, Di^b, Wr^a, Wr^b	Severe disease infrequent, mild disease risk
Dombrock	Do^a, Gy^a, Hy, Jo^a	Mild disease possible
Gerbich	Ge^2, Ge^3, Ge^4, Ls^a	Mild disease possible
Scianna	Sc2	Mild disease possible
I	I, i	Not associated with fetal hemolytic disease
Lewis	Le^a, Le^b	Not associated with fetal hemolytic disease

From de Haas, 2015; Moise, 2008; Weinstein, 1982.

CDE (Rh) Blood Group Incompatibility

The CDE system includes five red cell proteins or antigens: C, c, D, E, and e. There is no “d” antigen, and D-negativity is defined as the absence of the D antigen. Although most people are D positive or negative, more than 200 D antigen variants exist (Daniels, 2013). Rh was formerly termed *rhesus* because of a misconception that red cells from rhesus monkeys expressed human blood group antigen. In transfusion medicine, “rhesus” is no longer used (Sandler, 2017).

CDE antigens are clinically important. D-negative individuals may become sensitized after a single exposure to as little as 0.1 mL of fetal erythrocytes (Bowman, 1988). The two responsible genes—*RHD* and *RHCE*—are located on the short arm of chromosome 1 and are inherited together, independent of other blood group genes. The incidence of antigen positivity varies according to racial and ethnic origin. Nearly 85 percent of non-Hispanic white Americans are D-positive. The

incidence approximates 90 percent for Native Americans, 93 percent for African Americans and Hispanic Americans, and at least 99 percent for Asian individuals (Garratty, 2004).

The prevalence of D alloimmunization complicating pregnancy ranges from 0.5 to 0.9 percent (Koelewijn, 2008; Martin, 2005). Without anti-D immune globulin prophylaxis, a D-negative woman delivered of a D-positive, *ABO-compatible* newborn has a 16-percent likelihood of developing alloimmunization. Two percent will become sensitized by the time of delivery, 7 percent by 6 months postpartum, and the remaining 7 percent will be "sensibilized"—producing detectable antibodies only in a subsequent pregnancy (Bowman, 1985). If there is *ABO incompatibility*, the D alloimmunization risk approximates 2 percent without prophylaxis (Bowman, 2006). The reason for the differing rates relative to ABO blood type results from erythrocyte destruction of ABO-incompatible cells, which thereby limits sensitizing opportunities. D sensitization also may occur following first-trimester pregnancy complications, prenatal diagnostic procedures, and maternal trauma (Table 15-2).

TABLE 15-2

Causes of Fetomaternal Hemorrhage Associated with Red Cell Antigen Alloimmunization[a]

Pregnancy Loss
Ectopic pregnancy
Spontaneous abortion
Elective abortion
Fetal death (any trimester)
Procedures
Chorionic villus sampling
Amniocentesis
Fetal blood sampling
Evacuation of molar pregnancy
Other
Delivery
Abdominal trauma
Placental abruption
Unexplained vaginal bleeding during pregnancy
Manual placental removal
External cephalic version

[a]For each of the above, anti-D immune globulin is recommended.

Expanded from American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017; American College of Obstetricians and Gynecologists, 2017.

The C, c, E, and e antigens have lower immunogenicity than the D antigen but can cause hemolytic disease. Sensitization to E, c, and C antigens complicates approximately 0.3 percent of pregnancies in screening studies and accounts for about 30 percent of red cell alloimmunization cases (Howard, 1998; Koelewijn, 2008). Anti-E alloimmunization is the most common, but the need for fetal or neonatal transfusions is greater with anti-c alloimmunization than with anti-E or anti-C (de Haas, 2015; Hackney, 2004; Koelewijn, 2008).

The Grandmother Effect

In virtually all pregnancies, small amounts of maternal blood enter the fetal circulation. Real-time polymerase chain reaction (PCR) has been used to identify maternal D-positive DNA in peripheral blood from preterm and full-term D-negative newborns (Lazar, 2006). Thus, it is possible for a D-negative female fetus exposed to maternal D-positive red cells to develop sensitization. When such an individual reaches adulthood, she may produce anti-D antibodies even before or early in her first pregnancy. This mechanism is called the *grandmother effect or theory* because the fetus in the current pregnancy is jeopardized by maternal antibodies that were initially provoked by his or her *grandmother's* erythrocytes.

Alloimmunization to Minor Antigens

Because routine administration of anti-D immunoglobulin prevents anti-D alloimmunization, proportionately more cases of hemolytic disease are caused by red cell antigens other than D (American College of Obstetricians and Gynecologists, 2016; Koelewijn, 2008). These are also known as minor antigens. Kell antigens are among the most frequent. Other antigens with potential to cause severe alloimmunization include Duffy group A—Fy^a, MNS, and Kidd—Jk^a (de Hass, 2015; Moise, 2008). Most cases of sensitization to minor antigens result from incompatible blood transfusions. However, if an IgG red cell antibody is detected and there is any doubt as to its significance, the clinician should err on the side of caution, and the pregnancy should be evaluated for hemolytic disease.

Only a few blood group antigens pose *no* fetal risk. Lewis antibodies—Le^a and Le^b, as well as I antibodies, are cold agglutinins. They are predominantly IgM and are not expressed on fetal red cells (American College of Obstetricians and Gynecologists, 2016). Another antibody that does not cause fetal hemolysis is Duffy group B—Fy^b.

Kell Alloimmunization

Approximately 90 percent of non-Hispanic white Americans and up to 98 percent of African Americans are Kell negative. Kell type is not routinely determined. Transfusion history is important, as nearly 90 percent of Kell sensitization cases result from transfusion with Kell-positive blood.

Kell sensitization may develop more rapidly and may be more severe than with sensitization to D and other blood group antigens. This is because Kell antibodies attach to erythrocyte precursors in the fetal bone marrow, thereby impairing the normal hemopoietic response to anemia. With fewer erythrocytes produced, there is less hemolysis, and severe anemia may not be predicted by the maternal Kell antibody titer. One option is to use a lower critical titer—1:8—for Kell sensitization (Moise, 2012). The American College of Obstetricians and Gynecologists (2016) has recommended that antibody titers not be used to monitor Kell-sensitized pregnancies.

ABO Blood Group Incompatibility

Incompatibility for the major blood group antigens A and B is the most common cause of hemolytic disease in newborns, but it does not cause appreciable hemolysis in the fetus. Approximately 20 percent of newborns have ABO blood group incompatibility, yet only 5 percent are affected clinically. And in such cases, the resulting anemia is typically mild.

The condition differs from CDE incompatibility in several respects. First, ABO incompatibility is often seen in firstborn neonates, whereas sensitization to other blood group antigens is not. This is because most group O women have developed anti-A and anti-B isoagglutinins before pregnancy from exposure to bacteria displaying similar antigens. Second, ABO alloimmunization rarely becomes more severe in successive pregnancies. Last, ABO incompatibility is considered a pediatric disease—rarely of obstetrical concern. This is because most anti-A and anti-B antibodies are IgM and do not cross the placenta. Fetal red cells also have fewer A and B antigenic sites than adult cells and are thus less immunogenic.

Consequently, fetal surveillance and early delivery are not indicated in pregnancies with prior ABO incompatibility. Careful neonatal observation is essential, however, because hyperbilirubinemia may require treatment with phototherapy or occasionally transfusion (Chap. 33, Polycythemia and Hyperviscosity).

Management of the Alloimmunized Pregnancy

An estimated 25 to 30 percent of fetuses from D-alloimmunized pregnancies will have mild-to-moderate hemolytic anemia. And without treatment, up to 25 percent will develop hydrops (Tannirandorn, 1990). If alloimmunization is detected and the titer is below the critical value, the titer is generally repeated every 4 weeks for the duration of the pregnancy (American College of Obstetricians and Gynecologists, 2016). Importantly, if a prior pregnancy was complicated by alloimmunization, serial titer assessment is not indicated, and the pregnancy is assumed to be at risk regardless of titer. Management of such pregnancies is discussed subsequently. In any pregnancy in which an antibody titer has reached a critical value, there is no benefit to repeating it. The pregnancy is at risk even if the titer drops, and further evaluation is still required.

Determining Fetal Risk

Up to 40 percent of D-negative pregnant women carry a D-negative fetus. The presence of anti-D antibodies reflects maternal sensitization but does not indicate whether the fetus is D-positive. If a woman became sensitized in a prior pregnancy, her antibody titer might rise to high levels during the current pregnancy even if the current fetus is D-negative, due to an *amnestic response.* In a non-Hispanic white couple in which the woman is D-negative, there is an 85-percent chance that the man is D-positive. But, in 60 percent of these cases, he will be heterozygous at the D-locus. And, if he is heterozygous, then half of his children will be at risk for hemolytic disease. Transfusion history is relevant. Alloimmunization to a red cell antigen other than D may have occurred following a blood transfusion in the past, and if that antigen is not present on paternal erythrocytes, the pregnancy is not at risk.

Initial evaluation of alloimmunization begins with determining the paternal erythrocyte antigen status. *Provided that paternity is certain*, if the father is negative for the red cell antigen to which the mother is sensitized, the pregnancy is not at risk. In a D-alloimmunized pregnancy in which the father is D-positive, it is helpful to determine paternal zygosity for the D antigen using DNA-based analysis. If the father is heterozygous—or if paternity is not known—the woman should be offered assessment of fetal genotype. Traditionally, this was done with amniocentesis and PCR testing of uncultured amniocytes, which has a positive-predictive value of 100 percent and negative-predictive value of approximately 97 percent (American College of Obstetricians and Gynecologists, 2016; Van den Veyver, 1996). Fetal testing for other antigens—such as E/e, C/c, Duffy, Kell, Kidd, and M/N—is also available with this method. Chorionic villus sampling is not recommended because of greater risk for fetomaternal hemorrhage and subsequent worsening of alloimmunization.

Noninvasive fetal D genotyping has been performed using cell-free DNA (cfDNA) from maternal plasma (Chap. 13, Fetal DNA in the Maternal Circulation). The reported sensitivity exceeds 99 percent, the specificity exceeds 95 percent, and positive- or negative-predictive values are similarly very high (de Haas, 2016; Johnson, 2017; Moise, 2016; Vivanti, 2016). Fetal D genotyping with cfDNA is routinely used in parts of Europe. There are two potential indications in D-negative pregnant women: (1) in women *with* D alloimmunization, testing can identify fetuses that are also D-negative and do not require anemia surveillance, and (2) in women *without* D alloimmunization, anti-D immune globulin might be withheld if the fetus is D negative. In the case of the latter, the American College of Obstetricians and Gynecologists (2017) does not recommend routine cfDNA screening in D-negative pregnancies until it becomes cost-effective.

Management of the alloimmunized pregnancy is individualized and may consist of maternal antibody titer surveillance, sonographic monitoring of the fetal MCA peak systolic velocity, amnionic fluid bilirubin studies, or fetal blood sampling. Accurate pregnancy dating is critical. The gestational age at which fetal anemia developed in prior pregnancies is important because anemia tends to occur earlier and be sequentially more severe.

Middle Cerebral Artery Doppler Velocimetry

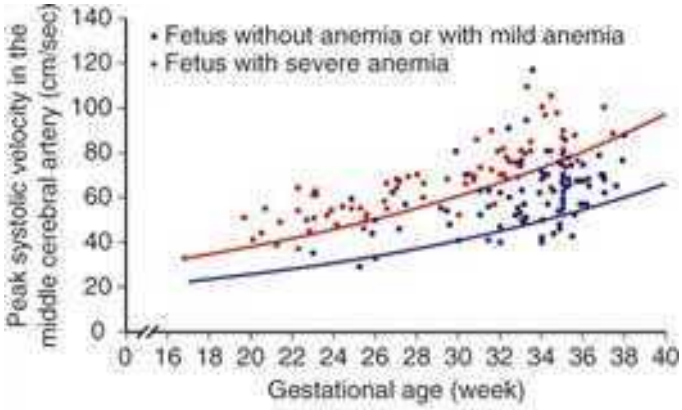
Serial measurement of the peak systolic velocity of the fetal MCA is the recommended test for detection of fetal anemia (Society for Maternal–Fetal Medicine, 2015a). The anemic fetus shunts blood preferentially to the brain to maintain adequate oxygenation. The velocity rises because of increased cardiac output and decreased

blood viscosity. The technique is discussed in Chapter 10 (Ductus Arteriosus) and requires training and experience (American College of Obstetricians and Gynecologists, 2016).

In a landmark study, Mari and coworkers (2000) measured the MCA peak systolic velocity serially in 111 fetuses at risk for anemia and in 265 normal control fetuses. The threshold value of 1.5 multiples of the median (MoM) for gestational age correctly identified all fetuses with moderate or severe anemia. This provided a sensitivity of 100 percent, with a false-positive rate of 12 percent.

The MCA peak systolic velocity is followed serially, and values are plotted on a curve like the one shown in Figure 15-1. If the velocity is between 1.0 and 1.5 MoM and the slope is rising—such that the value is approaching 1.5 MoM—surveillance is generally increased to weekly Doppler interrogation. If the MCA peak systolic velocity exceeds 1.5 MoM and the gestational age is younger than 34 or 35 weeks, fetal blood sampling should be considered and followed by fetal transfusion if needed (Society for Maternal–Fetal Medicine, 2015a). The false-positive rate of MCA peak systolic velocity increases significantly beyond 34 weeks, due to the normal augmentation in cardiac output that develops at this gestational age (Moise, 2008; Zimmerman, 2002).

FIGURE 15-1
Doppler measurements of the peak systolic velocity in the middle cerebral artery (MCA) in 165 fetuses at risk for severe anemia. The blue line indicates the median peak systolic velocity in normal pregnancies, and the red line shows 1.5 multiples of the median. (Reproduced with permission from Oepkes D, Seaward PG, Vandenbussche et al: Doppler ultrasonography versus amniocentesis to predict fetal anemia, N Engl J Med. 2006 Jul 13;355(2):156–164.)



Amniotic Fluid Spectral Analysis

This test is included for historical interest. More than 50 years ago, Liley (1961) demonstrated the utility of amnionic fluid spectral analysis to measure bilirubin concentration and to thereby estimate hemolysis severity. Amnionic fluid bilirubin concentration was measured by a spectrophotometer and was represented as the change in optical density absorbance at 450 nm—ΔOD_{450}. The likelihood of fetal anemia was determined by plotting the ΔOD_{450} value on a graph that was divided into zones. These zones roughly correlated with fetal hemoglobin concentration, and thus with anemia severity. The original Liley graph was valid from 27 to 42 weeks' gestation and was subsequently modified by Queenan (1993) to include gestational ages as early as 14 weeks. However, the amnionic fluid bilirubin level is normally high in midpregnancy, limiting the reliability of this technique.

Middle cerebral artery velocimetry is more accurate than ΔOD_{450} assessment and does not confer risks for increased alloimmunization associated with amniocentesis. It has replaced ΔOD_{450} assessment for this purpose.

Fetal Blood Transfusion

If there is evidence of severe fetal anemia, because of either elevated MCA peak systolic velocity or development of fetal hydrops, management is strongly influenced by gestational age. Fetal blood sampling and intrauterine transfusion are generally performed prior to 34 to 35 weeks (Society for Maternal-Fetal Medicine, 2015a). Intravascular transfusion into the umbilical vein under sonographic guidance is the preferred method of fetal transfusion. Transfusion into the fetal peritoneal cavity may be necessary with severe, early-onset hemolytic disease in the early second trimester, a time when the umbilical vein is too narrow to readily permit needle entry. With hydrops, although peritoneal absorption is impaired, some prefer to transfuse into both the fetal peritoneal cavity and the umbilical vein.

Transfusion is generally recommended only if the fetal hematocrit is <30 percent (Society for Maternal-Fetal Medicine, 2015a). Once hydrops has developed, the hematocrit is generally 15 percent or lower. The red cells transfused are type O, D-negative, cytomegalovirus-negative, packed to a hematocrit of approximately 80 percent to prevent volume overload, irradiated to prevent fetal graft-versus-host reaction, and leukocyte-poor. The fetal–placental volume allows rapid infusion of a relatively large quantity of blood. Before transfusion, a paralytic agent such as vecuronium may be given to the fetus to minimize movement. In a nonhydropic fetus, the target hematocrit is generally 40 to 50 percent. The volume transfused may be estimated by multiplying the estimated fetal weight in grams by 0.02 for each 10-percent rise in hematocrit needed (Giannina, 1998). In the severely anemic fetus at 18 to 24 weeks' gestation, less blood is transfused initially, and another transfusion may be planned for approximately 2 days later. Subsequent transfusions usually take place every 2 to 4 weeks, depending on the hematocrit.

The MCA peak systolic velocity threshold for severe anemia is higher following an initial transfusion—1.70 MoM rather than 1.50 MoM (Society for Maternal-Fetal Medicine, 2015a). It is hypothesized that the change in threshold compensates for the contribution of donor cells in the initial transfusion, because donor cells (from adults) have a smaller mean corpuscular volume. Alternately, the timing of subsequent transfusions is based on anemia severity and posttransfusion hematocrit.

Following transfusion, the fetal hematocrit generally drops by approximately 1 percent per day. A more rapid initial decline may be encountered in the setting of fetal hydrops.

Outcomes

Procedure-related complications have declined significantly at experienced centers in recent years, with overall survival rates exceeding 95 percent (Zwiers, 2017). Complications include fetal death in approximately 2 percent, need for emergent cesarean delivery in 1 percent, and infection and preterm rupture of membranes in 0.3 percent each, respectively. The stillbirth rate exceeds 15 percent if transfusion is required before 20 weeks (Lindenberg, 2013; Zwiers, 2017). Considering that fetal transfusion is potentially lifesaving in severely compromised fetuses, these risks should not dissuade therapy.

Van Kamp (2001) reported that if hydrops had developed, the survival rate approached 75 to 80 percent. However, of the nearly two thirds with resolution of hydrops following transfusion, more than 95 percent survived. The survival rate was <40 percent if hydrops persisted.

Lindenberg (2012) reviewed long-term outcomes following intrauterine transfusion in a cohort of more than 450 alloimmunized pregnancies. Alloimmunization was secondary to anti-D in 80 percent, anti-Kell in 12 percent, and anti-c in 5 percent. Approximately a fourth of affected fetuses had hydrops, and more than half also required exchange transfusion in the neonatal period. Among nearly 300 children aged 2 to 17 years who participated in neurodevelopmental testing, fewer than 5 percent had severe impairments. These included severe developmental delay in 3 percent, cerebral palsy in 2 percent, and deafness in 1 percent.

Prevention of Anti-D Alloimmunization

Anti-D immune globulin is one of the success stories of modern obstetrics. It has been used for nearly five decades to prevent D alloimmunization. In countries without access to anti-D immune globulin, up to 10 percent of D-negative pregnancies are complicated by hemolytic disease of the fetus and newborn (Zipursky, 2015). With immunoprophylaxis, however, the alloimmunization risk is reduced to <0.2 percent. Despite long-standing and widespread use, its mechanism of action is not completely understood.

As many as 90 percent of alloimmunization cases occur from fetomaternal hemorrhage at delivery. Routine postpartum administration of anti-D immune globulin to at-risk pregnancies within 72 hours of delivery lowers the alloimmunization rate by 90 percent (Bowman, 1985). Additionally, provision of anti-D immune globulin at 28 weeks' gestation reduces the third-trimester alloimmunization rate from approximately 2 percent to 0.1 percent (Bowman, 1988). *Whenever there is doubt whether to give anti–D immunoglobulin, it should be given.* If not needed, it will not cause harm, but failure to provide it when needed can have severe consequences.

Current preparations of anti-D immune globulin are derived from human plasma donated by individuals with high-titer anti-D immunoglobulin D antibodies. Formulations prepared by cold ethanol fractionation and ultrafiltration must be administered intramuscularly because they contain plasma proteins that could result in anaphylaxis if given intravenously. However, formulations prepared using ion exchange chromatography may be administered either intramuscularly or intravenously. This is important for treatment of significant fetomaternal hemorrhage, which is discussed subsequently. Both preparation methods effectively remove viral particles, including hepatitis and human immunodeficiency viruses. Depending on the preparation, the half-life of anti-D immune globulin ranges from 16 to 24 days, which is why it is given both in the third trimester and following delivery. The standard intramuscular dose of anti-D immune globulin—300 µg or 1500 IU—will protect the average-sized mother from a fetal hemorrhage of up to 30 mL of fetal whole blood or 15 mL of fetal red cells.

In the United States, anti-D immune globulin is given prophylactically to all D-negative, unsensitized women at approximately 28 weeks' gestation, and a second dose is given after delivery if the newborn is D-positive (American College of Obstetricians and Gynecologists, 2017). Before the 28-week dose of anti-D immune globulin, repeat antibody screening is recommended to identify individuals who have become alloimmunized (American Academy of Pediatrics, 2017). Following delivery, anti-D immune globulin should be given within 72 hours. Recognizing that 40 percent of neonates born to D-negative women are also D negative, administration of immune globulin is recommended only after the newborn is confirmed to be D positive (American College of Obstetricians and Gynecologists, 2017). If immune globulin is inadvertently not administered following delivery, it should be given as soon as the omission is recognized, because there may be some protection up to 28 days postpartum (Bowman, 2006). Anti-D immune globulin is also administered after pregnancy-related events that could result in fetomaternal hemorrhage (see Table 15-2).

Anti-D immune globulin may produce a weakly positive—1:1 to 1:4—indirect Coombs titer in the mother. This is harmless and should not be confused with development of alloimmunization. Additionally, as the body mass index increases above 27 to 40 kg/m^2, serum antibody levels decrease by 30 to 60 percent and may be less protective (MacKenzie, 2006; Woelfer, 2004). D-negative women who receive other types of blood products—including platelet transfusions and plasmapheresis—are also at risk of becoming sensitized, and this can be prevented with anti-D immune globulin. Rarely, a small amount of antibody crosses the placenta and results in a weakly positive direct Coombs test in cord and infant blood. Despite this, passive immunization does not cause significant fetal or neonatal hemolysis.

It is estimated that in 2 to 3 per 1000 pregnancies, the volume of fetomaternal hemorrhage exceeds 30 mL of whole blood (American College of Obstetricians and Gynecologists, 2017). A single dose of anti-D immune globulin would be insufficient in such situations. If additional anti-D immune globulin is considered only for women with risk factors such as those shown in Table 15-2, then *half* of those who require additional immune globulin may be missed. For this reason, all D-negative women should be screened at delivery, typically with a rosette test, followed by quantitative testing if indicated (American College of Obstetricians and Gynecologists, 2017).

The rosette test is a qualitative test that identifies whether fetal D-positive cells are present in the circulation of a D-negative woman. A sample of maternal blood is mixed with anti-D antibodies that coat any D-positive fetal cells present in the sample. Indicator red cells bearing the D-antigen are then added, and rosettes form around the fetal cells as the indicator cells attach to them by the antibodies. Thus, if rosettes are visualized, there are fetal D-positive cells in that sample. In the

setting of D incompatibility, or any time a large fetomaternal hemorrhage is suspected—regardless of antigen status, a Kleihauer-Betke test or flow cytometry test are used. These are discussed in Fetal Thrombocytopenia.

The dosage of anti-D immune globulin is calculated from the estimated volume of the fetal-to-maternal hemorrhage, as described in Fetal Thrombocytopenia. One 300-µg dose is given for each 15 mL of fetal red cells or 30 mL of fetal whole blood to be neutralized. If using an intramuscular preparation of anti-D immune globulin, no more than five doses may be given in a 24-hour period. If using an intravenous preparation, two ampules—totaling 600 µg—may be given every 8 hours. To determine if the administered dose was adequate, the indirect Coombs test may be performed. A positive result indicates that there is excess anti–D immunoglobulin in maternal serum, thus demonstrating that the dose was sufficient. Alternatively, a rosette test may be performed to assess whether circulating fetal cells remain.

Serological Weak D Phenotypes

Formerly called D^u, these are the most common antigenic D variants in the United States and Europe. Serological weak D phenotypes have been further refined into two general categories using molecular analysis—RHD genotyping. Molecular weak D phenotypes carry reduced numbers of intact D antigens on the red cell surface. Those designated partial D types have protein deletions associated with abnormal D antigens that lack epitopes (Sandler, 2017). When this distinction is known, it can have clinical consequences in terms of sensitization risk and need for anti-D immune globulin.

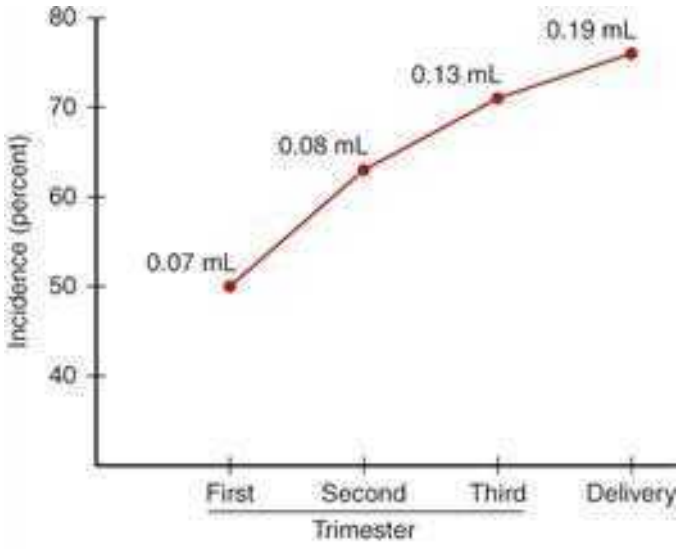
Traditionally, serological weak D individuals have been considered to be D-positive or -negative depending on the clinical situation. For the purposes of blood donation, they are categorized as D-positive, whereas transfusion recipients with weak D are considered D-negative. In pregnancy, weak D has also been considered D-negative, so that individuals receive immune globulin and avoid potential sensitization (American College of Obstetricians and Gynecologists, 2017; Sandler, 2015).

Many non-Hispanic white Americans who test positive for weak D have weak D phenotypes 1, 2, or 3. Individuals with these phenotypes may be managed as though they are D-positive. Because they are not at risk for alloimmunization, anti-D immune globulin is not needed (Sandler 2015, 2017). In contrast, individuals with partial D antigens may be at risk for D-sensitization and do require immune globulin. Molecular RHD genotyping has been suggested for pregnant women with weak D phenotype, but cost-benefit analysis of this strategy is presently lacking (American College of Obstetricians and Gynecologists, 2017). *If molecular genetic testing has not been performed in those with serologic weak D phenotype, D immunoprophylaxis should be administered to those with weak D phenotype.*

FETOMATERNAL HEMORRHAGE

A small amount of fetomaternal bleeding likely occurs in all pregnancies, and in two thirds, this may be sufficient to provoke an antigen-antibody reaction. As shown in Figure 15-2, the incidence increases with advancing gestation and the volume of fetal blood in the maternal circulation. Fortunately, a large blood loss—true fetomaternal hemorrhage—is rare. In one series of more than 30,000 pregnancies, fetomaternal hemorrhage ≥150 mL occurred in 1 per 2800 births (de Almeida, 1994). The prevalence of fetomaternal hemorrhage of at least 30 mL—the volume of fetal blood covered by a standard 300-µg dose of anti-D immune globulin—is estimated to be 3 per 1000 pregnancies (Wylie, 2010).

FIGURE 15-2
Incidence of fetal-to-maternal hemorrhage during pregnancy. The numbers at each data point represent total volume of fetal blood estimated to have been transferred into the maternal circulation. (Data from Choavaratana, 1997.)



Selected causes of fetomaternal hemorrhage are shown in Table 15-2. It also may occur with placenta previa, placental chorioangioma, or vasa previa (Giacoia 1997; Rubod, 2007). In each of these circumstances, however, fetomaternal hemorrhage is extremely uncommon if not rare. And, in more than 80 percent of cases, no cause is identified. With significant hemorrhage, the most common presenting complaint is decreased fetal movement (Bellussi, 2017; Wylie, 2010). A sinusoidal fetal heart rate pattern is infrequently seen but warrants immediate evaluation (Chap. 24, Periodic Fetal Heart Rate Changes). Sonography may demonstrate elevated MCA peak systolic velocity, and indeed this is reported to be the most accurate predictor (Bellusi, 2017; Wylie, 2010). Hydrops is an ominous finding. If fetomaternal hemorrhage is suspected, an elevated MCA peak systolic velocity or sonographic evidence of hydrops prompts consideration of urgent fetal transfusion or delivery.

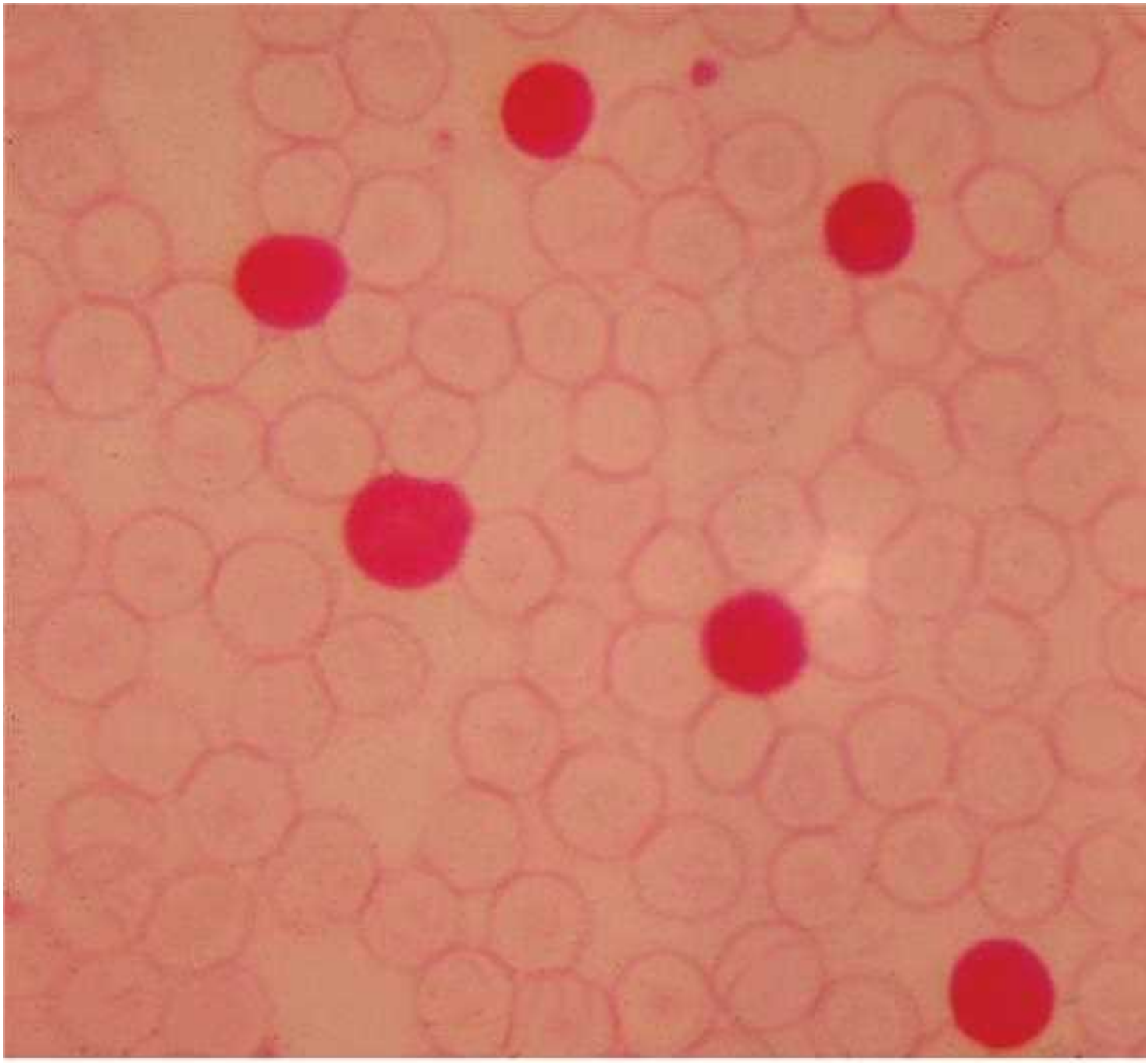
One limitation of quantitative tests for fetal cells in the maternal circulation is that they do not provide information regarding hemorrhage timing or chronicity (Wylie, 2010). In general, anemia developing gradually or chronically, as in alloimmunization, is better tolerated by the fetus than acute anemia. Chronic anemia may not produce fetal heart rate abnormalities until the fetus is moribund. In contrast, significant acute hemorrhage is poorly tolerated by the fetus and may cause profound fetal neurological impairment from cerebral hypoperfusion, ischemia, and infarction. In some cases, fetomaternal hemorrhage is identified during stillbirth evaluation (Chap. 35, Risk Factors).

Laboratory Tests

Once fetomaternal hemorrhage is recognized, the volume of fetal blood loss should be estimated. The volume is essential to calculate the appropriate dose of anti D-immune globulin if the woman is D-negative, and it may influence obstetrical management.

The most commonly used quantitative test for fetal red cells in the maternal circulation is the acid elution or *Kleihauer-Betke (KB) test* (Kleihauer, 1957). Fetal erythrocytes contain hemoglobin F, which is more resistant to acid elution than hemoglobin A. After exposure to acid, only fetal hemoglobin remains, such that after staining, the fetal erythrocytes appear red and adult erythrocytes appear as “ghosts” (Fig. 15-3). The fetal cells are then counted and expressed as a percentage of adult cells. The KB test is labor intensive. Importantly, there are two scenarios in which it may not be accurate: (1) maternal hemoglobinopathies such as β-thalassemia in which the fetal hemoglobin level is elevated and (2) pregnancies at or near term, when the fetus has already started to produce hemoglobin A.

FIGURE 15-3
Kleihauer-Betke test demonstrating massive fetal-to-maternal hemorrhage. After acid-elution treatment, fetal red cells rich in hemoglobin F stain darkly, whereas maternal red cells with only very small amounts of hemoglobin F stain lightly.



Hemorrhage Quantification

The volume of fetomaternal hemorrhage is calculated from the KB test result using the following formula:

$$\text{Fetal blood volume} = \frac{\text{MBV} \times \text{maternal Hct} \times \text{\% fetal cells in KB}}{\text{newborn Hct}}$$

One method is to estimate the maternal blood volume (MBV) as 5000 mL for a normal-size, normotensive women at term. Thus, for 1.7-percent positive KB-stained cells in a woman of average size with a hematocrit of 35 percent and whose fetus has a hematocrit of 50 percent:

$$\text{Fetal blood volume} = \frac{5000 \times 0.35 \times 0.017}{0.5} = 60 \text{ mL}$$

The fetal-placental blood volume at term approximates 125 mL/kg. For a 3000-g fetus, that would equate to 375 mL. Thus, this fetus lost approximately 15 percent (60 ÷ 375 mL) of the fetal-placental volume. Because the hematocrit is 50 percent in a term fetus, this 60 mL of whole blood represents 30 mL of red cells lost into the maternal circulation. This loss should be well tolerated hemodynamically but would require two 300-µg doses of anti-D immunoglobulin to prevent alloimmunization. A more precise method to estimate the maternal blood volume includes a calculation based on the maternal height, weight, and anticipated physiological maternal blood volume accrual (Table 41-1).

Fetomaternal hemorrhage can also be quantified using flow cytometry, which uses monoclonal antibodies to hemoglobin F or to the D antigen, followed by quantification of fluorescence (Chambers, 2012; Welsh, 2016). Flow cytometry is an automated test that can analyze a greater number of cells than the KB test. Further, it is unaffected by maternal levels of fetal hemoglobin or by fetal levels of hemoglobin A. Flow cytometry has been reported to be more sensitive and accurate than the KB test, however, it uses specialized technology not routinely available in many hospitals (Chambers, 2012; Corcoran, 2014; Fernandes, 2007).

FETAL THROMBOCYTOPENIA

Alloimmune Thrombocytopenia

This condition is also referred to as *neonatal alloimmune thrombocytopenia (NAIT)* or *fetal and neonatal alloimmune thrombocytopenia (FNAIT).* Alloimmune thrombocytopenia (AIT) is the most common cause of severe thrombocytopenia among term newborns, with a frequency of 1 to 2 per 1000 births (Kamphuis, 2010; Pacheco, 2013; Risson, 2012). FNAIT is caused by maternal alloimmunization to paternally inherited fetal platelet antigens. The resulting maternal antiplatelet antibodies cross the placenta in a manner similar to red cell alloimmunization (Red Cell Alloimmunization). Unlike *immune thrombocytopenia*, the maternal platelet count is normal with FNAIT. And, unlike anti-D alloimmunization, severe sequelae may affect the *initial* at-risk pregnancy.

Maternal platelet alloimmunization is most often against human platelet antigen-1a (HPA-1a). It accounts for 80 to 90 percent of cases and is associated with the greatest severity (Bussel, 1997; Knight, 2011; Tiller, 2013). This is followed in order of frequency by HPA-5b, HPA-1b, and HPA-3a. Alloimmunization to other antigens accounts for only 1 percent of reported cases.

Approximately 85 percent of non-Hispanic white individuals are HPA-1a positive. Two percent are homozygous for HPA-1b and thus at risk for alloimmunization. Importantly, however, only 10 percent of homozygous HPA-1b mothers who carry an HPA-1a fetus will produce anti-platelet antibodies. Approximately a third of affected fetuses or neonates will develop severe thrombocytopenia, and 10 to 20 percent of those with severe thrombocytopenia sustain an intracranial hemorrhage (ICH) (Kamphuis, 2010). As a result, population-based screening studies have identified FNAIT-associated ICH in 1 per 25,000 to 60,000 pregnancies (Kamphuis, 2010; Knight, 2011).

FNAIT may present in various ways. In some cases, neonatal thrombocytopenia may be an incidental finding or the newborn may manifest petechiae. In the other extreme, a fetus or neonate may develop devastating ICH—often before birth. Of 600 pregnancies with FNAIT identified through a large international registry, fetal or neonatal ICH complicated 7 percent of cases (Tiller, 2013). Hemorrhage affected the first-born child in 60 percent and occurred before 28 weeks' gestation in half. A third of affected children died soon after birth, and 50 percent of survivors had severe neurological disabilities. Bussel and coworkers (1997) evaluated fetal platelet counts before therapy in 107 fetuses with FNAIT. Thrombocytopenia severity was predicted by a prior sibling with perinatal ICH, and 98 percent of cases were identified this way. The initial platelet count was <20,000/μL in 50 percent. In cases in which the platelet count was initially >80,000/μL, they noted that it dropped by more than 10,000/μL each week in the absence of therapy.

Diagnosis and Management

Alloimmune thrombocytopenia is typically diagnosed following delivery of a neonate with severe and unexplained thrombocytopenia to a woman whose platelet count is normal. Rarely, the diagnosis is ascertained after identifying fetal ICH. The condition recurs in 70 to 90 percent of subsequent pregnancies, is often severe, and usually develops earlier with each successive pregnancy. Traditionally, fetal blood sampling was performed to detect fetal thrombocytopenia and to tailor therapy, with transfusion of platelets if the fetal platelet count was <50,000/μL. Because of procedure-related complications, however, experts recommend abandoning routine fetal platelet sampling in favor of empirical treatment with intravenous immune globulin (IVIG) and prednisone (Berkowitz, 2006; Pacheco, 2011).

Therapy is stratified according to whether a prior affected pregnancy was complicated by perinatal ICH, and if so, at what gestational age (Table 15-3). Pioneering work by Bussel (1996) and Berkowitz (2006) and their colleagues demonstrated the efficacy of such treatment. In one series of 50 pregnancies with fetal thrombocytopenia secondary to FNAIT, IVIG raised the platelet count by approximately 50,000/μL, and no fetus developed ICH (Bussel, 1996). Among pregnancies at particularly high risk—based on a platelet count <20,000/μL or sibling with FNAIT-associated ICH—the addition of corticosteroids to IVIG increased the platelet count in 80 percent of cases (Berkowitz, 2006). Cesarean delivery has been recommended at or near term. A *noninstrumental* vaginal delivery is generally considered only if fetal blood sampling has demonstrated a platelet count >100,000/μL (Pacheco, 2011).

TABLE 15-3

Fetal-Neonatal Alloimmune Thrombocytopenia (FNAIT) Treatment Recommendations

Risk Group	Criteria	Suggested Management
1	Prior fetus or newborn with ICH, but no maternal anti-HPA antibody identified	Maternal anti-HPA antibody screening and cross-matching with paternal platelets at 12, 24, and 32 weeks' gestation; no treatment for negative test results
2	Prior fetus or newborn with thrombocytopenia and maternal anti-HPA antibody, but no ICH	Beginning at 20 wks: IVIG 1g/kg/wk and prednisone 0.5 mg/kg/d ***or*** IVIG 2 g/kg/wk Beginning at 32 weeks: IVIG 2 g/kg/wk and prednisone 0.5 mg/kg/d. Continue until delivery
3	Prior fetus with 3rd-trimester ICH or prior newborn with ICH, and maternal anti-HPA antibody	Beginning at 12 wks: IVIG 1 g/kg/wk Beginning at 20 wks: either increase IVIG to 2 g/kg/wk ***or*** add prednisone 0.5 mg/kg/d Beginning at 28 wks: IVIG 2 g/kg/wk ***and*** prednisone 0.5 mg/kg/d. Continue until delivery
4	Prior fetus with ICH before the 3rd trimester and maternal anti-HPA antibody	Beginning at 12 wks: IVIG 2 g/kg/wk Beginning at 20 wks: add prednisone 1 mg/kg/d Continue both until delivery

HPA = human platelet antigen; ICH = intracerebral hemorrhage; IVIG = intravenous immunoglobulin G.

Data from Pacheco, 2011.

Additional considerations include risks and costs associated with therapy. Side effects of IVIG may include fever, headache, nausea/vomiting, myalgia, and rash. Maternal hemolysis also has been described (Rink, 2013). Costs for IVIG may exceed $70 per gram or nearly $10,000 for each weekly 2-g/kg infusion for an average-size pregnant woman (Pacheco, 2011).

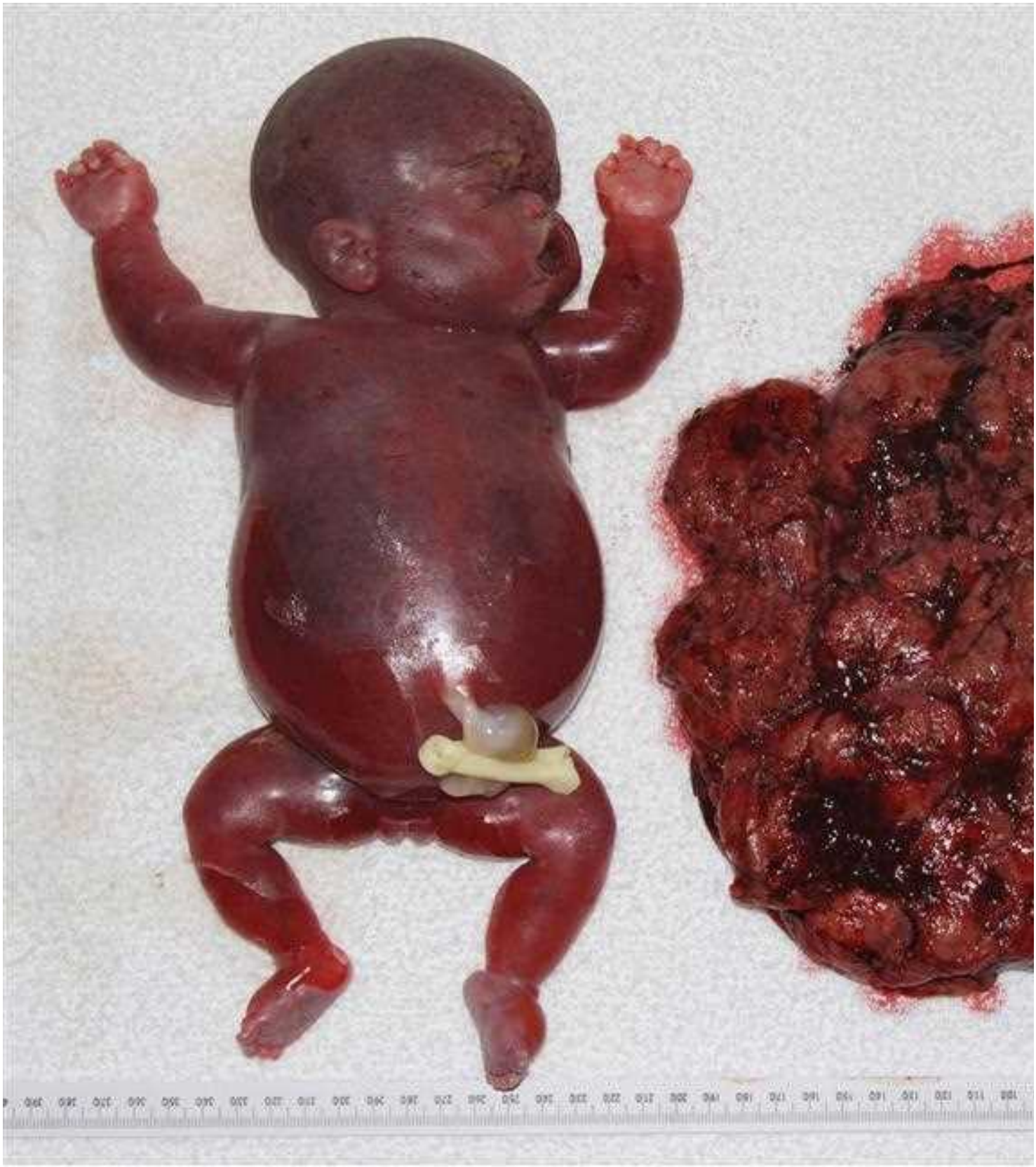
Immune Thrombocytopenia

Also known as immune or idiopathic thrombocytopenic purpura (ITP), this autoimmune disorder is characterized by antiplatelet IgG antibodies that attack platelet glycoproteins. In pregnancy, these antibodies may cross the placenta and cause fetal thrombocytopenia. Maternal ITP is discussed in Chapter 56 (Platelet Disorders). Fetal thrombocytopenia is usually mild. However, neonatal platelet levels may fall rapidly after birth, with a nadir at 48 to 72 hours of life. Neither the maternal platelet count, identification of antiplatelet antibodies, nor treatment with corticosteroids effectively predicts fetal or neonatal platelet counts (Hachisuga, 2014). Importantly, fetal platelet counts are usually adequate to allow vaginal delivery without an increased risk of ICH. In a recent review of more than 400 pregnancies with ITP, there was no case of fetal or neonatal ICH and no infant with any central nervous system abnormality (Wyszynski, 2016). Fetal bleeding complications are considered rare, and fetal blood sampling is not recommended (Neunert, 2011). Delivery mode is based on standard obstetrical indications.

HYDROPS FETALIS

This term refers to excessive accumulation of serous fluid. Strictly defined, *hydrops fetalis* is edema of the fetus. Traditionally, the diagnosis was made after delivery of a massively edematous neonate, often stillborn (Fig. 15-4). With sonography, hydrops has become a prenatal diagnosis. It is defined as two or more fetal effusions—pleural, pericardial, or ascites—or one effusion plus anasarca. As hydrops progresses in severity, edema is invariably a component, and is usually accompanied by placentomegaly and hydramnios. Clinically significant edema is defined sonographically as skin thickness >5 mm, and placentomegaly if the placenta thickness is at least 4 cm in the second trimester or 6 cm in the third trimester (Bellini, 2009; Society for Maternal–Fetal Medicine, 2015b). Hydrops may result from a wide range of conditions with varying pathophysiologies, each with the potential to make the fetus severely ill. It is divided into two categories. If found in association with red cell alloimmunization, it is termed *immune*, otherwise, it is *nonimmune.*

FIGURE 15-4
Hydropic, macerated stillborn infant and characteristically large placenta. The etiology was B19 parvovirus infection. (Used with permission from Dr. April Bleich.)



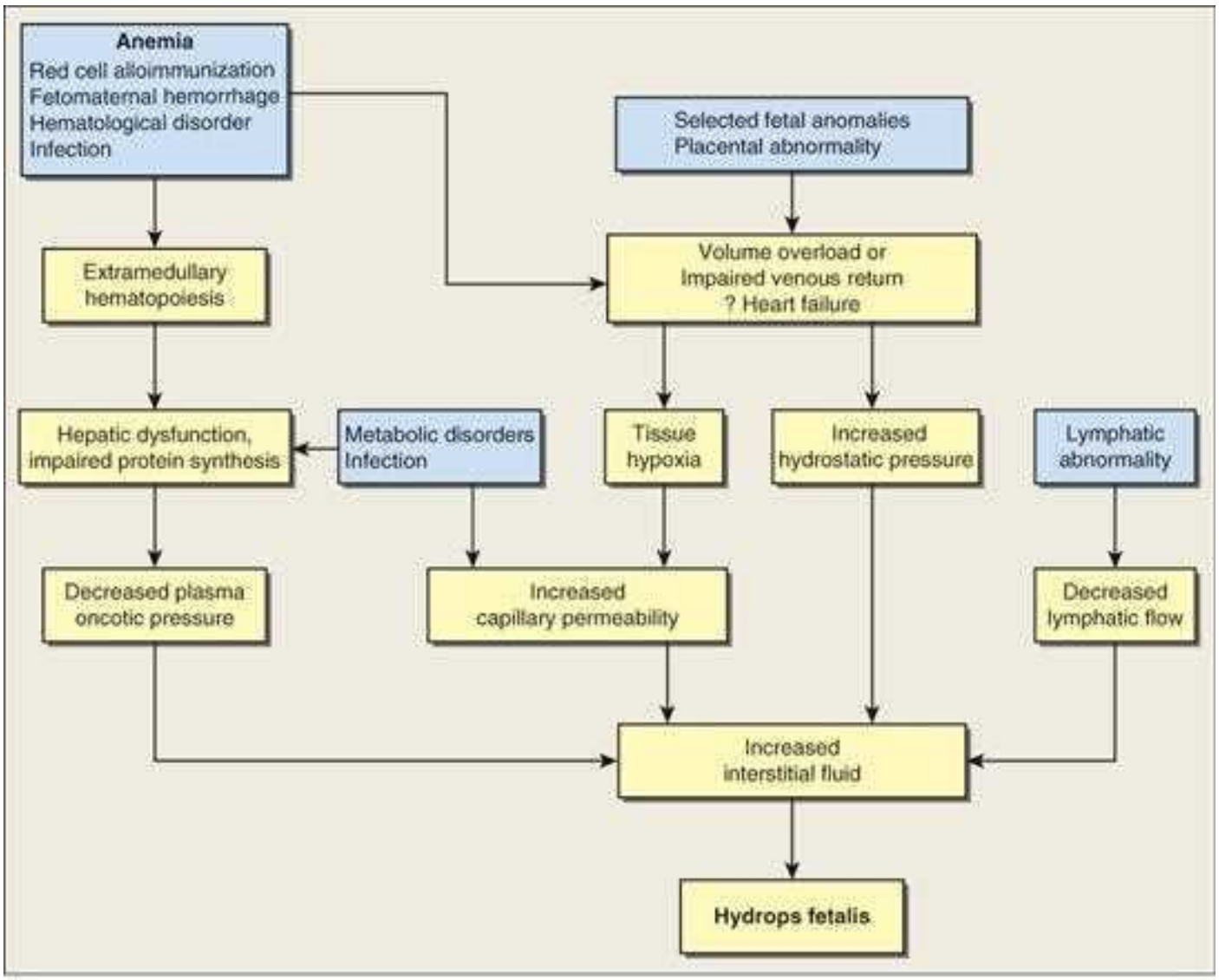
Immune Hydrops

The incidence of immune hydrops has dramatically declined with the advent of anti-D immune globulin, MCA Doppler studies for detection of severe anemia, and prompt fetal transfusion when needed (Fetal Blood Transfusion). However, fewer than 10 percent of hydrops cases are caused by red cell alloimmunization (Bellini, 2012; Santolaya, 1992).

The pathophysiology underlying hydrops remains unknown. Immune hydrops is postulated to share several physiological abnormalities with nonimmune hydrops. As shown in Figure 15-5, these include decreased colloid oncotic pressure, increased hydrostatic (or central venous) pressure, and enhanced vascular permeability. Immune hydrops results from transplacental passage of maternal antibodies that destroy fetal red cells. The resultant anemia stimulates marrow erythroid hyperplasia and extramedullary hematopoiesis in the spleen and liver. The latter likely causes portal hypertension and impaired hepatic protein synthesis, which lowers plasma oncotic pressure (Nicolaides, 1985). Fetal anemia also may raise central venous pressure (Weiner, 1989). Finally, tissue hypoxia from anemia may increase capillary permeability, such that fluid collects in the fetal thorax, abdominal cavity, and/or subcutaneous tissue.

FIGURE 15-5

Proposed pathogenesis of immune and nonimmune hydrops fetalis. (Adapted from Bellini, 2009; Lockwood, 2009.)



The degree of anemia in immune hydrops is typically severe. In a series of 70 pregnancies with fetal anemia from red cell alloimmunization, Mari and coworkers (2000) found that all those with immune hydrops had hemoglobin values *<5 g/dL*. As discussed in Fetal Blood Transfusion, immune hydrops is treated with fetal blood transfusions.

Nonimmune Hydrops

At least 90 percent of cases of hydrops are nonimmune (Bellini, 2012; Santolaya, 1992). The prevalence estimate is 1 per 1500 second-trimester pregnancies (Heinonen, 2000). The number of specific disorders that can lead to nonimmune hydrops is extensive. Etiologies and the proportion of births within each hydrops category from a review of more than 6700 affected pregnancies are summarized in Table 15-4. A cause is identified in at least 60 percent prenatally and in more than 80 percent postnatally (Bellini, 2009; Santo, 2011). Currently, approximately 20 percent of cases remain idiopathic (Bellini, 2015). As shown in Figure 15-5, several different pathophysiological processes are proposed to account for the final common pathway of hydrops fetalis.

TABLE 15-4

Categories and Etiologies of Nonimmune Hydrops Fetalis

Category	Percent[a]
Cardiovascular Structural defects: Ebstein anomaly, Fallot tetralogy with absent pulmonary valve, hypoplastic left or right heart, premature closure of ductus arteriosus, arteriovenous malformation (vein of Galen aneurysm) Cardiomyopathies Tachyarrhythmias Bradycardia, as may occur in heterotaxy syndrome with endocardial cushion defect or with anti-Ro/La antibodies	21
Chromosomal Turner syndrome (45,X), triploidy, trisomies 21, 18, and 13	13
Hematological Hemoglobinopathies, such as α4-thalassemia Erythrocyte enzyme and membrane disorders Erythrocyte aplasia/dyserythropoiesis Decreased erythrocyte production (myeloproliferative disorders) Fetomaternal hemorrhage	10
Lymphatic Abnormalities Cystic hygroma, systemic lymphangiectasis, pulmonary lymphangiectasis	8
Infections Parvovirus B19, syphilis, cytomegalovirus, toxoplasmosis, rubella, enterovirus, varicella, herpes simplex, coxsackievirus, listeriosis, leptospirosis, Chagas disease, Lyme disease	7
Syndromic Arthrogryposis multiplex congenita, lethal multiple pterygium, congenital lymphedema, myotonic dystrophy type I, Neu-Laxova, Noonan, and Pena-Shokeir syndromes	5
Thoracic Abnormalities Cystic adenomatoid malformation Pulmonary sequestration Diaphragmatic hernia Hydro/chylothorax Congenital high airway obstruction sequence (CHAOS) Mediastinal tumors Skeletal dysplasia with very small thorax	5
Gastrointestinal Meconium peritonitis, gastrointestinal tract obstruction	1
Kidney and Urinary Tract Kidney malformations Bladder outlet obstructions Congenital (Finnish) nephrosis, Bartter syndrome, mesoblastic nephroma	2
Placental, Twin, and Cord Abnormalities Placental chorioangioma, twin-twin transfusion syndrome, twin reversed arterial perfusion sequence, twin anemia polycythemia sequence, cord vessel thrombosis	5
Other Rare Disorders Inborn errors of metabolism: Gaucher disease, galactosialidosis, GM_1 gangliosidosis, sialidosis, mucopolysaccharidoses, mucolipidoses Tumors: sacrococcygeal teratoma, hemangioendothelioma with Kassabach-Merritt syndrome	5
Idiopathic	18

[a]Percentages reflect the proportion within each category from a systematic review of 6775 pregnancies with nonimmune hydrops.

Modified from Bellini, 2015.

Importantly, the etiology of nonimmune hydrops varies according to when in gestation it is identified. Of those diagnosed prenatally, aneuploidy accounts for approximately 20 percent, cardiovascular abnormalities for 15 percent, and infections for 14 percent—the most common of these being parvovirus B19 (Santo, 2011). Overall, only 40 percent of pregnancies with nonimmune hydrops result in a liveborn neonate, and of these, the neonatal survival rate is only about 50 percent. Sohan and colleagues (2001) reviewed 87 pregnancies with hydrops and found that 45 percent of those diagnosed before 24 weeks' gestation had a chromosomal abnormality. The most frequent aneuploidy was 45,X—*Turner syndrome*, and in such cases, the survival rate was <5 percent (Chap. 13, Polyploidy). If hydrops is detected in the first trimester, the aneuploidy risk is nearly 50 percent, and most have cystic hygromas (Fig. 10-22).

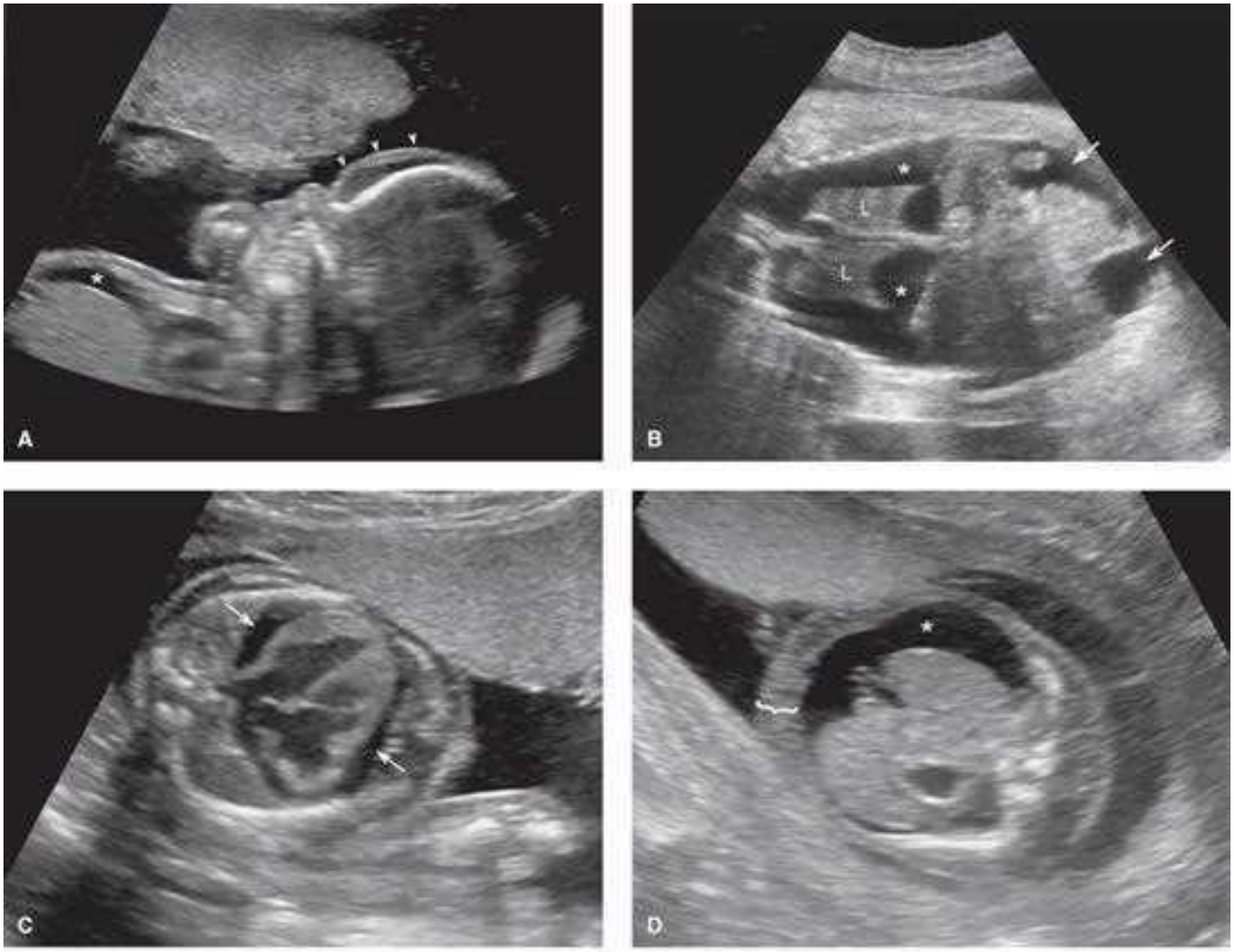
Although the prognosis of nonimmune hydrops is guarded, it is heavily dependent on etiology. In large series from Thailand and Southern China, α4-thalassemia is the predominant cause of nonimmune hydrops, accounting for 30 to 50 percent of cases and conferring an extremely poor prognosis (Liao, 2007; Ratanasiri, 2009; Suwanrath-Kengpol, 2005). In contrast, treatable etiologies such as parvovirus, chylothorax, and tachyarrhythmias, which each comprise about 10 percent of cases, can result in survival in two thirds of cases with fetal therapy (Sohan, 2001).

Diagnostic Evaluation

Hydrops is readily detected sonographically. As noted, two effusions or one effusion plus anasarca are required for diagnosis. Edema may be particularly prominent around the scalp, or equally obvious around the trunk and extremities. Effusions are visible as fluid outlining the lungs, heart, or abdominal viscera (Fig. 15-6).

FIGURE 15-6

Hydropic features. **A.** This profile of a 23-week fetus with nonimmune hydrops secondary to B19 parvovirus infection depicts scalp edema (*arrowheads*) and ascites (*). **B.** This 34-week fetus had hydrops secondary to an arteriovenous malformation in the brain, known as a vein of Galen aneurysm. In this coronal image, prominent pleural effusions (*) outline the lungs (L). Fetal ascites is also present (*arrows*), as is anasarca. **C.** This axial (transverse) image depicts a pericardial effusion (*arrows*) in a 23-week fetus with hydrops from B19 parvovirus infection. The degree of cardiomegaly is impressive, and the ventricular hypertrophy raises concern for myocarditis, which can accompany parvovirus infection. **D.** This axial (transverse) image depicts fetal ascites (*) in a 15-week fetus with hydrops secondary to large cystic hygromas. Anasarca is also seen (*bracket*).



In many cases, targeted sonographic and laboratory evaluation will identify the underlying cause of fetal hydrops. These include cases due to fetal anemia, arrhythmia, structural abnormality, aneuploidy, placental abnormality, or complications of monochorionic twinning. Depending on the circumstances, initial evaluation includes the following:

1. Indirect Coombs test for alloimmunization
2. Targeted sonographic fetal and placental examination, including:
   - A detailed anatomical survey to assess for the structural abnormalities listed in Table 15-4
   - MCA Doppler peak systolic velocity to assess for fetal anemia
   - Fetal echocardiography with M-mode evaluation
3. Amniocentesis for fetal karyotype and for parvovirus B19, cytomegalovirus, and toxoplasmosis testing as discussed in Chapter 64. Consideration of chromosomal microarray analysis if fetal anomalies are present
4. Kleihauer-Betke test for fetomaternal hemorrhage if anemia is suspected, depending on findings and test results
5. Consideration of testing for alpha-thalassemia and/or inborn errors of metabolism.

Isolated Effusion or Edema

Although one effusion or anasarca alone is not diagnostic for hydrops, the above evaluation should be considered if these are encountered, as hydrops may develop. For example, an isolated pericardial effusion may be the initial finding in fetal parvovirus B19 infection (Chap. 64, West Nile Virus). An isolated pleural effusion may represent a chylothorax, which is amenable to prenatal diagnosis, and for which fetal therapy may be lifesaving if hydrops develops (Chap. 16, Percutaneous Procedures). Isolated ascites also may be the initial finding in fetal parvovirus B19 infection, or it may result from a gastrointestinal abnormality such as meconium peritonitis. Finally, isolated edema, particularly involving the upper torso or the dorsum of the hands and feet, may be found in Turner or Noonan syndrome or may represent congenital lymphedema syndrome (Chap. 13, Polyploidy).

Mirror Syndrome

An association between fetal hydrops and development of maternal edema in which the fetus *mirrors* the mother is attributed to Ballantyne. He called the condition *triple edema* because the fetus, mother, and placenta all became edematous. The etiology of the hydrops is not related to development of mirror syndrome. It has been associated with hydrops from D alloimmunization, twin-twin transfusion syndrome, placental chorioangioma, and with fetal cystic hygroma, Ebstein anomaly, sacrococcygeal teratoma, chylothorax, bladder outlet obstruction, supraventricular tachycardia, vein of Galen aneurysm, and various congenital infections (Braun, 2010).

In a review of more than 50 cases of mirror syndrome, Braun (2010) found that approximately 90 percent of women had edema, 60 percent had hypertension, 40 percent had proteinuria, 20 percent had liver enzyme elevation, and nearly 15 percent had headache and visual disturbances. Based on these findings, it is reasonable to consider mirror syndrome a form of severe preeclampsia (Espinoza, 2006; Midgley, 2000). Others, however, have suggested that it is a separate disease process with hemodilution rather than hemoconcentration (Carbillon, 1997; Livingston, 2007).

Some reports describe the same imbalance of angiogenic and antiangiogenic factors that is observed with preeclampsia, and this suggests a common pathophysiology (Espinoza, 2006; Goa, 2013; Llurba, 2012). These findings, which include elevated concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1), decreased placental growth factor (PlGF) levels, and elevation of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) concentrations, are discussed further Chapter 40 (Endothelial Cell Injury).

In most cases with mirror syndrome, prompt delivery is indicated and followed by resolution of maternal edema and other findings (Braun, 2010). However, in isolated cases of fetal anemia, supraventricular tachycardia, hydrothorax, and bladder outlet obstruction, successful fetal treatment resulted in resolution of both fetal hydrops and maternal mirror syndrome (Goa, 2013; Livingston, 2007; Llurba, 2012; Midgley, 2000). Normalization of the angiogenic imbalance has also been described following fetal transfusion for parvovirus B19 infection. Fetal therapy for these conditions is reviewed in Chapter 16. Given the parallels to severe preeclampsia, delaying delivery to effect fetal therapy should be considered only with caution. If the maternal condition deteriorates, delivery is recommended.

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CHAPTER 16: Fetal Therapy

Minor grades of hydramnios rarely require active treatment. On the other hand, when the abdomen is immensely distended and respiration is seriously hampered, the termination of pregnancy is urgently indicated. In such cases, the symptoms can be promptly relieved by perforating the membranes through the cervix, after which the amniotic fluid drains off and labour pains set in.

—J. Whitridge Williams (1903)

INTRODUCTION

The concept of fetal therapy—even amniocentesis—was not considered by Williams in his first edition. Aside from a few destructive procedures to aid vaginal delivery, any type of fetal treatment is not mentioned as even a remote possibility. Again, fast forward to this 25th edition, when interventions developed during the past three decades have dramatically altered the course of selected fetal anomalies and conditions. Reviewed in this chapter are fetal disorders amenable to treatment with either maternal medication or surgical procedures. The management of fetal anemia and thrombocytopenia is reviewed in Chapter 15, and treatment of some fetal infections is discussed in Chapters 64 and 65.

MEDICAL THERAPY

Fetal pharmacotherapy uses medications administered to the mother and then transported transplacentally to the fetus. As described here, it can be used to treat an array of serious conditions.

Arrhythmias

Fetal cardiac rhythm disturbances may be broadly categorized as *tachyarrhythmias,* heart rates >180 beats per minute (bpm); *bradyarrhythmia,* heart rate <110 bpm; and ectopy, typically premature atrial contractions. If these are identified, fetal M-mode sonography is performed to measure the atrial and ventricular rates and to clarify the relationship between atrial and ventricular beats, thereby diagnosing the type of rhythm disturbance.

Premature Atrial Contractions

This is by far the most common arrhythmia and is identified in 1 to 2 percent of pregnancies (Hahurij, 2011; Strasburger, 2010). Generally a benign finding, premature atrial contractions represent immaturity of the cardiac conduction system, and they typically resolve later in gestation or in the neonatal period. If the premature atrial contraction is conducted, it sounds like an extra beat when auscultated with handheld Doppler or fetoscope. However, premature atrial contractions are more commonly blocked and sound like dropped beats.

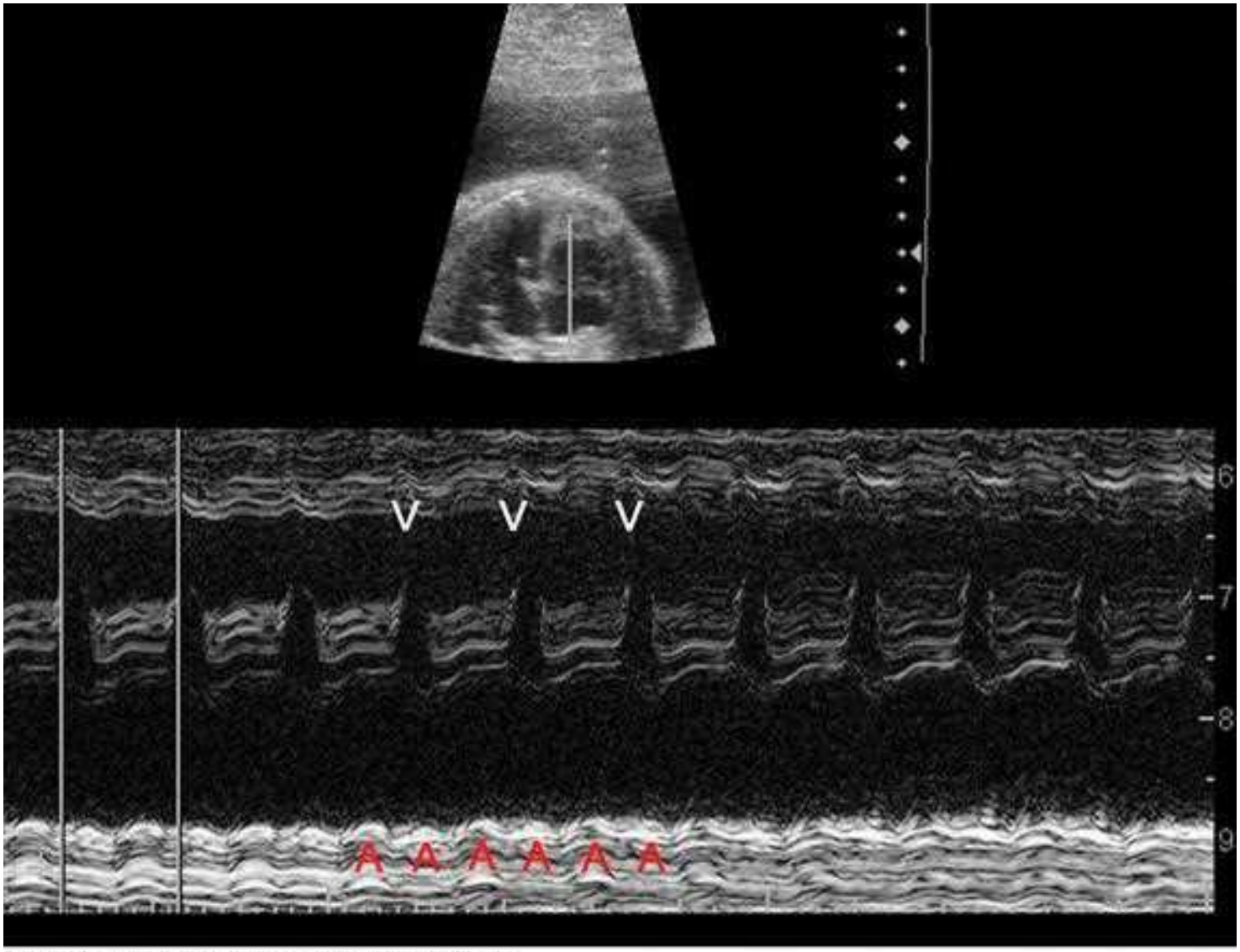
In general, premature atrial contractions are not associated with major structural cardiac abnormalities, although they sometimes occur with an atrial septal aneurysm. As shown in Figure 10-34, M-mode evaluation demonstrates that the dropped beat is a compensatory pause following the premature atrial contraction. They may occur as frequently as every other beat, known as *blocked atrial bigeminy*. This results in an auscultated fetal ventricular rate as low as 60 to 80 bpm. Unlike other causes of bradycardia, atrial bigeminy is benign and does not require treatment (Strasburger, 2010).

Approximately 2 percent of fetuses with premature atrial contractions are later found to have a *supraventricular tachycardia* (Copel, 2000; Srinivasan, 2008). Given the importance of identifying and treating supraventricular tachyarrhythmias, a fetus with premature atrial contractions is often monitored with heart rate assessment every 1 to 2 weeks until the ectopy resolves. This requires neither sonography nor fetal echocardiography, as the rate and rhythm may be easily ascertained with handheld Doppler.

Tachyarrhythmias

The two most common tachyarrhythmias are *supraventricular tachycardia* (SVT) and *atrial flutter.* SVT is characterized by an abrupt increase in the fetal heart rate to 180 to 300 bpm with 1:1 atrioventricular concordance. The typical range is 200 to 240 bpm. SVT may develop secondary to an ectopic focus or to an accessory atrioventricular pathway leading to a reentrant tachycardia. Atrial flutter is characterized by a much higher atrial rate, generally 300 to 500 bpm, with varying degrees of atrioventricular block. As a result, the ventricular rate in a fetus with atrial flutter may range from below normal to approximately 250 bpm (Fig. 16-1). In contrast, fetal *sinus tachycardia* typically presents with a gradual heart rate rise to a rate that is only slightly above normal. With this, readily discernible causes may be maternal fever or hyperthyroidism, or rarely, fetal anemia or infection.

FIGURE 16-1
Atrial flutter. In this M-mode image at 28 weeks' gestation, calipers mark the ventricular rate, which is approximately 225 bpm. There are two atrial beats (*A*) for each ventricular beat (*V*), such that the atrial rate is approximately 450 bpm with 2:1 atrioventricular block.



If a fetal tachyarrhythmia is identified, it is important to determine whether it is *sustained*—defined as present for at least 50 percent of the time. It may be necessary to monitor the fetal heart rate for 12 to 24 hours upon initial detection, and then periodically to reassess (Srinivasan, 2008). Unsustained or intermittent tachyarrhythmias generally do not require treatment, provided that fetal surveillance is reassuring.

Sustained fetal tachyarrhythmia with ventricular rates exceeding 200 bpm impairs ventricular filling to a degree that the risk for hydrops is significant. With atrial flutter, lack of coordinated atrioventricular contractions may further compound this risk. Maternal administration of antiarrhythmic agents that cross the placenta may convert the rhythm to normal or lower the baseline heart rate to forestall heart failure. Therapy may require dosages at the upper end of the therapeutic adult range. Thus, a maternal electrocardiogram is obtained before and during therapy.

Antiarrhythmic medications most commonly used include digoxin, sotalol (Betapace), flecainide (Tambocor), and procainamide (Pronestyl). Their selection depends on the type of tachyarrhythmia as well as provider familiarity and experience with the drug. Traditionally, digoxin has been the initial preferred treatment, although it may poorly transfer to the fetus after hydrops has developed. Many centers now use flecainide or sotalol as first-line therapy (Jaeggi, 2011; Shah, 2012). In many cases, additional agents are needed, particularly if hydrops has developed. SVT is generally more likely than atrial flutter to convert to a normal rhythm. With either arrhythmia, however, the overall neonatal survival rate now exceeds 90 percent (Ekman-Joelsson, 2015; Jaeggi, 2011; van der Heijden, 2013).

Bradyarrhythmia

The most common etiology of pronounced fetal bradycardia is *congenital heart block*. Approximately 50 percent of cases occur in the setting of a structural cardiac abnormality involving the conduction system. These include *heterotaxy*, in particular *left-atrial isomerism*; *endocardial cushion defect*; and less commonly *corrected transposition of the great vessels* (Srinivasan, 2008). The prognosis of heart block secondary to a structural cardiac anomaly is extremely poor, and fetal loss rates exceed 80 percent (Glatz, 2008; Strasburger, 2010).

In a structurally normal heart, 85 percent of atrioventricular block cases develop secondary to transplacental passage of maternal anti-SSA/Ro or anti-SSB/La antibodies (Buyon, 2009). Many of these women have, or subsequently develop, systemic lupus erythematosus or other connective tissue disease (Chap. 59, Perinatal Mortality and Morbidity). The risk of third-degree heart block with these antibodies is small—only about 2 percent. But, the risk may reach 20 percent if a

prior infant has been affected. Immune-mediated congenital heart block confers a mortality rate of 20 to 30 percent, requires permanent pacing in two thirds of surviving children, and also poses a risk for cardiomyopathy (Buyon, 2009). If associated with effusions, bradyarrhythmias, or endocardial fibroelastosis, neonatal status may progressively worsen after birth (Cuneo, 2007).

Initial research efforts focused on maternal corticosteroid therapy to potentially reverse fetal heart block or forestall it. Friedman and colleagues (2008, 2009) conducted a prospective multicenter trial of pregnancies with anti-SSA/Ro antibodies—the PR Interval and Dexamethasone (PRIDE) study. Weekly sonographic surveillance was performed, and heart block was treated with maternal oral dexamethasone 4 mg daily. Unfortunately, progression from second- to third-degree block was not prevented with maternal dexamethasone therapy, and third-degree atrioventricular block was *irreversible*. In rare cases, there was a potential benefit in reversing first-degree atrioventricular block. However, first-degree block did not generally progress even without treatment. In a subsequent review of 156 pregnancies with isolated second- or third-degree fetal heart block, dexamethasone therapy similarly did not affect disease progression, need for pacemaker in the neonatal period, or overall survival rates (Izmirly, 2016). Thus, dexamethasone use cannot be recommended for this indication.

More recent efforts have turned to potential therapy with hydroxychloroquine (Plaquenil), a mainstay of treatment for systemic lupus erythematosus (Chap. 59, Perinatal Mortality and Morbidity). In a multicenter review of more than 250 pregnancies in women whose prior pregnancies had been complicated by neonatal lupus, recurrence of congenital heart block was significantly lower if the woman had been treated with hydroxychloroquine during pregnancy (Izmirly, 2012). Research in this area is ongoing.

Maternal terbutaline has also been given to increase the fetal heart rate in cases with sustained bradycardia of any cause in which the fetal heart rate is below 55 bpm. Reversal of hydrops with this therapy has been reported (Cuneo, 2007, 2010).

Congenital Adrenal Hyperplasia

Several autosomal recessive enzyme deficiencies cause impaired fetal synthesis of cortisol from cholesterol by the adrenal cortex. This results in congenital adrenal hyperplasia (CAH). CAH is the most common etiology of androgen excess in females with 46,XX disorders of sex development, formerly female pseudohermaphroditism (Chap. 3, Bladder and Perineal Abnormalities). Lack of cortisol stimulates adrenocorticotrophic hormone (ACTH) secretion by the anterior pituitary, and the resulting androstenedione and testosterone overproduction leads to virilization of female fetuses. Sequelae may include formation of labioscrotal folds, persistence of a urogenital sinus, or even creation of a penile urethra and scrotal sac.

More than 90 percent of CAH cases are caused by 21-hydroxylase deficiency, which is found in classic and nonclassic forms. The incidence of classic CAH approximates 1:15000 births overall and is higher in selected populations. For example, it has been reported in approximately 1:300 Yupik Eskimos (Nimkarn, 2010). Among those with classic CAH, 75 percent are at risk for *salt-wasting adrenal crises* and require postnatal treatment with mineralocorticoids and glucocorticoids to prevent hyponatremia, dehydration, hypotension, and cardiovascular collapse. The remaining 25 percent with classic CAH have the *simple virilizing type* and also require glucocorticoid supplementation. As discussed in Chapter 32 (Routine Newborn Care), all states mandate newborn screening for CAH.

The efficacy of maternal dexamethasone treatment to suppress fetal androgen overproduction and either obviate or ameliorate virilization of female fetuses has been recognized for more than 30 years (David, 1984; New, 2012). Prenatal corticosteroid therapy is considered successful in 80 to 85 percent of cases (Miller, 2013; Speiser, 2010). The alternative is consideration of postnatal genitoplasty, a complex and somewhat controversial surgical procedure (Braga, 2009).

The typical preventive regimen is oral dexamethasone given to the mother at a dosage of 20 µg/kg/d—up to 1.5 mg per day, divided in three doses. The critical period for external genitalia development is 7 to 12 weeks' gestation, and treatment to prevent virilization should be initiated by 9 weeks—*before it is known whether the fetus is at risk.* Because this is an autosomal recessive condition, affected females make up only 1 in 8 at-risk conceptions.

Typically, carrier parents are identified after the birth of an affected child. Molecular genetic testing is clinically available, initially using sequence analysis of the *CYP21A2* gene, which encodes the 21-hydroxylase enzyme (Nimkarn, 2016). If this is uninformative, gene-targeted deletion/duplication analysis is performed, and additional testing such as whole exome sequencing may be considered (Chap. 13, Whole Genome Sequencing and Whole Exome Sequencing).

A goal of prenatal diagnosis is to limit dexamethasone exposure in males and in unaffected females. Prenatal diagnosis with molecular genetic testing may be performed on chorionic villi—at 10 to 12 weeks' gestation—or on amniocytes after 15 weeks. Cell-free DNA testing of maternal serum has potential to replace invasive tests such as chorionic villus sampling and amniocentesis for CAH (Chap. 13, Fetal DNA in the Maternal Circulation). Determination of fetal gender using cell-free fetal DNA has at least 95-percent sensitivity when performed at or beyond 7 weeks' gestation (Devaney, 2011). In the research setting, cell-free DNA testing using hybridization probes flanking the *CYP21A2* gene can be effective as early as $5^{6/7}$ weeks' gestation (New, 2014).

Maternal treatment with dexamethasone has become a topic of significant controversy. The Endocrine Society recommends that treatment be given only in the context of research protocols (Miller, 2013; Speiser, 2010). It should be noted that if therapy is initiated shortly before 9 weeks, the dose of dexamethasone used is not considered to have significant teratogenic potential because organogenesis of major organs has already taken place (McCullough, 2010). Ongoing concerns, however, focus on the potential effects of either excess *endogenous* androgens or excess *exogenous* dexamethasone on the developing brain. Although maternal dexamethasone has been used for many years to prevent virilization of female fetuses with CAH, long-term safety data are relatively limited.

Congenital Cystic Adenomatoid Malformation

Sonographically, this malformation is a well-circumscribed lung mass that may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 10-24). Lesions with cysts ≥5 mm are termed macrocystic, whereas microcystic lesions have smaller cysts or appear solid (Adzick, 1985). Also called congenital pulmonary airway malformation (CPAM), it represents a hamartomatous overgrowth of terminal bronchioles. Therapy for macrocystic congenital cystic adenomatoid malformation (CCAM) is discussed later (Percutaneous Procedures).

Occasionally, a microcystic CCAM may demonstrate rapid growth, generally between 18 and 26 weeks' gestation. The mass may become so large that it causes mediastinal shift, which may compromise cardiac output and venous return, resulting in hydrops (Cavoretto, 2008). A CCAM-volume ratio (CVR) has been used to quantify size and risk for hydrops in these severe cases (Crombleholme, 2002). This ratio is an estimate of the CCAM volume (length × width × height × 0.52) divided by the head circumference. In a series of 40 pregnancies with microcystic CCAM, the mean CVR was 0.5 at 20 weeks' gestation, peaking in size at 1.0 at 26 weeks, followed by a pronounced decline prior to delivery (Macardle, 2016). A third of fetuses had no increase in mass size. In the absence of a dominant cyst, a CVR exceeding 1.6 is associated with a hydrops risk as high as 60 percent. However, CCAM growth resulting in hydrops develops in fewer than 2 percent of cases if the initial CVR is below 1.6 (Ehrenberg-Buchner, 2013; Peranteau, 2016). Importantly, a CVR in the range of 1.6 indicates that the mass essentially fills the thorax, and thus it is not unexpected that ascites or hydrops may develop.

If the CVR exceeds 1.6 or if signs of hydrops develop, corticosteroid treatment has been used in an effort to improve outcome. Regimens include dexamethasone—6.25 mg every 12 hours for four doses, or betamethasone—12.5 mg intramuscularly every 24 hours for two doses. Following a single course of corticosteroids, hydrops resolved in approximately 80 percent of cases, and 90 percent of treated fetuses survived (Loh, 2012; Peranteau, 2016). Recently, multiple courses of steroids—generally two—have been advocated for fetuses with large CCAM lesions and with persistent or worsening hydrops or ascites despite a single course of medication (Derderian, 2015; Peranteau, 2016).

Thyroid Disease

Identification of fetal thyroid disease is rare and usually prompted by sonographic detection of a fetal goiter. If a goiter is found, determination of fetal hyper- or hypothyroidism is essential, and thyroid hormone levels may be measured in amnionic fluid or fetal blood. Traditionally, fetal blood sampling, described in Chapter 14 (Fetal Blood Sampling), is preferred to amniocentesis for guiding treatment, although data are limited (Abuhamad, 1995; Ribault, 2009). Goals of therapy are correction of the physiological abnormality and diminished goiter size. The goiter may compress the trachea and esophagus to such a degree that severe hydramnios or neonatal airway compromise may develop. Hyperextension of the fetal neck by a goiter can create labor dystocia.

Fetal Thyrotoxicosis

Untreated fetal thyrotoxicosis may present with goiter, tachycardia, growth restriction, hydramnios, accelerated bone maturation, and even heart failure and hydrops (Huel, 2009; Peleg, 2002). The cause is usually maternal Graves disease with transplacental passage of IgG thyroid-stimulating immunoglobulins. Fetal blood sampling may confirm the diagnosis (Duncombe, 2001; Heckel, 1997; Srisupundit, 2008). Confirmed fetal thyrotoxicosis is followed by maternal antithyroid treatment. During this, if the mother develops hypothyroidism, she is given supplemental levothyroxine (Hui, 2011).

Fetal Hypothyroidism

In a woman receiving medication for Graves disease, transplacental passage of methimazole or propylthiouracil may cause *fetal hypothyroidism* (Bliddal, 2011a). Other potential causes of fetal hypothyroidism resulting in goiter include transplacental passage of thyroid peroxidase antibodies, fetal thyroid dyshormonogenesis, and maternal overconsumption of iodine supplements (Agrawal, 2002; Overcash, 2016).

Goitrous hypothyroidism may lead to hydramnios, neck hyperextension, and delayed bone maturation. If the mother is receiving antithyroid medication, discontinuation is generally recommended, along with intraamnionic levothyroxine injection. Numerous case reports describe intraamnionic levothyroxine treatment. However, optimal dosage and frequency have not been established, and reported dosages range from 50 to 800 µg every 1 to 4 weeks (Abuhamad, 1995; Bliddal, 2011b; Ribault, 2009).

SURGICAL THERAPY

Also called *maternal-fetal surgery*, these procedures are offered for selected congenital abnormalities in which the likelihood of fetal deterioration is so great that delaying treatment until after delivery would risk fetal death or substantially greater postnatal morbidity. Open fetal surgery is a highly specialized intervention performed at relatively few centers in the United States and for only a few fetal conditions. Criteria for consideration of fetal surgery are listed in Table 16-1. In many cases, data regarding the safety and efficacy of these procedures are limited. The Agency for Healthcare Research and Quality stresses that when considering fetal surgery, the overriding concern must be maternal and fetal safety. Accomplishing the fetal goals of the procedure is secondary (Walsh, 2011).

TABLE 16-1

Guiding Principles for Fetal Surgical Procedures

Accurate prenatal diagnosis for the defect is available, with staging if applicable
The defect appears isolated, with no evidence of other abnormality or underlying genetic syndrome that would significantly worsen survival or quality of life
The defect results in a high likelihood of death or irreversible organ destruction, and postnatal therapy is inadequate
The procedure is technically feasible, and a multidisciplinary team is in agreement regarding the treatment plan
Maternal risks from the procedure are well documented and considered acceptable
There is comprehensive parental counseling
It is recommended that there be an animal model for the defect and procedure

Modified from Deprest, 2010; Harrison, 1982; Vrecenak, 2013; Walsh, 2011.

Some abnormalities amenable to fetal surgical treatment, antepartum or intrapartum, are shown in Table 16-2. An overview of these procedures, their indications, and complications is provided here to assist with initial patient evaluation and counseling. Additional content is also found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition.

TABLE 16-2

Selected Fetal Abnormalities Amenable to Fetal Surgery

Open Fetal Surgery
Myelomeningocele
Congenital cystic adenomatoid malformation (CCAM)
Extralobar pulmonary sequestration
Sacrococcygeal teratoma
Fetoscopic Surgery
Twin-twin transfusion: laser of placental anastomoses
Diaphragmatic hernia: fetal endoscopic tracheal occlusion (FETO)
Posterior urethral valves: cystoscopic laser
Congenital high airway obstruction: vocal cord laser
Amnionic band release
Percutaneous Procedures
Shunt therapy
Posterior-urethral valves/bladder outlet obstruction
Pleural effusion: chylothorax or sequestration
Dominant cyst in CCAM
Radiofrequency ablation
Twin-reversed arterial perfusion (TRAP) sequence
Monochorionic twins with severe anomaly in 1 twin
Chorioangioma
Fetal intracardiac catheter procedures
Aortic or pulmonic valvuloplasty for stenosis
Atrial septostomy for hypoplastic left heart with restrictive atrial septum
Ex-Utero Intrapartum Treatment (EXIT) Procedures
Congenital diaphragmatic hernia after FETO
Congenital high airway obstruction sequence (CHAOS)
Severe micrognathia
Tumors involving neck or airway
EXIT-to-resection: resection of fetal thoracic or mediastinal mass
EXIT-to-extracorporeal membrane oxygenation (ECMO): congenital diaphragmatic hernia

Open Fetal Surgery

These procedures require extensive preoperative counseling and multidisciplinary care. The mother must undergo general endotracheal anesthesia to suppress both uterine contractions and fetal responses. Using intraoperative sonographic guidance to avoid the placental edge, a low-transverse hysterotomy incision is made with a stapling device that seals the edges for hemostasis. To replace amnionic fluid losses, warmed fluid is continuously infused into the uterus thorough a rapid infusion device. The fetus is gently manipulated to permit pulse oximetry monitoring and to establish venous access, in case fluids or blood are emergently needed. The surgical procedure is then performed. After completion, the hysterotomy is closed and tocolysis begun. Tocolysis typically includes intravenous magnesium sulfate for 24 hours, oral indomethacin for 48 hours, and, at some centers, oral nifedipine until delivery (Wu, 2009). Prophylactic antibiotics are also administered and generally continued for 24 hours following the procedure. Cesarean delivery is needed later in gestation and for all future deliveries.

Risks

Morbidities associated with fetal surgery are well characterized. In a review of 87 open procedures, Golombeck and coworkers (2006) reported the following morbidities: pulmonary edema—28 percent, placental abruption—9 percent, blood transfusion—13 percent, premature rupture of membranes—52 percent, and preterm delivery—33 percent. Wilson and associates (2010) reviewed subsequent pregnancy outcomes following open fetal surgery and reported that 14 percent of women experienced uterine rupture and 14 percent had uterine dehiscence. Morbidities identified in the recent *Management of Myelomeningocele Study (MOMS)* are shown in Table 16-3 (Adzick, 2011). Other potential risks include maternal sepsis and fetal death during or following the procedure, particularly if hydrops is present.

TABLE 16-3

Benefits and Risks of Fetal Myelomeningocele Surgery versus Postnatal Repair

	Fetal Surgery (n = 78)	Postnatal Surgery (n = 80)	*p* value
Benefits (Primary Outcomes)			
Perinatal death or shunt by 12 months[a]	68%	98%	<0.001
Shunt placement by 12 months	40%	82%	<0.001
Composite developmental score[a,b]	149 ± 58	123 ± 57	0.007
Hindbrain herniation (any)	64%	96%	<0.001
Brainstem kinking (any)	20%	48%	<0.001
Independent walking (30 months)	42%	21%	0.01
Risks			
Maternal pulmonary edema	6%	0	0.03
Placental abruption	6%	0	0.03
Maternal transfusion at delivery	9%	1%	0.03
Oligohydramnios	21%	4%	0.001
Gestational age at delivery	34 ± 3	37 ± 1	<0.001
Preterm birth			
<37 weeks	79%	15%	<0.001
<35 weeks	46%	5%	
<30 weeks	13%	0	

[a]Each primary outcome had two components. The perinatal death components of the primary outcomes as well as the Bayley Mental Development Index at 30 months did not differ between the two study cohorts.

[b]Score derived from Bayley Mental Development Index and difference between functional and anatomical level of lesion (30 months).

Data from Adzick, 2011.

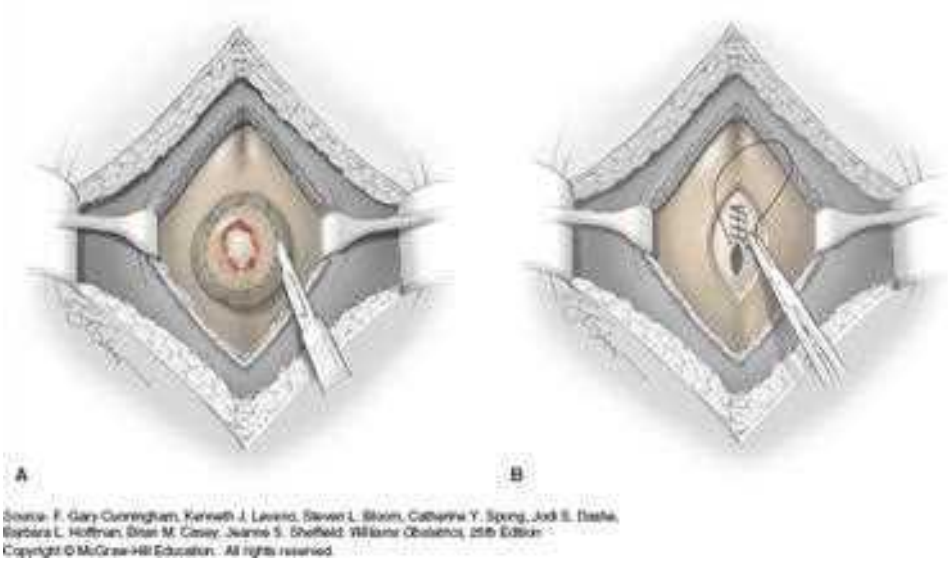
Myelomeningocele Surgery

Even with postnatal repair, children with myelomeningocele generally have varying degrees of paralysis, bladder and bowel dysfunction, developmental delays, and brainstem dysfunction from the Arnold-Chiari II malformation (Chap. 10, Ventriculomegaly). Damage is postulated to result from abnormal embryonic neurulation and from ongoing exposure of neural elements to amnionic fluid (Adzick, 2010; Meuli, 1995, 1997). Fetal myelomeningocele meets the criteria listed in Table 16-1 and is the first nonlethal birth defect for which fetal surgery has been offered (Fig. 16-2).

FIGURE 16-2

Fetal myelomeningocele surgery. **A.** With the edges of both the laparotomy and hysterotomy incisions retracted, the skin around the defect is incised. Subsequently, the neural placode is sharply dissected from the arachnoid membrane. **B.** The dural membrane is reflected to the midline to cover the neural placode and is

reapproximated using suture. In some cases a patch is needed (not shown). The fetal skin incision is subsequently sutured. Last, hysterotomy and laparotomy are then closed. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



In preliminary reports, infants following antepartum defect repair were more likely to have reversal of the Arnold-Chiari II malformation and were less likely to require ventriculoperitoneal shunt placement (Bruner, 1999; Sutton, 1999). Spurred by this, the randomized, multicenter MOMS trial was conducted (Adzick, 2011). Criteria for trial participation included: (1) a singleton fetus at 19.0 to 25.9 weeks' gestation; (2) an upper myelomeningocele boundary between T1 and S1 confirmed by fetal magnetic resonance (MR) imaging; (3) evidence of hindbrain herniation; and (4) a normal karyotype and no evidence of a fetal anomaly unrelated to the myelomeningocele. Women at risk for preterm birth or placental abruption, those with a contraindication to fetal surgery, and women with body mass index >35 kg/m^2 were excluded.

The MOMS findings demonstrated improved early childhood outcomes in the prenatal surgery cohort (see Table 16-3). Children who had undergone prenatal surgery were twice as likely to walk independently by 30 months. They had significantly less hindbrain herniation and were only half as likely to undergo ventriculoperitoneal shunting by the age of 1 year. A primary outcome was a composite score that was derived from the Bayley Mental Development Index and from the difference between the functional and anatomical level of the lesion at 30 months. This primary outcome was also significantly better in the prenatal surgery group.

When counseling prospective families, however, results are placed in perspective. For example, despite improvements in the proportion with independent ambulation, *most* children who received fetal surgery were not able to ambulate independently, and nearly 30 percent were not able to ambulate at all. Prenatal surgery did not confer improvements in fetal or neonatal death rates or in the Bayley Mental Development Index score at age 30 months. And, as shown in Table 16-3, surgery was associated with a small but significant risk for placental abruption and maternal pulmonary edema. Moreover, nearly half were delivered before 34 weeks, which significantly increased the risk for respiratory distress syndrome (Adzick, 2011). Long-term surveillance data have only recently become available for children who underwent fetal myelomeningocele repair prior to the MOMS trial. At a median follow-up of 10 years, these children have higher rates of behavioral problems and adverse executive functioning compared with population norms (Danzer, 2016).

Since publication of the MOMS findings, fetal myelomeningocele surgery rates have grown. Expansion of centers offering this procedure has raised concerns about the importance of training and ongoing experience, adherence to the MOMS research criteria, and need for a registry to ensure that future efforts have similar success rates (Cohen, 2014; Vrecenak, 2013).

Thoracic Masses

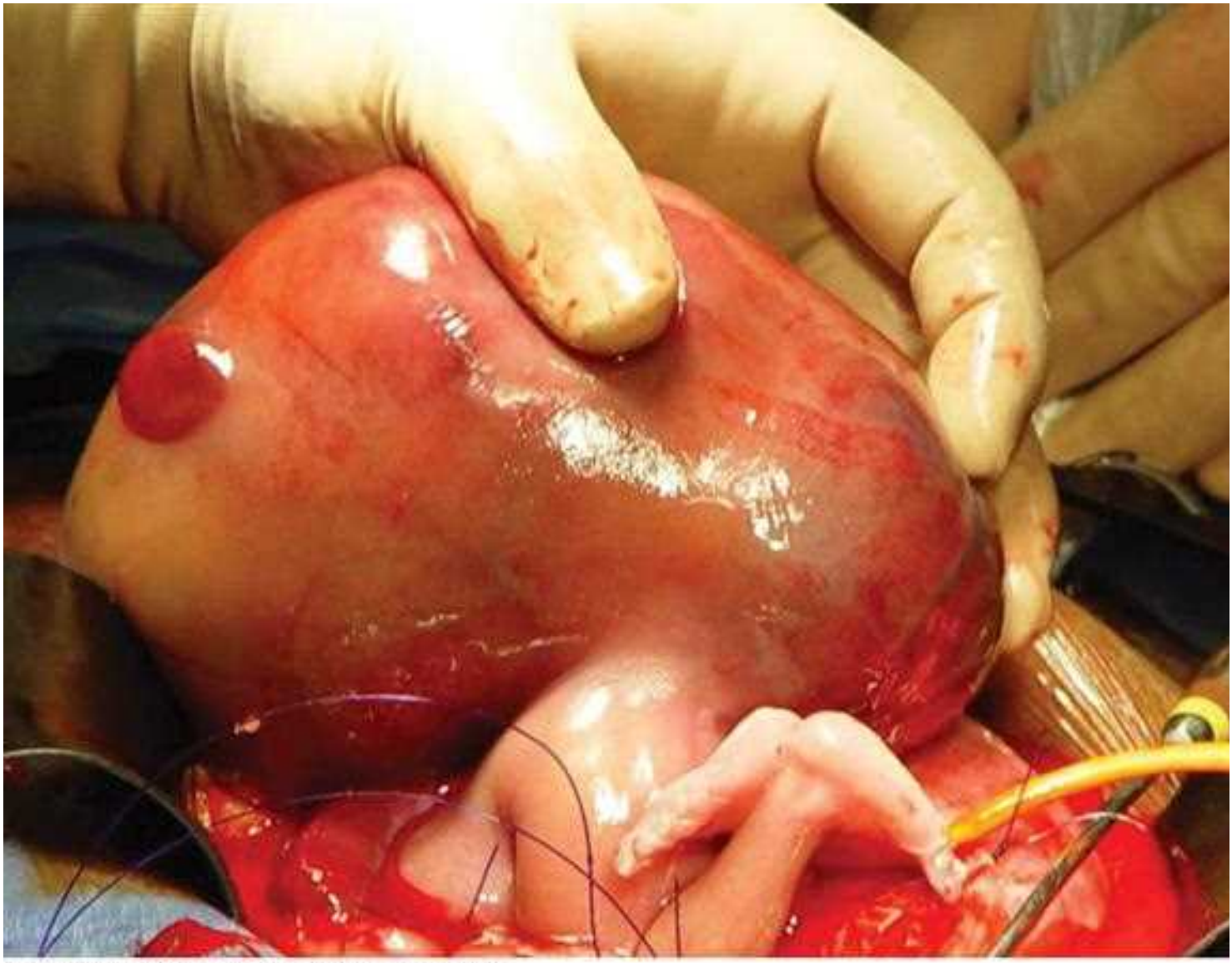
In the past, if hydrops developed in a fetus with a large pulmonary sequestration or cystic adenomatoid malformation without a dominant cyst, open fetal surgery with lobectomy was the only treatment available other than preterm delivery. Most thoracic masses are small and have a benign prognosis, and larger masses are generally treated with corticosteroids (Surgical Therapy). Fetal surgery is generally reserved for cases prior to 32 weeks in which hydrops is developing, and in selected cases, the survival rate following open lobectomy approximates 60 percent (Vrecenak, 2013). Use of the ex-utero intrapartum treatment procedure in the treatment of fetal lung masses at delivery is discussed later in Ex-Utero Intrapartum Treatment.

Sacrococcygeal Teratoma

This germ cell tumor has a prevalence of approximately 1 per 28,000 births (Derikx, 2006; Swamy, 2008). Sonographically, a sacrococcygeal teratoma (SCT) is a solid and/or cystic mass that arises from the anterior sacrum (Fig. 16-3). Fetal MR imaging can aid evaluation of the extent of the internal tumor component. The mass may grow rapidly, usually extending inferiorly and externally (Fig. 10-18). Hydramnios is common, and hydrops may develop from high-output cardiac failure, either as a consequence of tumor vascularity or secondary to bleeding within the tumor and resultant anemia. *Mirror syndrome*—maternal preeclampsia developing along with fetal hydrops—may occur in this setting (Chap. 15, Mirror Syndrome).

FIGURE 16-3

Fetal surgery for sacrococcygeal teratoma resection. Following laparotomy and hysterotomy, the caudal portion of the fetus has been delivered onto the surgical field. The tumor is held by the surgeon's hand. (Used with permission from Dr. Timothy M. Crombleholme.)



The perinatal mortality rate for cases of SCT diagnosed prenatally approximates 40 percent (Hedrick, 2004; Shue, 2013). Poor prognostic factors include a solid component comprising more than 50 percent of the tumor mass and a tumor volume-to-fetal weight ratio (tumor volume divided by estimated fetal weight) exceeding 12 percent prior to 24 weeks' gestation (Akinkuotu, 2015). Fetal loss rates approach 100 percent if hydrops or placentomegaly develop (Vrecenak, 2013). The group at the Children's Hospital of Philadelphia recommends consideration of open fetal surgery for SCT only in cases in which the tumor is completely external (Type I) and in which high cardiac output with early hydrops has developed in the second trimester (Vrecenak, 2013). For excision, hysterotomy is performed, and the external component is resected. The coccyx and any deep tumor are left in place for postnatal removal. Because tumor debulking interrupts the pathological vascular steal, normal fetal physiology may be restored.

Fetoscopic Surgery

As with open fetal surgeries, these procedures are performed at highly specialized centers, and some are considered investigational. To accomplish them, fiberoptic endoscopes only 1 to 2 mm in diameter are used to penetrate the maternal abdominal wall, the uterine wall, and membranes. Instruments such as lasers fit through 3- to 5-mm cannulas that surround the endoscope. Morbidities are generally lower than with open fetal surgery, but they still may be formidable, particularly if maternal laparotomy is required for access (Golombeck, 2006). Examples of some conditions treated by fetoscopy are listed in Table 16-2.

Twin-Twin Transfusion Syndrome

Indications and Technique

As discussed in Chapter 45 (Diagnosis), fetoscopic laser ablation of placental anastomoses is the preferred management for severe twin-twin transfusion syndrome (TTTS). It is generally performed between 16 and 26 weeks' gestation for monochorionic-diamnionic twin pregnancies with stage II to stage IV TTTS. These categories of the Quintero Staging System are described in Chapter 45 (Diagnosis) (Quintero, 1999; Society for Maternal-Fetal Medicine, 2013).

For the procedure, a fetoscope is used to view the vascular equator that separates the placental cotyledons supplying each twin (Fig. 16-4). Arteriovenous anastomoses along the placental surface of the vascular equator are photocoagulated using a 600-µm diameter diode laser or a 400-µm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Fig. 16-5). The procedure is typically performed under epidural or local analgesia. At the end, amnioreduction is performed to decrease the single deepest pocket of amnionic fluid to below 5 cm, and antibiotics are injected into the amnionic cavity.

FIGURE 16-4

Selective laser photocoagulation for twin-twin transfusion syndrome. The fetoscope is inserted into the recipient-twin sac and positioned over the vascular equator, which lies in between the two placental cord insertion sites. Arteriovenous anastomoses along the placental surface are individually photocoagulated using the laser. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)

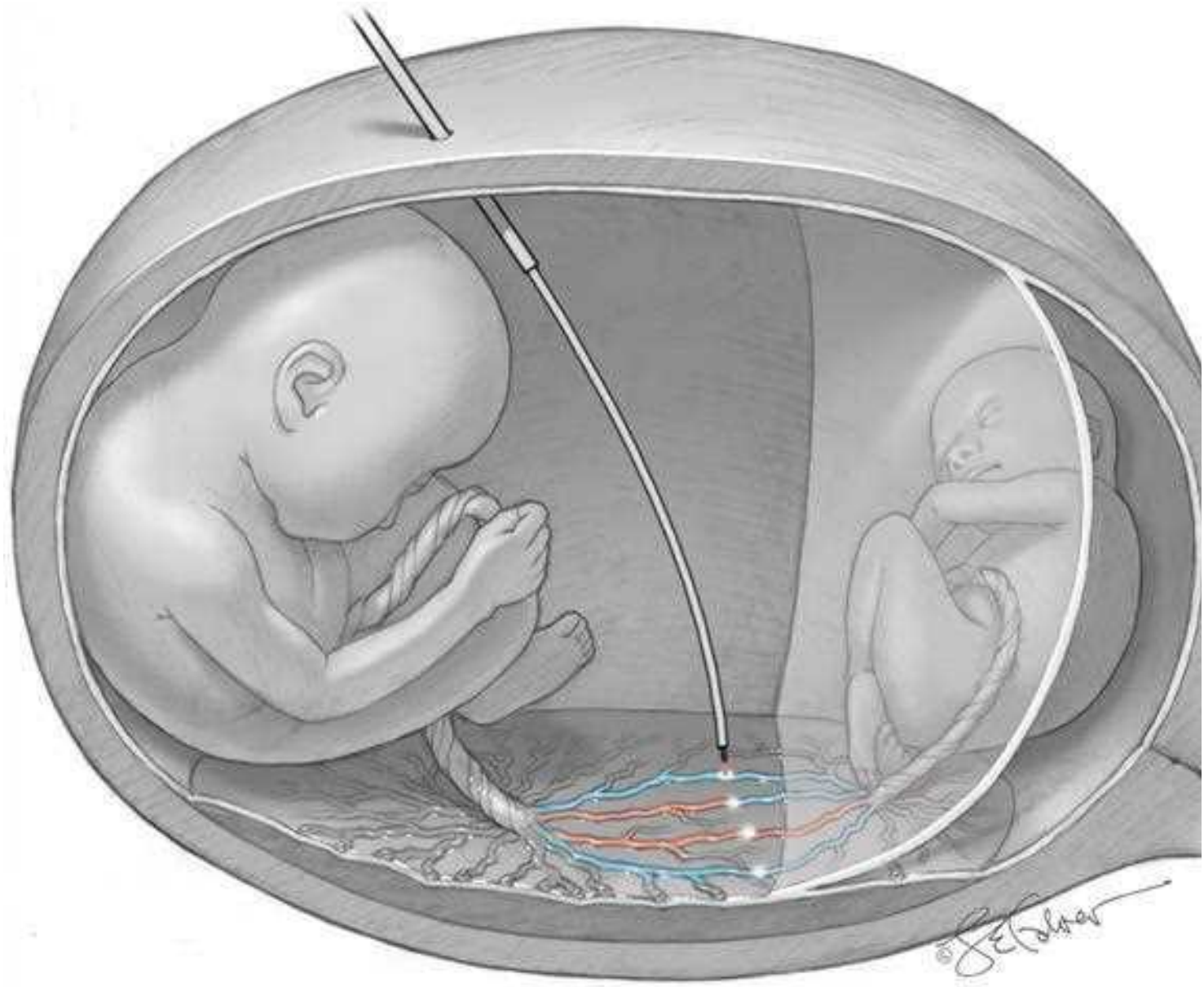
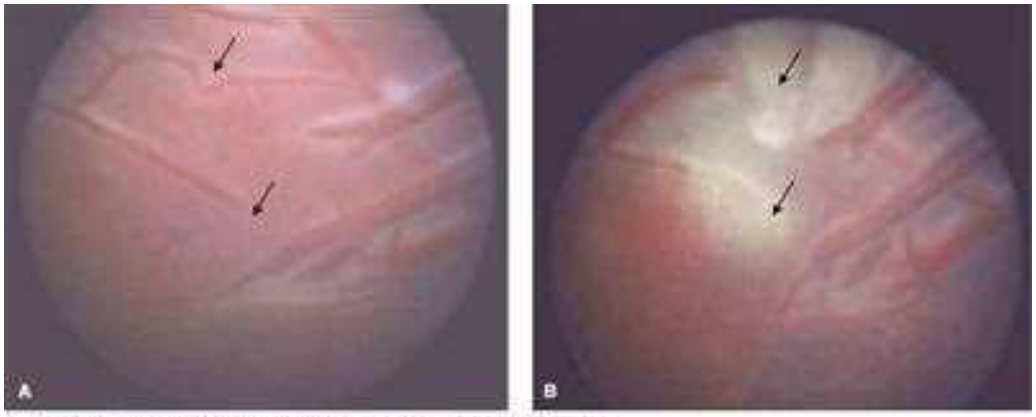


FIGURE 16-5

Fetoscopic photograph of laser photocoagulation for twin-twin transfusion syndrome. **A.** Vascular anastomoses (*arrows*) are shown before photocoagulation is performed. **B.** The ablation sites appear as blanched yellow-white areas (*arrows*). (Used with permission from Dr. Timothy M. Crombleholme.)



With *selective laser photocoagulation,* anastomoses crossing between the twins along the vascular equator are individually coagulated (Ville, 1995). Unfortunately, residual anastomoses remain in up to a third of cases and may lead to TTTS recurrence or to the development of twin-anemia polycythemia sequence (TAPS). The latter is a feto-fetal transfusion characterized by large differences in hemoglobin concentrations between a pair of monochorionic twins. To address these complications, the *Solomon technique* was developed. With this, after selective photocoagulation, the laser is used to coagulate the entire vascular equator, from one edge of the placenta to the other (Slaghekke, 2014a). The Solomon technique lowers the proportion of pregnancies with recurrent TTTS and TAPS in multiple trials. Also, placental dye-injection studies confirm a significant reduction in the number of residual anastomoses (Ruano, 2013; Slaghekke, 2014b).

Complications

Families should have reasonable expectations of procedural success and potential complications. Without treatment, the perinatal mortality rate for severe TTTS is 70 to 100 percent. Following laser therapy, the anticipated perinatal mortality rate approximates 30 to 50 percent, with a 5- to 20-percent risk for long-term neurological handicap (Society for Maternal-Fetal Medicine, 2013). Cystic periventricular leukomalacia and grade III to IV interventricular hemorrhage are identified neonatally in up to 10 percent of laser-treated cases (Lopriore, 2006).

Procedure-related complications include preterm prematurely ruptured membranes in up to 25 percent, placental abruption in 8 percent, vascular laceration in 3 percent, amnionic band syndrome resulting from laser laceration of the membranes in 3 percent, and TAPS in 16 percent with photocoagulation and 3 percent with the Solomon modification (Habli, 2009; Robyr, 2006; Slaghekke, 2014b). Finally, most laser-treated TTTS pregnancies deliver before 34 weeks.

Congenital Diaphragmatic Hernia

The prevalence of congenital diaphragmatic hernia (CDH) is approximately 1 in 3000 to 4000 births, and the overall survival rate is 50 to 60 percent. Associated anomalies occur in 40 percent of cases and confer a considerably lower survival rate. The main causes of mortality among those with isolated CDH are pulmonary hypoplasia and pulmonary hypertension. And, the major risk factor is liver herniation, which complicates at least half of cases and is associated with a 30-percent reduction in the survival rate (Mullassery, 2010, Oluyomi-Obi, 2017).

Because of maternal and fetal risks associated with fetal surgical intervention, efforts have focused on identifying those least likely to survive with postnatal therapy alone. Fetuses with associated anomalies are typically excluded, as are those without liver herniation. Prediction is further hampered because of improvements in neonatal care for newborns with CDH. These include permissive hypercapnia, “gentle ventilation” to avoid barotrauma, and delayed surgery.

Lung-to-Head Ratio

This sonographic ratio was developed to improve prediction of survival in fetuses with isolated left-sided CDH diagnosed before 25 weeks’ gestation (Metkus, 1996). The lung-to-head ratio (LHR) is a measurement of the right lung area, taken at the level of the four-chamber view of the heart, divided by the head circumference (Fig. 10-23). Investigators found that the survival rate was 100 percent if the LHR was >1.35, and there were no survivors if it was <0.6. Nearly three fourths of pregnancies had values between 0.6 and 1.35, and prediction was difficult in this large group because the overall survival rate approximated 60 percent (Metkus, 1996).

As of 2017, trials underway have selected a threshold LHR of <1.0 or an observed-to-expected LHR <25 percent for study inclusion. An observed LHR is obtained sonographically from the affected fetus, whereas the expected LHR is an established reference value from normal fetuses (Peralta, 2005). In a recent metaanalysis, the odds ratio for survival with an LHR <1.0 was only 0.14 (Oluyomi-Obi, 2017). Similarly, with an observed-to-expected LHR <25 percent, survival rates ranged from 13 to 30 percent. In contrast, an observed-to-expected LHR >35 percent was associated with survival rates ranging from 65 to 88 percent.

Magnetic Resonance Imaging

This has been used to estimate the total volume of lung tissue, both ipsilateral and contralateral to the diaphragmatic hernia, which may then be compared with a gestational age-matched reference. Mayer and coworkers (2011) performed a metaanalysis of 19 studies involving more than 600 pregnancies in which isolated CDH was evaluated with fetal MR imaging. Factors significantly associated with neonatal survival included the side of the defect, total fetal lung volume, observed-to-expected lung volume, and fetal liver position.

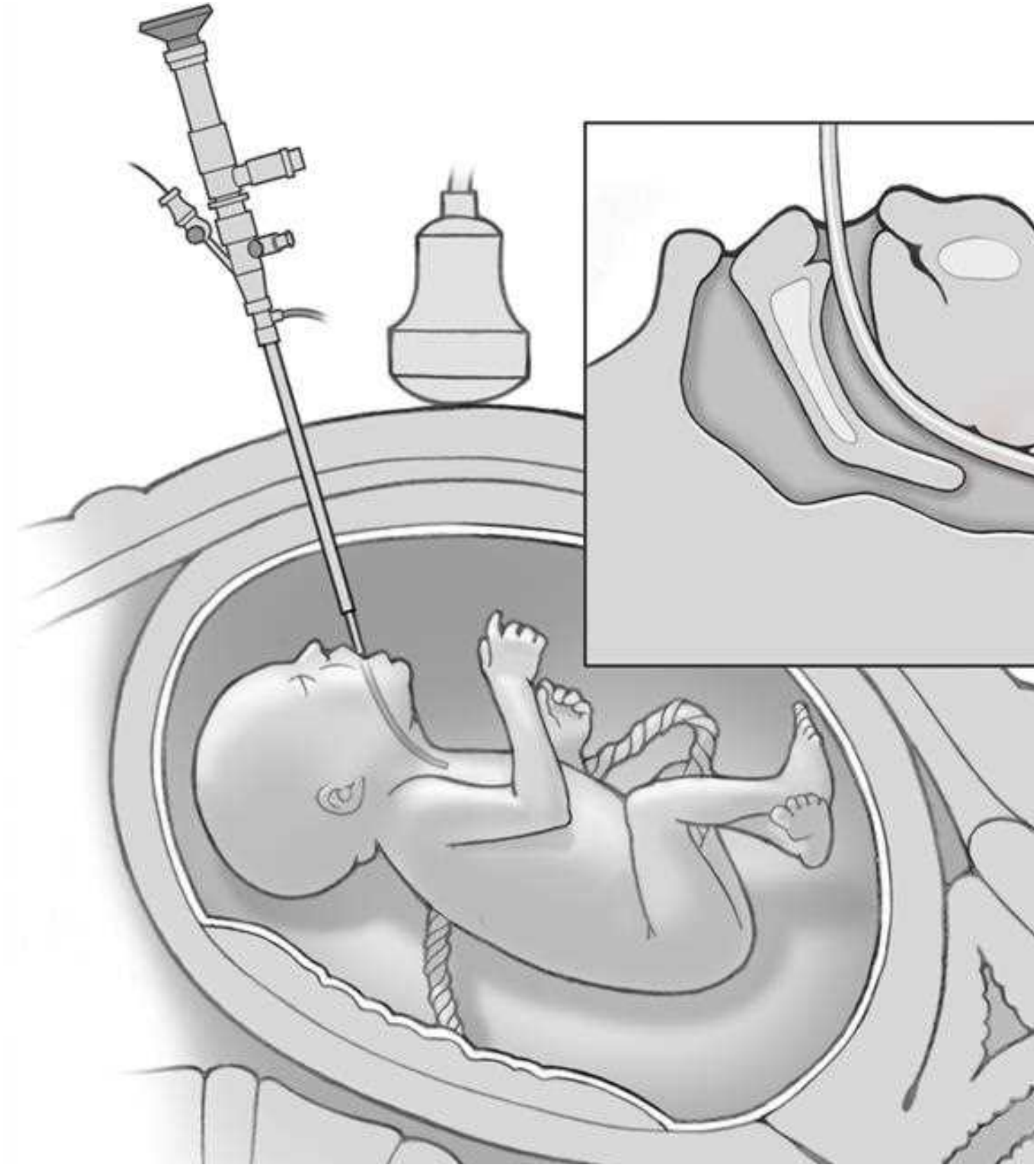
Fetal MR imaging has also been used to quantify the volume of herniated liver (Fig. 10-57). Two reasons underlie the rationale for assessing liver volume. First, liver herniation is perhaps the strongest predictor of outcome in fetuses with isolated CDH. Second, liver volume might be a more reliable predictor because lungs are inherently more compressible than liver. Indeed, these MR parameters—lung volumes and degree of liver herniation—correlate well with postnatal survival rates and may be more useful predictors than sonographic parameters (Bebbington, 2014; Ruano, 2014; Worley, 2009).

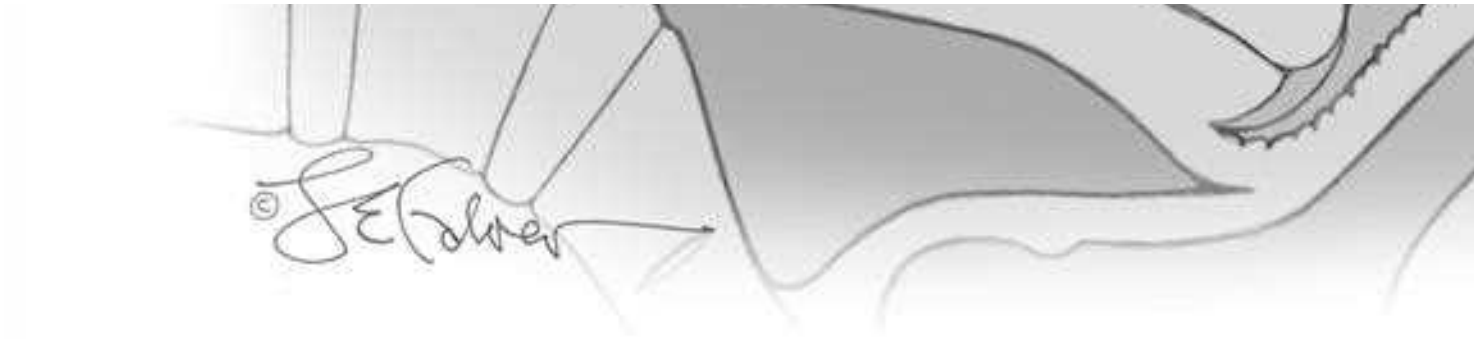
Tracheal Occlusion

Early attempts to treat severe diaphragmatic herniation used open fetal surgery to reposition the liver into the abdomen, which unfortunately kinked the umbilical vein and led to fetal demise (Harrison, 1993). Knowledge that lungs normally produce fluid and that fetuses with upper airway obstruction develop hyperplastic lungs formed the rationale for tracheal occlusion. The idea was to "plug the lung until it grows" (Hedrick, 1994). Initial efforts focused on occluding the trachea with an external clip (Harrison, 1993). Subsequently, a detachable silicone balloon was placed within the trachea endoscopically (Fig. 16-6).

FIGURE 16-6

Fetoscopic tracheal occlusion (FETO). The endoscope enters the fetal oropharynx and advances down the trachea. Inset: The balloon is inflated to occlude the trachea, and then the endoscope is removed. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)





The balloon technique—termed *fetal endoscopic tracheal occlusion (FETO)*—uses a 3-mm operating sheath and fetoscopes as small as 1 mm (Deprest, 2011; Ruano, 2012). The procedure is generally performed between 27 and 30 weeks' gestation, with the goal of removing the balloon at approximately 34 weeks, either through a second fetoscopic procedure or by ultrasound-guided puncture (Jiménez, 2017). If these are unsuccessful, the balloon is removed during an ex-utero intrapartum treatment procedure at delivery (Ex-Utero Intrapartum Treatment).

In 2003, a randomized trial of the FETO procedure in pregnancies with isolated CDH, liver herniation, and LHR <1.4 did not identify a benefit from fetal therapy (Harrison, 2003). Survival rates 90 days after birth were unexpectedly high in both groups and approximated 75 percent. Following this study, however, enthusiasm for the technique continued, particularly outside the United States. Using a lower LHR threshold of 1.0 in addition to liver herniation as prerequisites for inclusion, significantly higher postnatal survival rates have been reported. Rates improved from <25 percent with postnatal therapy to approximately 50 percent with FETO (Jani, 2009; Ruano, 2012). In a recent metaanalysis of five trials that included 211 pregnancies, those treated with FETO were 13 times more likely to survive (Al-Maary, 2016). At present, FETO is available in the United States only in research trials.

Endoscopic Myelomeningocele Repair

After publication of the MOMS findings, research efforts focused on whether maternal morbidities associated with open fetal myelomeningocele repair might be mitigated if the procedure was accomplished endoscopically. Araujo Junior and associates (2016) conducted a systematic review that included 456 open cases and 84 endoscopic surgeries. The endoscopic procedures were generally performed by inserting instruments through the maternal abdominal wall and then through the uterine wall, with partial carbon dioxide insufflation of the uterus. The rate of maternal myometrial dehiscence or attenuation was only 1 percent following endoscopy compared with 26 percent following open procedures. However, endoscopy was associated with significantly increased rates of preterm delivery before 34 weeks—80 versus 45 percent, and of perinatal mortality—14 versus 5 percent.

Belfort and colleagues (2017) recently described their outcomes in 22 pregnancies with fetal myelomeningocele using a technique in which the maternal abdomen was opened, the uterus exteriorized, and the procedure then performed endoscopically using warmed carbon dioxide insufflation. In contrast with earlier endoscopic reports, most treated pregnancies were delivered at term, with no perinatal losses. Further, the proportion of infants requiring hydrocephalus treatment prior to 1 year of age—approximately 40 percent—was similar to that with open fetal surgery in the MOMS trial (Adzick, 2011; Belfort, 2017). Research efforts in this area will undoubtedly continue.

Percutaneous Procedures

Sonographic guidance can be used to permit therapy with a shunt, radiofrequency ablation needle, or angioplasty catheter. With these procedures, desired instruments cross the maternal abdominal wall, uterine wall, and membranes to reach the amnionic cavity and fetus. Risks include maternal infection, preterm labor or prematurely ruptured membranes, and fetal injury or loss.

Thoracic Shunts

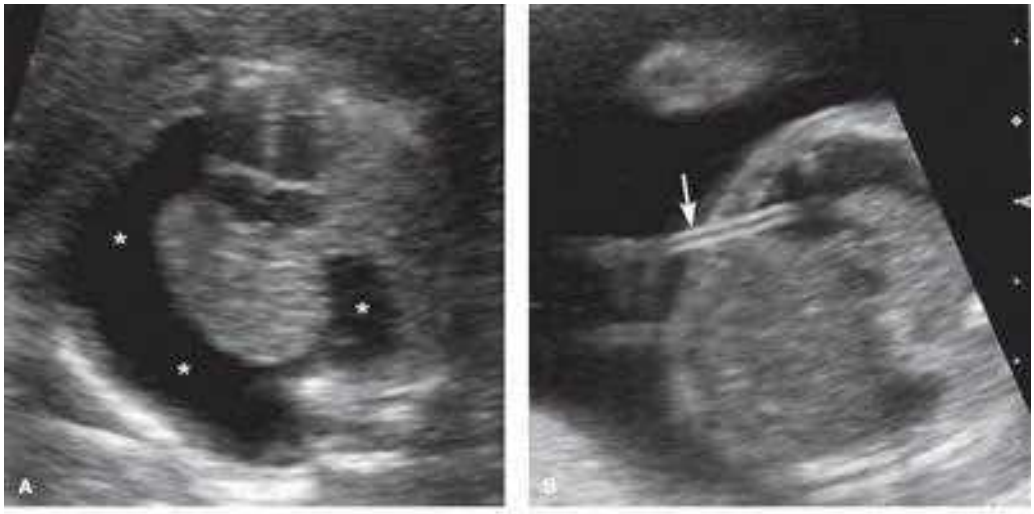
A shunt placed from the fetal pleural cavity into the amnionic cavity may be used to drain pleural fluid (Fig. 16-7). A large effusion may cause a significant mediastinal shift, resulting in pulmonary hypoplasia or in heart failure and hydrops. The most common etiology of a primary effusion is *chylothorax*—caused by lymphatic obstruction. Pleural effusions may also form secondary to congenital viral infection or aneuploidy, or they may be associated with a malformation such as *pulmonary sequestration.* Yinon and associates (2010) reported aneuploidy in approximately 5 percent and associated anomalies in 10 percent of cases.

Typically, the effusion is first drained using a 22-gauge needle with sonographic guidance. Tests for aneuploidy and infection are performed, as well as a cell count. A pleural-fluid cell count with greater than 80-percent lymphocytes, in the absence of infection, is diagnostic of chylothorax. If the fluid reaccumulates, a trocar and cannula may be inserted through the fetal chest wall, and a double-pigtail shunt may be placed to drain the effusion. If the effusion is right-sided, the shunt is placed in the lower third of the chest to permit maximum expansion of the lung. If left-sided, the shunt is placed along the upper axillary line to allow the heart to return to normal position (Mann, 2010). The overall survival rate is 70 percent, and that for hydropic fetuses approximates 50 percent (Mann, 2010; Yinon, 2010). Shunt displacement into the amnionic cavity is not uncommon. If the shunt remains in place, it must be clamped immediately upon delivery of the newborn to avoid pneumothorax.

FIGURE 16-7

Thoracoamnionic shunt placement. **A.** A large, right-sided fetal pleural effusion (*asterisks*) and ascites were identified at 18 weeks' gestation. The effusion was drained but rapidly reaccumulated. The xanthochromic fluid contained 95-percent lymphocytes, consistent with chylothorax. **B.** A double-pigtail shunt (*arrow*) was

inserted under ultrasound guidance. Following shunt placement, the effusion and ascites resolved.



Shunts can also drain a dominant cyst in fetuses with macrocystic *congenital cystic adenomatoid malformation*. However, cysts rarely are large enough to pose a risk for hydrops or pulmonary hypoplasia. Shunt placement may improve survival to 90 percent in the absence of hydrops and to more than 75 percent with hydrops (Litwinska, 2017).

Urinary Shunts

Vesicoamnionic shunts are used in selected fetuses with severe bladder-outlet obstruction in which diminished amnionic fluid portends a grim prognosis (Fig. 16-8). Distal obstruction of the urinary tract occurs more often in male fetuses. The most common etiology is *posterior urethral valves,* followed by *urethral atresia* and by *prune belly syndrome*, which is also called *Eagle-Barrett syndrome*. Sonographic findings include dilation of the bladder and proximal urethra, termed the “keyhole” sign, along with bladder wall thickening (Fig. 10-45). Associated oligohydramnios before midpregnancy leads to pulmonary hypoplasia. Unfortunately, postnatal renal function may be poor even when amnionic fluid volume is normal.

Evaluation includes a careful search for concurrent anomalies, which may coexist in 40 percent of cases, and for aneuploidy, which has been reported in 5 to 8 percent of cases (Hayden, 1988; Hobbins, 1984; Mann, 2010). Fetal urine sampled at vesicocentesis may be used to perform genetic studies. As with other structural fetal abnormalities, chromosomal microarray analysis is recommended. Because visualization may be limited due to lack of amnionic fluid, counseling should include the increased likelihood that associated anomalies may be missed sonographically.

Potential candidates are fetuses without other severe anomalies or genetic syndromes and without sonographic features that confer poor prognosis, for example, renal cortical cysts. Therapy is generally offered only if the fetus is male, because in females, the underlying anomaly tends to be even more severe. Serial bladder drainage—vesicocentesis—performed under sonographic guidance at approximately 48-hour intervals is used to evaluate fetal urine electrolyte and protein content. Fetal urine is normally hypotonic due to tubular resorption of sodium and chloride, whereas isotonic urine in the setting of obstruction suggests renal tubular damage. Serial assessment permits classification of the renal prognosis as good or poor and helps guide candidate selection (Table 16-4).

TABLE 16-4

Fetal Urinary Analyte Values with Bladder Outlet Obstruction

Analyte	Good Prognosis	Poor Prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<80 mmol/L	>90 mmol/L
Calcium	<7 mg/dL	>8 mg/dL
Osmolality	<180 mmol/L	>200 mmol/L
β_2-Microglobulin	<6 mg/L	>10 mg/L
Total protein	<20 mg/dL	>40 mg/dL

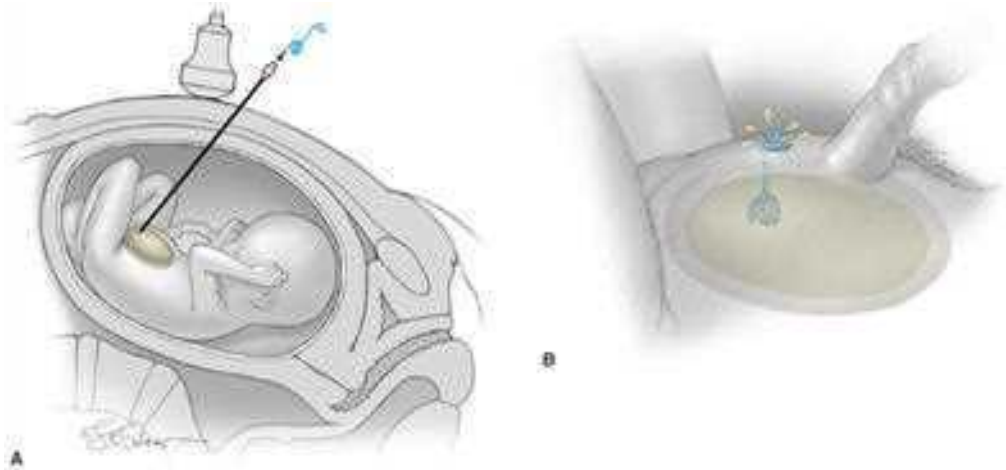
Good or poor prognosis is based on values from serial vesicocentesis performed between 18 and 22 weeks' gestation, using the last specimen obtained.

Data from Mann, 2010.

Shunt placement allows urine to drain from the bladder into the amnionic cavity. When successful, this often prevents pulmonary hypoplasia, however, renal function is not reliably preserved. Before shunting, amnioinfusion of warmed lactated Ringer solution is generally performed to aid catheter placement. Amnioinfusion also aids sonographic evaluation of fetal anatomy. A small trocar and cannula are then inserted into the fetal bladder under sonographic guidance. The shunt is placed as low as possible within the bladder to avoid dislodgement after bladder decompression. A double-pigtail catheter is used. The distal end lies within the fetal bladder, and the proximal end drains into the amnionic cavity.

FIGURE 16-8

Vesicoamnionic shunt placement. **A.** After amnioinfusion is performed, a trocar is inserted into the distended fetal bladder under sonographic guidance. The pigtail catheter is threaded into the trocar. **B.** The double-pigtail shunt has been deployed down the trocar, and the trocar has been removed. The distal end of the shunt is coiled within the fetal bladder, and the proximal end is draining into the amnionic cavity. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Complications include displacement of the shunt out of the fetal bladder in up to 40 percent of cases, urinary ascites in about 20 percent, and development of gastroschisis in 10 percent (Freedman, 2000; Mann, 2010). Preterm delivery is common, and neonatal survival rates range from 50 to 90 percent (Biard, 2005; Walsh, 2011). A third of surviving children have required dialysis or renal transplantation, and almost half have respiratory problems (Biard, 2005). In one randomized trial, vesicoamnionic shunt placement was compared with conservative management in 31 cases (Morris, 2013). Those receiving shunts had higher survival rates. However, only two children had normal renal function at age 2 years.

Radiofrequency Ablation

With this procedure, high-frequency alternating current is used to coagulate and desiccate tissue. Radiofrequency ablation (RFA) has become a favored modality for treatment of *twin-reversed arterial perfusion (TRAP) sequence,* also known as *acardiac twin* (Chap. 45, Twin Anemia–Polycythemia Sequence). Without treatment, the mortality rate for the normal or pump twin in severe TRAP sequence exceeds 50 percent. The procedure is also used for selective termination with other monochorionic twin complications (Bebbington, 2012).

Under sonographic guidance, a 17- to 19-gauge RFA needle is directed into the base of the umbilical cord of the acardiac twin and inserted into its abdomen. After a 2-cm area of coagulation is achieved, color Doppler sonography is applied to verify absent flow into the acardius. In several centers, survival rates for the normal twin following RFA have significantly improved (Lee, 2007; Livingston, 2007). RFA was performed at approximately 20 weeks' gestation in 98 pregnancies with TRAP sequence reported by the North American Fetal Therapy Network (NAFTNet). The median gestational age at delivery was 37 weeks, and the neonatal survival rate was 80 percent. The major complication was prematurely ruptured membranes and preterm birth. Twelve percent were delivered at approximately 26 weeks (Lee, 2013).

RFA has generally been offered for TRAP sequence when the volume of the acardiac twin is large. In the NAFTNet series cited above, the median size of the acardius relative to the pump twin was 90 percent (Lee, 2013). Considering procedure-related risks, expectant management with close fetal surveillance is instead considered if the estimated weight of the acardius is below 50 percent of the pump twin (Jelin, 2010). Finally, acardiac twins are more likely to complicate monoamnionic gestations. In one recent series, pump twin survival following RFA was 88 percent in monochorionic diamnionic pregnancies but only 67 percent in monoamnionic pregnancies (Sugibayashi, 2016).

Fetal Intracardiac Catheter Procedures

Selected fetal cardiac lesions may worsen during gestation, further complicating or even obviating options for postnatal repair. Severe narrowing of a cardiac outflow tract may result in progressive myocardial damage in utero, and a goal of fetal intervention is to permit muscle growth and preserve ventricular function (Walsh, 2011). These innovative procedures include *aortic valvuloplasty* for critical aortic stenosis; *atrial septostomy* for hypoplastic left heart syndrome with intact interatrial septum; and *pulmonary valvuloplasty* for pulmonary atresia with intact interventricular septum.

Fetal aortic valvuloplasty is the most commonly performed cardiac procedure, accounting for 75 percent of cases reported by the International Fetal Cardiac Intervention Registry (Moon-Grady, 2015). It is offered for selected cases of critical aortic stenosis in which the left ventricle is either normal sized or dilated. The goal is to prevent progression to hypoplastic left heart and to permit postnatal biventricular repair (McElhinney, 2009). Under sonographic guidance, an 18-gauge cannula is inserted through uterus and fetal chest wall and into the left ventricle. Although the procedure is ideally performed percutaneously—through the maternal abdominal wall—laparotomy may be needed if the fetal position is unfavorable. The cannula tip is positioned in front of the stenotic aortic valve, and a 2.5- to 4.5-mm balloon catheter is then guided into the aortic annulus and inflated. Fetal bradycardia requiring treatment complicates a third of cases, and hemopericardium requiring drainage affects approximately 20 percent (Moon-Grady, 2015).

From the first 100 cases at Boston Children's Hospital, 85 children survived, 38 of whom achieved biventricular circulation (Freud, 2014). Despite these successes, the mortality rate and risk for neurodevelopmental impairment in childhood appear to be similar to cases treated with postnatal repair (Laraja, 2017; Moon-Grady, 2015).

Fetal atrial septostomy, also using a percutaneous balloon catheter, is offered in select cases of hypoplastic left heart with an intact or highly restrictive interatrial septum. This condition has a postnatal mortality rate of nearly 80 percent (Glantz, 2007). In an effort to ensure patency, atrial septal stent placement has also been performed. Of 37 cases of atrial septostomy, survival to hospital discharge was almost 50 percent (Moon-Grady, 2015).

Fetal pulmonary valvuloplasty has been offered in cases of pulmonary atresia with intact interventricular septum to prevent development of hypoplastic right heart syndrome. Although success is achieved in approximately two thirds of cases, it is not yet clear whether outcomes are improved compared with standard postnatal repair (Arzt, 2011; McElhinney, 2010).

Ex-Utero Intrapartum Treatment

This procedure allows the fetus to remain perfused by the placenta after being partially delivered, so that lifesaving treatment can be performed before completing the delivery. The technique was first developed to obtain an airway with fetal tumors involving the oropharynx and neck (Catalano, 1992; Kelly, 1990; Langer, 1992). An ex-utero intrapartum treatment (EXIT) procedure is performed by a multidisciplinary team, which may include an obstetrician, maternal-fetal medicine specialist, pediatric surgeon(s), pediatric otolaryngologist, pediatric cardiologist, anesthesiologists for the mother and fetus, and neonatologists, as well as specially trained nursing personnel. Components of the procedure are shown in Table 16-5.

TABLE 16-5

Components of the Ex-Utero Intrapartum Treatment (EXIT) Procedure

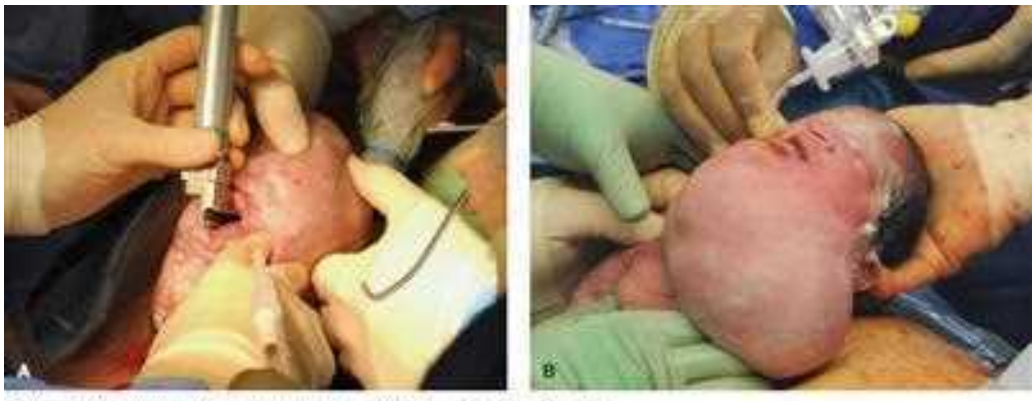
Comprehensive preoperative evaluation: specialized sonography, fetal echocardiography, magnetic resonance imaging, fetal karyotype if possible
Uterine relaxation with deep general anesthesia and tocolysis
Intraoperative sonography to confirm placental margin and fetal position and to visualize vessels at uterine entry
Placement of stay-sutures followed by use of uterine stapling device to decrease uterine entry bleeding
Maintenance of uterine volume during the procedure via continuous amnioinfusion of warmed physiological solution to help prevent placental separation
Delivery of the fetal head, neck, and upper torso to permit access as needed
Fetal injection of intramuscular vecuronium, fentanyl, and atropine
Fetal peripheral intravenous access, pulse oximeter, and cardiac ultrasound
Following procedure, umbilical lines placed prior to cord clamping
Uterotonic agents administered as needed

Data from Moldenhauer, 2013.

Selected indications are listed in Table 16-2. EXIT is the preferred procedure for intrapartum management of large venolymphatic malformations of the neck such as the one shown in Figure 16-9. At the Children's Hospital of Philadelphia, criteria for EXIT with a cervical venolymphatic malformation include compression, deviation, or obstruction of the airway by the mass, and also involvement of the floor of the mouth (Laje, 2015). In a review of 112 pregnancies with fetal cervical venolymphatic malformations, only about 10 percent met these criteria. Other indications for EXIT include severe *micrognathia* and *congenital high airway obstruction sequence (CHAOS)*, which are discussed in Chapter 10 (Figs. 10-20 and 10-26). Criteria for an EXIT procedure for micrognathia include a fetal jaw measurement below the 5th percentile along with indirect evidence of obstruction, such as hydramnios, an absent stomach bubble, or glossoptosis (Morris, 2009b). Case selection for EXIT procedures is generally based on fetal MR imaging findings (Chap. 10, Adjunct to Fetal Therapy).

FIGURE 16-9

Ex-utero intrapartum treatment (EXIT) procedure for a venolymphatic malformation. **A.** Upon delivery of the head, placental circulation was maintained and an airway was established over the course of 20 minutes by a team of pediatric subspecialists that included a surgeon, anesthesiologist, and otolaryngologist. **B.** Following a controlled intubation, the fetus was ready for delivery and transfer to the neonatal intensive care unit team. (Used with permission from Drs. Stacey Thomas and Patricia Santiago-Muñoz.)



In some cases, an EXIT procedure has been used as a bridge to other procedures. For example, resection of large thoracic masses may be accomplished by fetal thoracotomy performed with intact placental circulation. In a series of 16 fetuses with CCAM volume ratios >1.6 or hydrops, all of whom had mediastinal compression, Cass and colleagues (2013) reported that nine infants undergoing *EXIT-to-resection* survived. In contrast, there were no survivors with urgent postnatal surgery alone. Similarly, Moldenhauer (2013) reported that 20 of 22 newborns treated with EXIT-to-resection for lung masses survived. The EXIT procedure has also been used as a bridge to extracorporeal membrane oxygenation—*EXIT-to-ECMO*—in pregnancies with severe congenital diaphragmatic hernia. However, it has not been found to clearly confer survival benefit in such cases (Morris, 2009a; Shieh, 2017; Stoffan, 2012).

Counseling prior to an EXIT procedure includes procedure-related risks such as hemorrhage from placental abruption or uterine atony, need for cesarean delivery in future pregnancies, higher risk for subsequent uterine rupture or dehiscence, possible need for hysterectomy, and fetal death or permanent neonatal disability. Compared with cesarean delivery, the EXIT procedure is associated with greater blood loss, a higher incidence of wound complications, and a longer operating time—approximately 40 minutes longer depending on the procedure (Noah, 2002).

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CHAPTER 17: Fetal Assessment

> *The rate of the foetal heart is subject to considerable variations, which affords us a fairly reliable means of judging as to the well-being of the child. As a general rule, its life should be considered in danger when the heart-beats fall below 100 or exceed 160.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

More than 100 years ago, the approach to fetal assessment was rather primitive. Since that time, and especially since the 1970s, technology to evaluate the health of the fetus has advanced remarkably. Techniques employed today to forecast fetal well-being focus on fetal biophysical findings that include heart rate, movement, breathing, and amnionic fluid production. These findings aid antepartum fetal surveillance to prevent fetal death and avoid unnecessary interventions, which are stated goals of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (2017).

Most fetuses will be healthy, and usually a negative—that is, normal—antepartum test result is highly reassuring, because fetal deaths within 1 week of a normal test are rare. Indeed, negative-predictive values—a true negative test—for most of the tests described are 99.8 percent or higher. In contrast, estimates of the positive-predictive values—a true positive test—for abnormal test results are low and range between 10 and 40 percent. Importantly, fetal surveillance is primarily based on circumstantial evidence. No definitive randomized clinical trials have been conducted for obvious ethical reasons (American College of Obstetricians and Gynecologists, 2016).

FETAL MOVEMENTS

Physiology

Passive unstimulated fetal activity commences as early as 7 weeks' gestation and becomes more sophisticated and coordinated by the end of pregnancy (Sajapala, 2017; Vindla, 1995). Indeed, beyond 8 menstrual weeks, fetal body movements are never absent for periods exceeding 13 minutes (DeVries, 1985). Between 20 and 30 weeks' gestation, general body movements become organized, and the fetus starts to show rest-activity cycles (Sorokin, 1982). Fetal movement maturation continues until approximately 36 weeks, when behavioral states are established in most normal fetuses. Nijhuis and colleagues (1982) described four fetal behavioral states:

State 1F is a quiescent state—quiet sleep—with a narrow oscillatory bandwidth of the fetal heart rate.

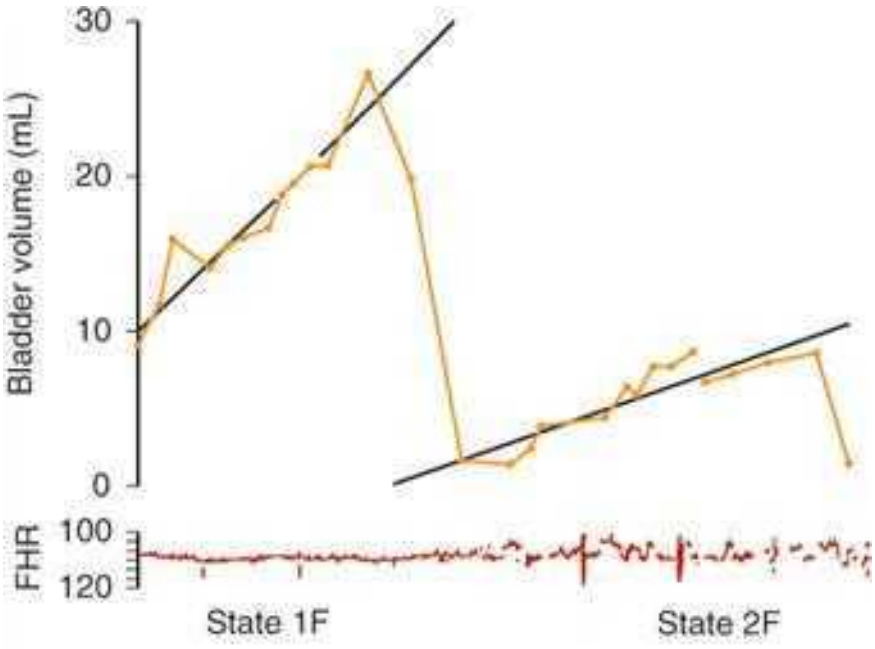
State 2F includes frequent gross body movements, continuous eye movements, and wider oscillation of the fetal heart rate. This state is analogous to rapid eye movement (REM) or active sleep in the neonate.

State 3F includes continuous eye movements in the absence of body movements and no heart rate accelerations. The existence of this state is disputed (Pillai, 1990a).

State 4F is one of vigorous body movement with continuous eye movements and heart rate accelerations. This state corresponds to the awake state in newborns.

Fetuses spend most of their time in states 1F and 2F. For example, at 38 weeks, 75 percent of time is spent in these two states. These behavioral states—particularly 1F and 2F, which correspond to quiet sleep and active sleep—have been used to develop an increasingly sophisticated understanding of fetal behavior. In a study of fetal urine production, bladder volumes increased during state 1F quiet sleep (Fig. 17-1). During state 2F, the fetal heart rate baseline bandwidth increased appreciably, and bladder volume was significantly diminished due to decreased urine production and infrequent fetal voiding. These phenomena were interpreted to represent reduced renal blood flow during active sleep.

FIGURE 17-1
Fetal bladder volume measurements together with fetal heart rate (FHR) variation recorded in relation to 1F or 2F behavior states. State 1F fetal heart rate has a narrow bandwidth consistent with quiet sleep. State 2F heart rate shows wide oscillation of the baseline consistent with active sleep. (Modified with permission from Oosterhof H, vd Stege JG, Lander M, et al: Urine production rate is related to behavioural states in the near term human fetus, Br J Obstet Gynaecol. 1993 Oct;100(10):920–922.)



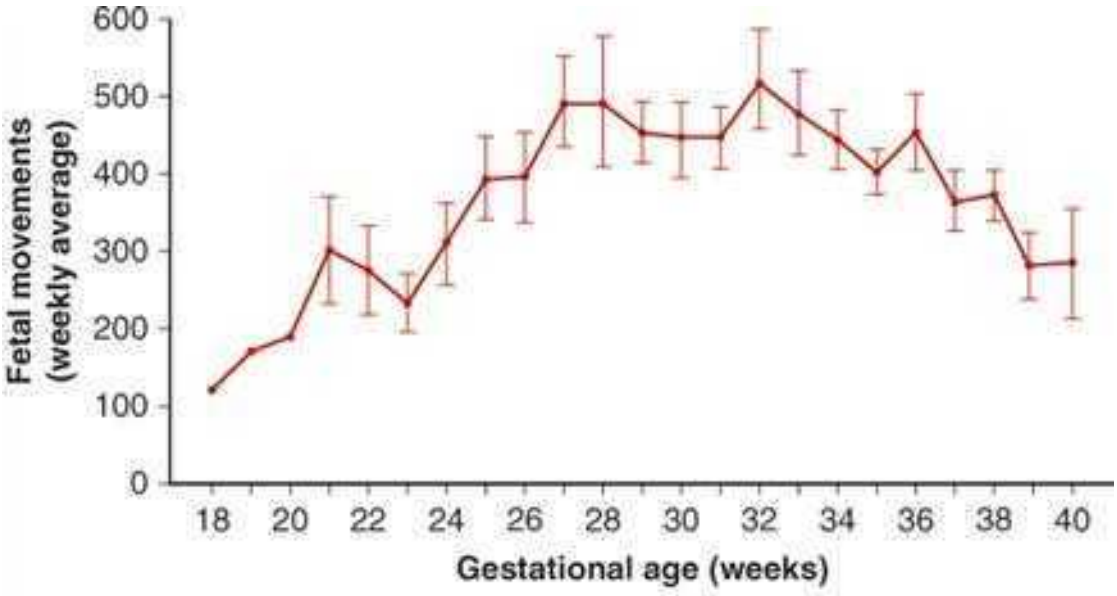
An important determinant of fetal activity appears to be sleep-awake cycles, which are independent of maternal ones. Fetal sleep cyclicity varies from approximately 20 minutes to as much as 75 minutes. In one study, the mean length of the quiet or inactive state for term fetuses was 23 minutes (Timor-Tritsch, 1978). Patrick and associates (1982) measured gross fetal body movements with real-time sonography for 24-hour periods in 31 normal pregnancies and found the longest period of inactivity to be 75 minutes. *Amnionic fluid volume* is another important determinant of fetal activity. Sherer and colleagues (1996) assessed the number of fetal movements in 465 pregnancies during biophysical profile testing in relation to amnionic fluid volume. They observed decreased fetal activity with diminished amnionic volumes and suggested that a restricted uterine space might physically limit fetal movements.

Sadovsky and coworkers (1979b) classified fetal movements into three categories according to both maternal perceptions and independent recordings using piezoelectric sensors. Weak, strong, and rolling movements were described, and their relative contributions to total weekly movements throughout the last half of pregnancy were quantified. As pregnancy advances, the rate of weak movements decreases, more vigorous movements increase for several weeks, and then rates of these subside at term. Presumably, declining amnionic fluid and space account for diminished activity at term. Figure 17-2

shows fetal movements during the last half of gestation in 127 pregnancies with normal outcomes. The mean number of weekly movements calculated from 12-hour daily recording periods rose from approximately 200 at 20 weeks' gestation to a maximum of 575 movements at 32 weeks. Fetal movements then declined to an average of 282 at 40 weeks. Normal weekly maternal counts of fetal movements ranged between 50 and 950. Count showed large daily variations, with included counts as low as 4 to 10 per 12-hour period in normal pregnancies.

FIGURE 17-2

Graph depicts averages of fetal movements counted during 12-hour periods (mean ± SEM). (Data from Sadovsky, 1979a.)



Clinical Application

Diminished fetal activity may be a harbinger of impending fetal death (Sadovsky, 1973). To quantify fetal movement, clinical methods include use of a uterine contraction tocodynamometer, visualization with sonography, and maternal subjective perceptions.

Most, but not all, investigators report excellent correlation between maternally perceived fetal motion and movements documented by instrumentation. For example, Rayburn (1980) found that 80 percent of all movements observed during sonographic monitoring were perceived by the mother. In contrast, Johnson and colleagues (1992) reported that beyond 36 weeks, mothers perceived only 16 percent of fetal body movements. Fetal motions lasting more than 20 seconds were more likely to be identified than shorter episodes. Although several fetal-movement counting protocols have been used, neither the optimal number of movements nor the ideal duration for counting them has been defined. For example, in one method, perception of 10 fetal movements in up to 2 hours is considered normal (Moore, 1989). Commonly, women may present in the third trimester complaining of subjectively reduced fetal movement. Harrington and associates (1998) reported that 7 percent of nearly 6800 women presented with a complaint of decreased fetal movement. Fetal heart rate monitoring tests were employed if sonographic scans for fetal growth or Doppler velocimetry were abnormal. Pregnancy outcomes for women who complained of decreased fetal movement were not significantly different from those for women without this complaint. Scala and colleagues (2015) reported that 6 percent of women at term reported decreased fetal movements at 36 weeks or more. Women with two or more episodes of reduced fetal movements had greater risks of growth-restricted newborns and abnormal Doppler uterine artery flow studies. However, stillbirth rates were not increased. Measurement of the myocardial performance index did not improve accuracy (Ho, 2017).

Grant and coworkers (1989) performed an unparalleled investigation of maternally perceived fetal movements and pregnancy outcome. More than 68,000 pregnancies were randomly assigned between 28 and 32 weeks' gestation. Women in the fetal movement arm of the study were instructed by specially employed midwives to record the time needed to feel 10 movements each day. This required an average of 2.7 hours each day. Women in the control group were informally asked about movements during prenatal visits. Reports of decreased fetal motion were evaluated with tests of fetal well-being. Antepartum death rates for otherwise normal singleton fetuses were similar in the two study groups. Despite the counting policy, most stillborn fetuses were dead by the time the mothers reported for medical attention. Importantly, rather than concluding that maternal perceptions of fetal activity were meaningless, these investigators concluded that informal maternal perceptions were as valuable as formally recorded fetal movement.

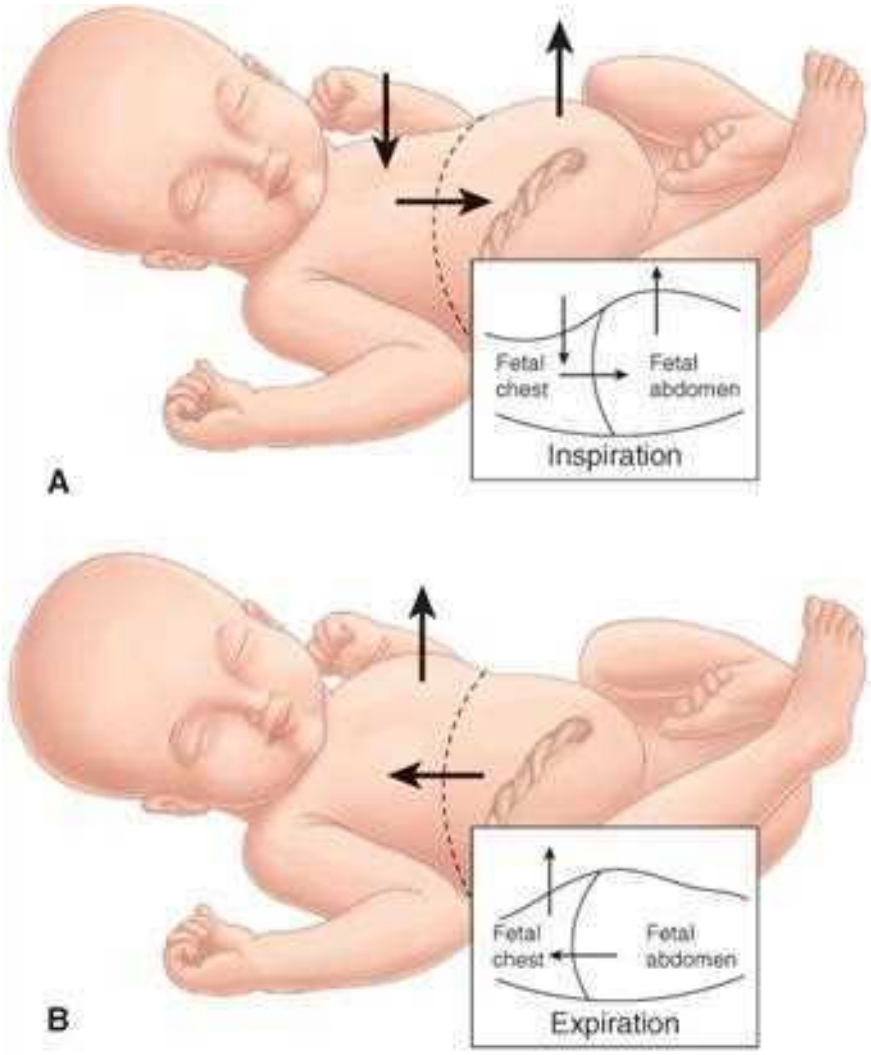
Saastad and associates (2011) reported a total of 1076 women who were randomly assigned to standardized fetal movement counting from gestational week 28 versus no counting. Growth-restricted fetuses were identified before birth significantly more often when fetal movement counting was used. The rate of 1-minute Apgar scores ≤3 was significant reduced (0.4 versus 2.3 percent) when counting was used. Also, Warrander and coworkers (2012) described placental pathology in pregnancies complicated by diminished fetal movements. Decreased movement was associated with various placental abnormalities including infarction.

FETAL BREATHING

After decades of uncertainty as to whether the fetus normally breathes, Dawes and coworkers (1972) showed small inward and outward flows of tracheal fluid in fetal sheep, indicating thoracic movement. These chest wall movements differed from those following birth in that they were discontinuous. Another interesting feature of fetal respiration was *paradoxical chest wall movement* (Fig. 17-3). In the newborn or adult, the opposite occurs. One interpretation of the paradoxical respiratory motion might be coughing to clear amnionic fluid debris. Although the physiological basis for the breathing reflex is not completely understood, such exchange of amnionic fluid appears to be essential for normal lung development (Chap. 7, Respiratory System). Dawes (1974) identified two types of respiratory movements. The first are *gasps* or *sighs,* which occurred at a frequency of 1 to 4 per minute. The second, *irregular bursts of breathing,* occurred at rates up to 240 cycles per minute. These latter rapid respiratory movements were associated with rapid eye movement. Badalian and associates (1993) studied the maturation of normal fetal breathing using color flow and spectral Doppler analysis of nasal fluid flow as an index of lung function. They suggested that fetal respiratory rate declined in conjunction with increased respiratory volume at 33 to 36 weeks and coincidental with lung maturation.

FIGURE 17-3

Paradoxical chest movement with fetal respiration. During inspiration **(A)**, the chest wall paradoxically *collapses* and the abdomen protrudes, whereas during expiration **(B)**, the chest wall *expands*. (Adapted from Johnson, 1988.)

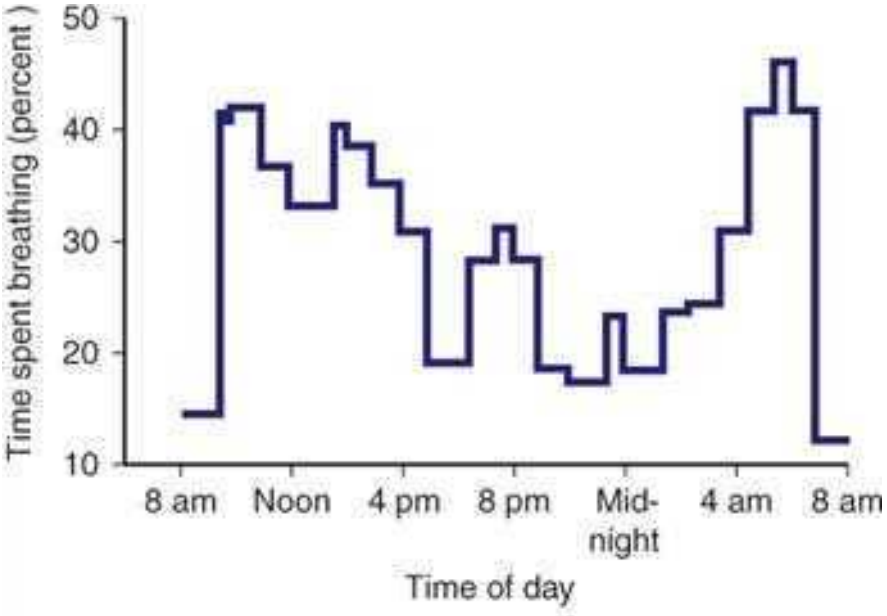


Many investigators have examined fetal breathing movements using sonography to determine whether chest wall movements might reflect fetal health. Several variables in addition to hypoxia were found to affect fetal respiratory movements. These included hypoglycemia, sound stimuli, cigarette smoking, amniocentesis, impending preterm labor, gestational age, the fetal heart rate itself, and labor—during which it is normal for respiration to cease.

Because fetal breathing movements are episodic, interpretation of fetal health when respirations are absent may be tenuous. Patrick and associates (1980) performed continuous 24-hour observation using sonography to characterize fetal breathing patterns during the last 10 weeks of pregnancy. A total of 1224 hours of fetal observation in 51 pregnancies were collected, and Figure 17-4 displays the percentages of time spent breathing near term. Clearly, there is diurnal variation, because breathing substantively diminishes during the night. In addition, breathing activity increases somewhat following maternal meals. Total absence of breathing was observed in some of these normal fetuses for up to 122 minutes, indicating that fetal evaluation to diagnose absent respiratory motion may require long periods of observation.

FIGURE 17-4

The percentage of time spent breathing by 11 fetuses at 38 to 39 weeks. There is a significant increase in fetal breathing activity after breakfast. Breathing activity diminished during the day and reached its minimum between 20:00 and 24:00 hours. There was a significant increase in the percentage of time spent breathing between 04:00 and 07:00 hours, when mothers were asleep. (Adapted with permission from Patrick J, Campbell K, Carmichael L, et al: Patterns of human fetal breathing during the last 10 weeks of pregnancy, Obstet Gynecol. 1980 Jul;56(1):24–30.)



The potential for breathing activity to be an important marker of fetal health is unfulfilled because of the multiplicity of factors that normally affect breathing. Most clinical applications have included assessment of other fetal biophysical indices, such as heart rate. As discussed subsequently, fetal breathing has become a component of the *biophysical profile.*

CONTRACTION STRESS TESTING

As amnionic fluid pressure rises with uterine contractions, myometrial pressure exceeds collapsing pressure for vessels coursing through uterine muscle. This ultimately lowers blood flow to the intervillous space. Brief periods of impaired oxygen exchange result, and if uteroplacental pathology is present, these elicit late fetal heart rate decelerations (Chap. 24, Late Deceleration). Contractions also may produce a pattern of variable decelerations as a result of cord compression, suggesting oligohydramnios, which is often a concomitant of placental insufficiency.

Ray and colleagues (1972) used this concept in 66 complicated pregnancies and developed the *oxytocin challenge test,* which was later called the *contraction stress test.* Intravenous oxytocin is used to stimulate contractions, and the criterion for a positive test result, that is, an abnormal result, is uniform repetitive late fetal heart rate decelerations. These reflected the uterine contraction waveform and had an onset at or beyond the contraction acme. Such late decelerations could be the result of uteroplacental insufficiency. In their study, the tests were generally repeated on a weekly basis, and the investigators concluded that negative contraction stress test results, that is, normal results, forecasted fetal health. A major disadvantage is that the average contraction stress test requires 90 minutes to complete.

To perform the test, the fetal heart rate and uterine contractions are recorded simultaneously with an external monitor. If at least three spontaneous contractions of 40 seconds or longer are present in 10 minutes, no uterine stimulation is necessary (American College of Obstetricians and Gynecologists, 2016). Contractions are induced with either oxytocin or nipple stimulation if there are fewer than three in 10 minutes. For oxytocin use, a dilute intravenous infusion is initiated at a rate of 0.5 mU/min and doubled every 20 minutes until a satisfactory contraction pattern is established (Freeman, 1975). The results of the contraction stress test are interpreted according to the criteria shown in Table 17-1.

Nipple stimulation to induce uterine contractions is usually successful for contraction stress testing (Huddleston, 1984). One method involves a woman rubbing one nipple through her clothing for 2 minutes or until a contraction begins. This 2-minute nipple stimulation ideally will induce a pattern of three contractions per 10 minutes. If not, after a 5-minute interval, she is instructed to retry nipple stimulation to achieve the desired pattern. If this is unsuccessful, then dilute oxytocin may be used.

Advantages include reduced cost and shortened testing times. Some have reported unpredictable uterine hyperstimulation and fetal distress, whereas others did not find excessive activity to be harmful (Frager, 1987; Schellpfeffer, 1985).

TABLE 17-1

Criteria for Interpretation of the Contraction Stress Test

Negative: no late or significant variable decelerations
Positive: late decelerations following 50% or more of contractions (even if the contraction frequency is fewer than three in 10 minutes)
Equivocal-suspicious: intermittent late decelerations or significant variable decelerations
Equivocal-hyperstimulatory: fetal heart rate decelerations that occur in the presence of contractions more frequent than every 2 minutes or lasting longer than 90 seconds
Unsatisfactory: fewer than three contractions in 10 minutes or an uninterpretable tracing

NONSTRESS TESTS

Freeman (1975) and Lee and colleagues (1975) introduced the *nonstress test* to describe fetal heart rate acceleration in response to fetal movement as a sign of fetal health. This test involved the use of Doppler-detected fetal heart rate acceleration coincident with fetal movements perceived by the mother. By the end of the 1970s, the nonstress test had become the primary method of testing fetal health. The nonstress test was easier to perform, and normal results were used to further discriminate false-positive contraction stress tests. Simplistically, the nonstress test is primarily a test of *fetal condition,* and it differs from the contraction stress test, which is considered a test of *uteroplacental function.* Currently, nonstress testing is the most widely used primary testing method for assessment of fetal well-being. It has also been incorporated into the biophysical profile testing system, subsequently discussed.

Fetal Heart Rate Acceleration

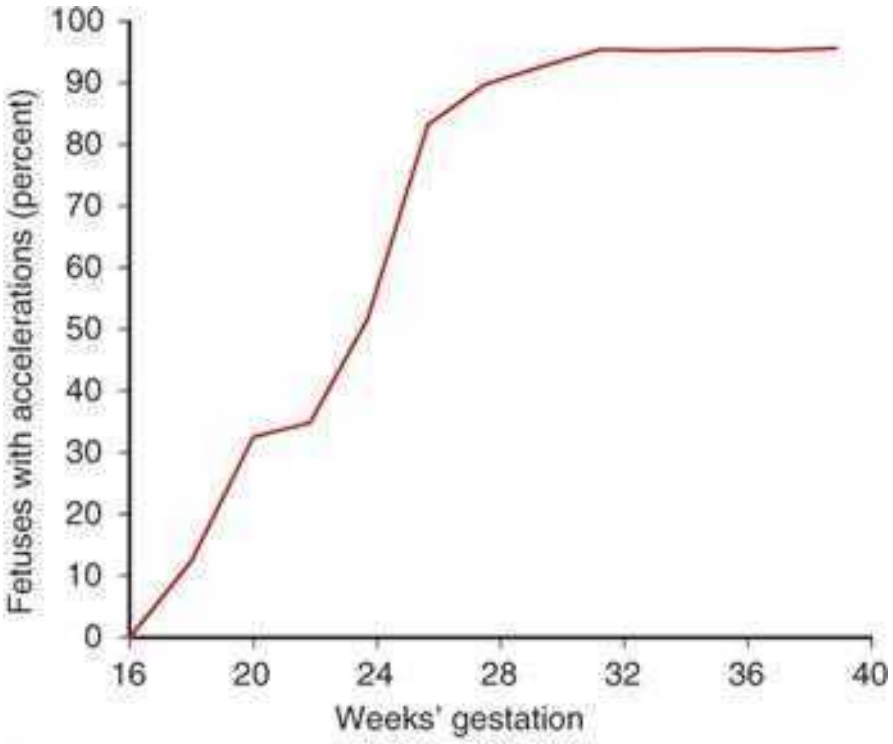
Autonomic influences are mediated by sympathetic or parasympathetic impulses from brainstem centers to normally raise or slow the fetal heart rate. *Beat-to-beat variability* is also under the control of the autonomic nervous system (Matsuura, 1996). Consequently, pathological loss of fetal heart rate acceleration may be seen in conjunction with significantly decreased beat-to-beat variability (Chap. 24, Cardiac Arrhythmia). Loss of such reactivity, however, is most commonly associated with sleep cycles. It also may be caused by central depression from medications or cigarette smoking (Jansson, 2005).

The nonstress test is based on the hypothesis that the heart rate of a fetus that is not acidemic as a result of hypoxia or neurological depression will temporarily accelerate in response to fetal movement. Fetal movements during testing are identified by maternal perception and recorded. As hypoxia develops, these fetal heart rate accelerations diminish (Smith, 1988).

Gestational age influences acceleration or reactivity of the fetal heart rate. Pillai and James (1990b) studied the development of fetal heart rate acceleration patterns during normal pregnancy. The percentage of body movements that is accompanied by accelerations and the amplitude of these accelerations both increase with gestational age (Fig. 17-5). Guinn and colleagues (1998) studied nonstress test results between 25 and 28 weeks' gestation in 188 normal fetuses. Only 70 percent of these normal fetuses demonstrated the required 15 beats per minute (bpm) or more of heart rate acceleration. Lesser degrees of acceleration, that is, 10 bpm, occurred in 90 percent of the fetuses.

FIGURE 17-5

Percentage of fetuses with at least one acceleration of 15 bpm sustained for 15 seconds concurrent with fetal movement. (Redrawn from Pillai M, James D: The development of fetal heart rate patterns during normal pregnancy, Obstet Gynecol. 1990 Nov;76(5 Pt 1):812–816.)



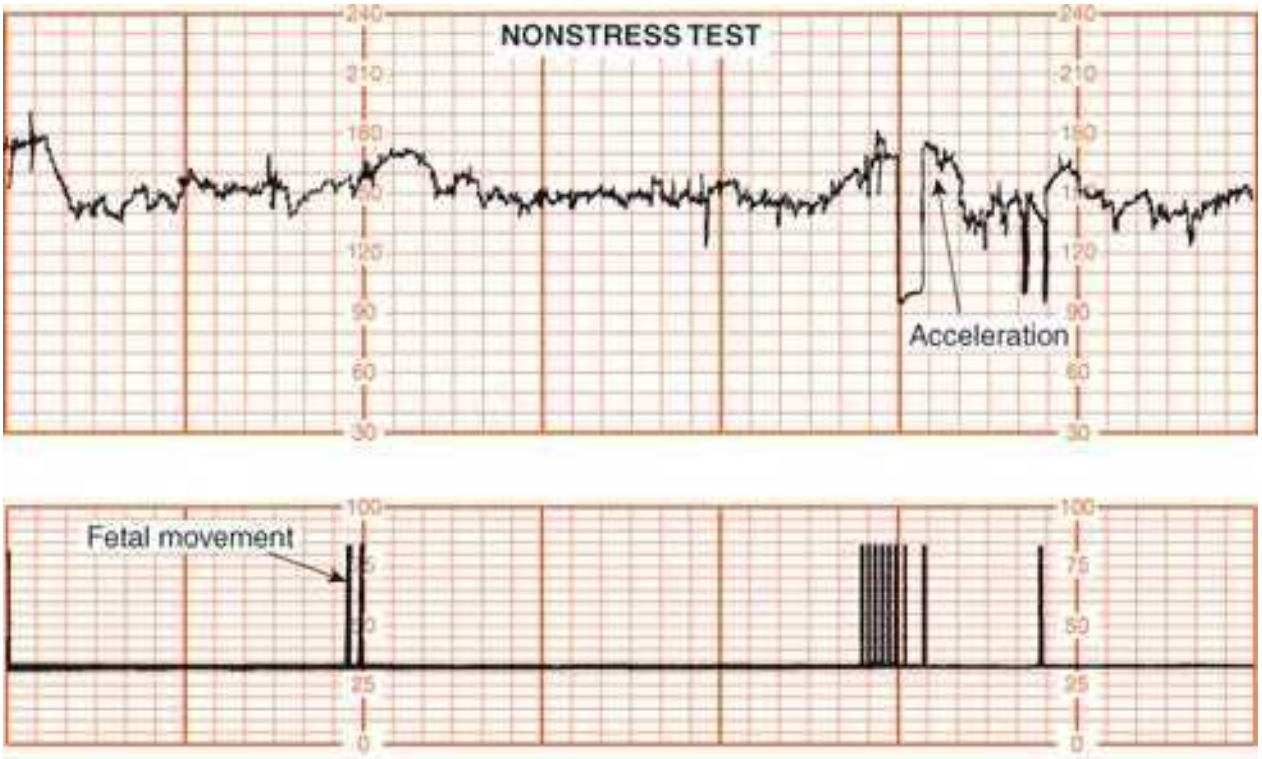
The National Institute of Child Health and Human Development Fetal Monitoring Workshop defined normal acceleration based on gestational age (Macones, 2008). In fetuses at or beyond 32 weeks' gestation, the acceleration acme is 15 bpm or more above the baseline rate, and the acceleration lasts 15 seconds or longer but less than 2 minutes. Before 32 weeks, normal accelerations are defined as having an acme that is 10 bpm or more above baseline for 10 seconds or longer. Cousins and associates (2012) compared the Workshop criteria recommended before 32 weeks, that is, 10 bpm/10 seconds, with standard 15 bpm/15 seconds criteria in a randomized trial of 143 women. They found no differences in perinatal outcomes.

Normal Nonstress Tests

Criteria to define normal nonstress test results differ. They vary regarding the number, amplitude, and duration of accelerations and the test duration. The definition recommended by the American College of Obstetricians and Gynecologists (2016) requires two or more accelerations peaking at 15 bpm or more above baseline, each lasting 15 seconds or more, and all occurring within 20 minutes of beginning the test (Fig. 17-6). It is also recommended that accelerations with or without fetal movements be accepted, and that a 40-minute or longer tracing—to account for fetal sleep cycles—should be performed before concluding that fetal reactivity is insufficient. Miller and coworkers (1996b) reviewed outcomes in fetuses with nonstress tests considered as nonreactive because there was only one acceleration. They concluded that one acceleration was just as reliable as two in predicting healthy fetal status.

FIGURE 17-6

Reactive nonstress test. In the upper panel, notice the increase of fetal heart rate by more than 15 beats/min for longer than 15 seconds following fetal movements, which are indicated by the vertical marks (*lower panel*).



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

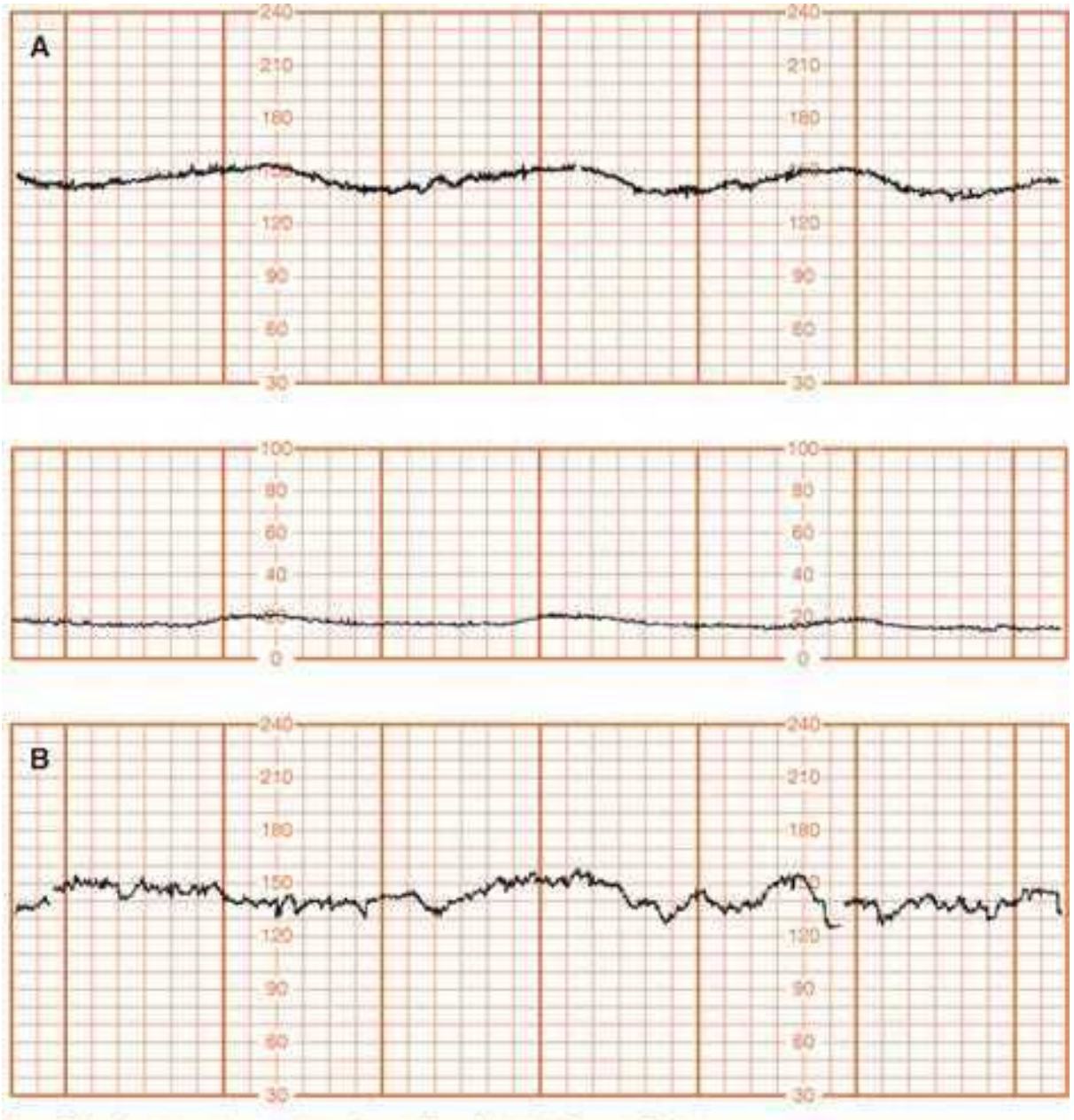
Although a normal number and amplitude of accelerations seems to reflect fetal well-being, their absence does not invariably predict fetal compromise. Indeed, some investigators have reported 90-percent or higher false-positive rates (Devoe, 1986). Because healthy fetuses may not move for periods of up to 75 minutes, some have considered that a longer duration of nonstress testing might increase the positive-predictive value of an abnormal, that is, nonreactive, test (Brown, 1981). In this scheme, either the test became reactive during a period up to 80 minutes or the test remained nonreactive for 120 minutes, which indicated that the fetus was very ill.

Not only do definitions of normal nonstress test results differ, but the reproducibility of interpretations is problematic (Hage, 1985). Thus, although nonstress testing is popular, the reliability of test interpretation needs improvement.

Abnormal Nonstress Tests

Based on the foregoing, an abnormal nonstress test is not always ominous and can be seen with a sleeping fetus. Also, an abnormal test can revert to normal as the fetal condition changes, such as the example shown in Figure 17-7. Importantly, a normal nonstress test can become abnormal if the fetal condition deteriorates.

FIGURE 17-7
Two antepartum fetal heart rate (FHR) tracings in a 28-week pregnant woman with diabetic ketoacidosis. **A.** FHR tracing (*upper panel*) and accompanying contraction tracing (*second panel*). Tracing, obtained during maternal and fetal acidemia, shows absence of accelerations, diminished variability, and late decelerations with weak spontaneous contractions. **B.** Fetal heart rate tracing shows return of normal accelerations and variability of the fetal heart rate following correction of maternal acidemia.



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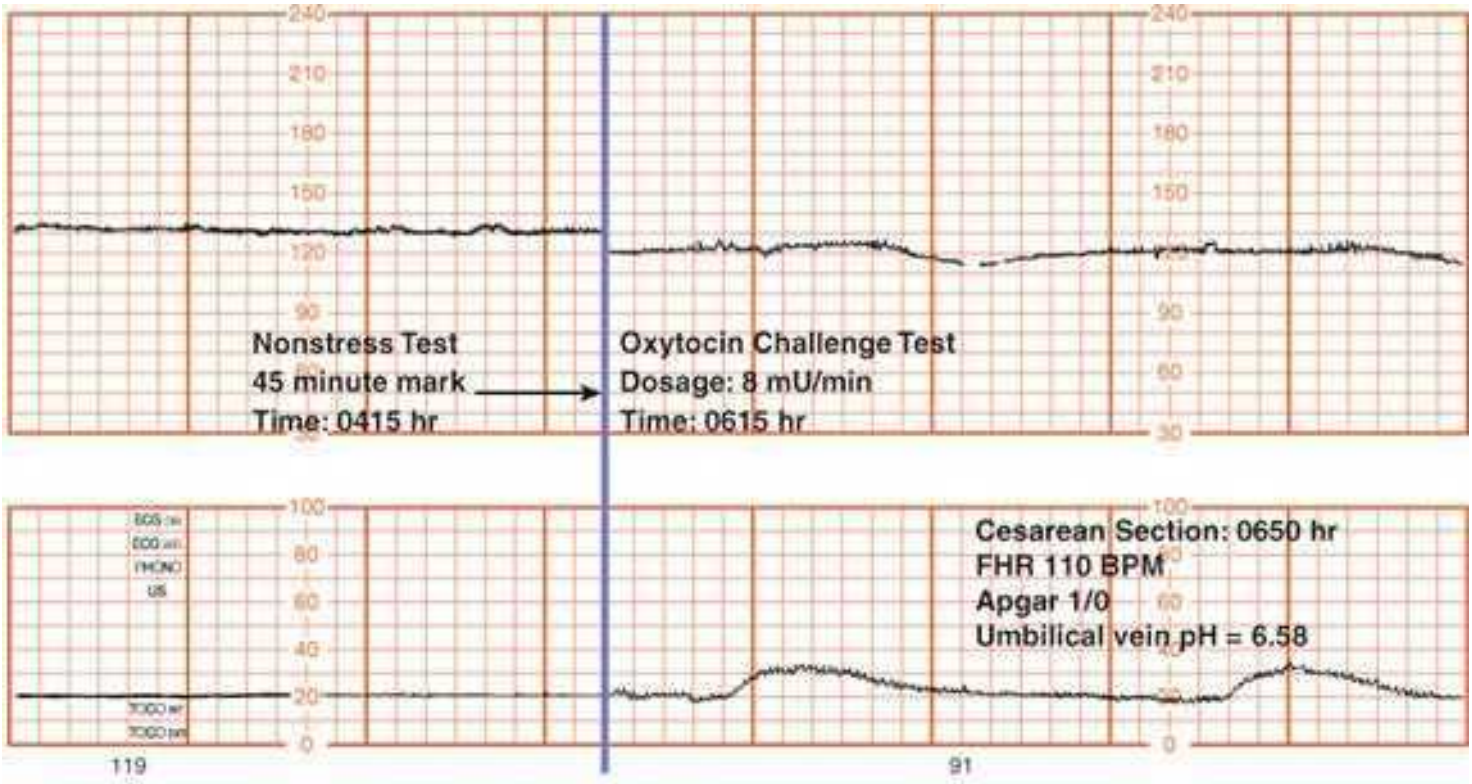
There are abnormal patterns that reliably forecast severe fetal jeopardy (Fig. 17-8). Devoe and coworkers (1985) concluded that nonstress tests that were nonreactive for 90 minutes were almost invariably—93 percent—associated with significant perinatal pathology. Hammacher and coworkers (1968) described tracings with what they termed a *silent oscillatory pattern* that he considered dangerous. This pattern consisted of a fetal heart rate baseline that oscillated less than 5 bpm and presumably indicated absent acceleration and beat-to-beat variability.

FIGURE 17-8

Nonreactive nonstress test (*left side of tracing*) followed by contraction stress test showing mild, late decelerations (*right side of tracing*). Cesarean delivery was performed, and the severely acidemic fetus could not be resuscitated.



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Visser and associates (1980) described a *terminal cardiotocogram,* which included: (1) baseline oscillation of less than 5 bpm, (2) absent accelerations, and (3) late decelerations with spontaneous uterine contractions. These results were similar to experiences from Parkland Hospital in which absence of accelerations during an 80-minute recording period in 27 fetuses was associated consistently with evidence of uteroplacental pathology (Leveno, 1983). The latter included fetal-growth restriction in 75 percent, oligohydramnios in 80 percent, fetal acidemia in 40 percent, meconium in 30 percent, and placental infarction in 93 percent.

Interval between Testing

Set originally rather arbitrarily at 7 days, the interval between tests appears to have been shortened as experience evolved with nonstress testing. According to the American College of Obstetricians and Gynecologists (2016), more frequent testing is advocated by some investigators for women with postterm pregnancy, multifetal gestation, pregestational diabetes, fetal-growth restriction, or pregnancy hypertension. In these circumstances, some investigators perform twice-weekly tests, with additional testing completed for maternal or fetal deterioration regardless of the time elapsed since the last test. Others perform nonstress tests daily or even more frequently, such as with severe preeclampsia remote from term.

Decelerations During Nonstress Testing

Fetal movements commonly produce heart rate decelerations. Timor-Tritsch and associates (1978) reported this during nonstress testing in half to two thirds of tracings, depending on the vigor of the fetal motion. This high incidence of decelerations inevitably makes interpretation of their significance problematic. Indeed, Meis and coworkers (1986) reported that variable fetal heart rate decelerations during nonstress tests were not a sign of fetal compromise. The American College of Obstetricians and Gynecologists (2016) has concluded that variable decelerations, if nonrepetitive and brief—less than 30 seconds—do not indicate fetal compromise or the need for obstetrical intervention. In contrast, repetitive variable decelerations—at least three in 20 minutes—even if mild, have been associated with a greater risk of cesarean delivery for

fetal distress. Decelerations lasting 1 minute or longer have been reported to have an even worse prognosis (Bourgeois, 1984; Druzin, 1981; Pazos, 1982).

Hoskins and associates (1991) attempted to refine interpretation of testing that shows variable decelerations by adding sonographic estimation of amnionic fluid volume. The incidence of cesarean delivery for intrapartum fetal distress progressively rose concurrently with the severity of variable decelerations and decline of amnionic fluid volume. Severe variable decelerations during a nonstress test plus an amnionic fluid index (AFI) ≤5 cm resulted in a 75-percent cesarean delivery rate. Fetal distress in labor, however, also frequently developed in those pregnancies with variable decelerations but with normal amounts of amnionic fluid. Similar results were reported by Grubb and Paul (1992).

False-Normal Nonstress Tests

Smith and associates (1987) performed a detailed analysis of the causes of fetal death within 7 days of normal nonstress tests. The most common indication for testing was postterm pregnancy. The mean interval between testing and death was 4 days, with a range of 1 to 7 days. The single most common autopsy finding was meconium aspiration, often associated with some type of umbilical cord abnormality. They concluded that an acute asphyxial insult had provoked fetal gasping. They also concluded that nonstress testing was inadequate to preclude such an acute asphyxial event and that other biophysical characteristics might be beneficial. Importantly, assessment of amnionic fluid volume was considered valuable. Other ascribed frequent causes of fetal death included intrauterine infection, abnormal cord position, malformations, and placental abruption.

ACOUSTIC STIMULATION TESTS

Loud external sounds have been used to startle the fetus and thereby provoke heart rate acceleration—an *acoustic stimulation nonstress test*. A commercially available acoustic stimulator is positioned on the maternal abdomen, and a stimulus of 1 to 2 seconds is applied (Eller, 1995). This may be repeated up to three times for up to 3 seconds (American College of Obstetricians and Gynecologists, 2016). A positive response is defined as the rapid appearance of a qualifying acceleration following stimulation (Devoe, 2008). In a randomized trial of 113 women undergoing nonstress testing, vibroacoustic stimulation shortened the average time of testing from 24 to 15 minutes (Perez-Delboy, 2002). Similar results were reported by Turitz and coworkers (2012). Laventhal and colleagues (2003) reported that fetal tachyarrhythmia could be provoked with vibroacoustic stimulation.

BIOPHYSICAL PROFILE

Manning and colleagues (1980) proposed the combined use of five fetal biophysical variables as a more accurate means of assessing fetal health than a single element. Typically, these tests require 30 to 60 minutes of examiner time. Shown in Table 17-2 are the five fetal biophysical components assessed: (1) heart rate acceleration, (2) breathing, (3) movements, (4) tone, and (5) amnionic fluid volume. Normal variables were assigned a score of 2 each, and abnormal variables were given a score of 0. Thus, the highest score possible for a normal fetus is 10. Maternal medications such as narcotics and sedatives can significantly lower the score (Kopecky, 2000). Ozkaya and associates (2012) found that biophysical test scores were higher if a test was performed in late evening—20:00 to 22:00 hours—compared with 08:00 to 10:00 hours.

TABLE 17-2

Components and Scores for the Biophysical Profile

Component	Score 2	Score 0
Nonstress test[a]	≥2 accelerations of ≥15 beats/min for ≥15 sec within 20–40 min	0 or 1 acceleration within 20–40 min
Fetal breathing	≥1 episode of rhythmic breathing lasting ≥30 sec within 30 min	<30 sec of breathing within 30 min
Fetal movement	≥3 discrete body or limb movements within 30 min	<3 discrete movements
Fetal tone	≥1 episode of extremity extension and subsequent return to flexion	0 extension/flexion events
Amnionic fluid volume[b]	A pocket of amnionic fluid that measures at least 2 cm in two planes perpendicular to each other (2 × 2 cm pocket)	Largest single vertical pocket ≤2 cm

[a]May be omitted if all four sonographic components are normal.

[b]Further evaluation warranted, regardless of biophysical composite score, if largest vertical amnionic fluid pocket ≤2 cm.

Manning and colleagues (1987) tested more than 19,000 pregnancies using the biophysical profile interpretation and management shown in Table 17-3. More than 97 percent of the pregnancies tested had normal test results. They reported a false-normal test rate—defined by an antepartum death of a structurally normal fetus—of approximately 1 per 1000. The most common identifiable causes of fetal death after a normal biophysical profile include fetomaternal hemorrhage, umbilical cord accidents, and placental abruption (Dayal, 1999).

TABLE 17-3

Interpretation of Biophysical Profile Score

Biophysical Profile Score	Interpretation	Recommended Management
10	Normal, nonasphyxiated fetus	No fetal indication for intervention; repeat test weekly except in diabetic patients and postterm pregnancy (twice weekly)
8/10 (Normal AFV)	Normal, nonasphyxiated fetus	No fetal indication for intervention; repeat testing per protocol
8/8 (NST not done)		
8/10 (Decreased AFV)	Chronic fetal asphyxia suspected	Deliver
6	Possible fetal asphyxia	If amnionic fluid volume abnormal, deliver
		If normal fluid at >36 weeks with favorable cervix, deliver
		If repeat test ≤6, deliver
		If repeat test >6, observe and repeat per protocol
4	Probable fetal asphyxia	Repeat testing same day; if biophysical profile score ≤6, deliver
0 to 2	Almost certain fetal asphyxia	Deliver

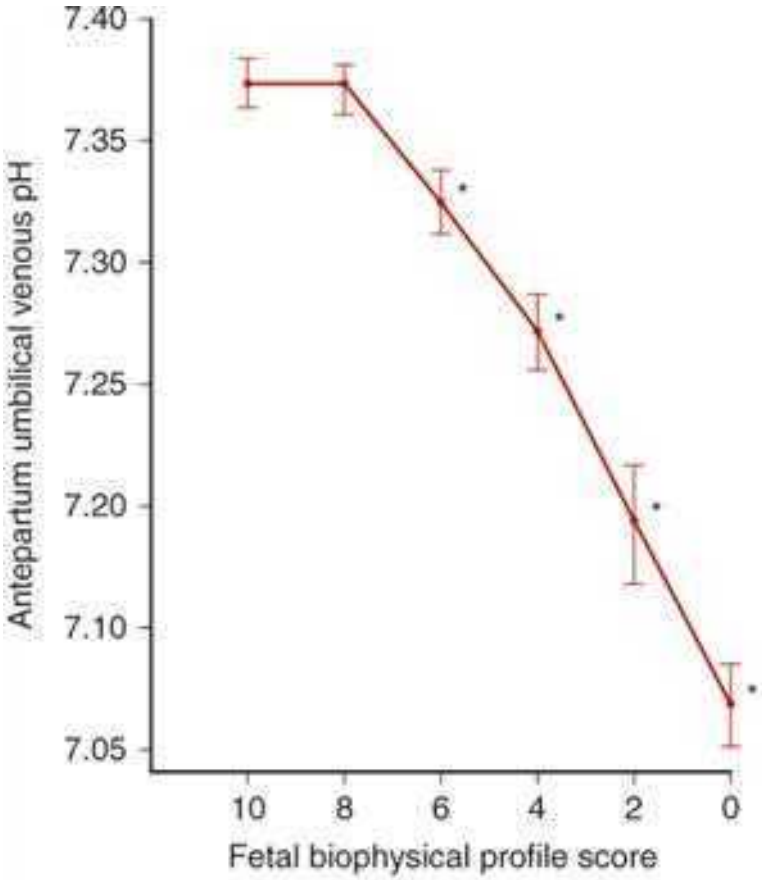
AFV = amnionic fluid volume; NST = nonstress test.

Reproduced with permission from Manning FA, Morrison I, Harman CR, et al: Fetal assessment based on fetal biophysical profile scoring: experience in 19,221 referred high-risk pregnancies. II. An analysis of false-negative fetal deaths, Am J Obstet Gynecol. 1987 Oct;157(4 Pt 1):880–884.

Manning and coworkers (1993) published a remarkable description of 493 fetuses in which biophysical scores were performed immediately before measurement of umbilical venous blood pH values obtained via antepartum cordocentesis. Approximately 20 percent of tested fetuses had growth restriction, and the remainder had alloimmune hemolytic anemia. As shown in Figure 17-9, a biophysical score of 0 was almost invariably associated with significant fetal acidemia, whereas a normal score of 8 or 10 was associated with normal pH. An equivocal test result—a score of 6—was a poor predictor of abnormal outcome. As the abnormal score dropped from 2 or 4 down to 0, this decline was a more accurate predictor of abnormal fetal outcome. Thus overall, these scores provide poor sensitivity to predict cord blood pH.

FIGURE 17-9

Mean umbilical vein pH (±2 SD) obtained by cordocentesis in relation to fetal biophysical profile score category. (Data from Manning, 1993.)



Similar studies have substantiated these findings. Salvesen and associates (1993) concluded that the biophysical profile was of limited value in the prediction of fetal pH. Weiner and coworkers (1996) assessed 135 overtly growth-restricted fetuses and came to a similar conclusion. Kaur and colleagues (2008) performed daily biophysical profiles to ascertain the optimal delivery time in 48 growth-restricted preterm fetuses that weighed less than 1000 g. Despite scores of 8 in 27 fetuses and 6 in 13, there were six deaths and 21 acidemic fetuses. Lalor and associates (2008) performed a Cochrane review and concluded that there is insufficient evidence to support the use of the biophysical profile as a fetal well-being test in high-risk pregnancies.

Modified Biophysical Profile

Because the biophysical profile is labor intensive and requires a person trained in sonography, Clark and coworkers (1989) used an abbreviated biophysical profile as a first-line screening test in 2628 singleton pregnancies. Specifically, a vibroacoustic nonstress test was performed twice weekly and combined with AFI determination for which ≤5 cm was considered abnormal (Chap. 11, Oligohydramnios). This abbreviated biophysical profile required approximately 10 minutes to perform, and they concluded that it was a superb antepartum surveillance method because there were no unexpected fetal deaths.

Nageotte and colleagues (1994) also combined biweekly nonstress tests with the AFI and considered measures ≤5 cm to be abnormal. They performed 17,429 modified biophysical profiles in 2774 women and concluded that such testing was an excellent fetal surveillance tool. Miller and associates (1996a) reported results with more than 54,000 modified biophysical

profiles performed in 15,400 high-risk pregnancies. They described a false-negative rate of 0.8 per 1000 and a false-positive rate of 1.5 percent.

The American College of Obstetricians and Gynecologists (2016) has concluded that the modified biophysical profile test is as predictive of fetal well-being as other approaches to biophysical fetal surveillance.

AMNIONIC FLUID VOLUME

The importance of amnionic fluid volume estimation is indicated by its inclusion into virtually all schemes in which fetal health is assessed (Frøen, 2008). This is based on the rationale that diminished uteroplacental perfusion may lead to lower fetal renal blood flow, decreased urine production, and ultimately, oligohydramnios (Chap. 11, Pregnancy Outcomes). The American College of Obstetricians and Gynecologists (2016) concludes that data available from randomized trials indicate that the use of the deepest vertical pocket measurement, as opposed to the AFI, to diagnose oligohydramnios is associated with a reduction in unnecessary interventions without an increase in adverse perinatal outcomes (Nabhan, 2008; Reddy, 2014).

DOPPLER VELOCIMETRY

Blood flow velocity measured by Doppler ultrasound reflects downstream impedance (Chap. 10, Doppler). For growth-restricted fetuses, several fetal vascular circuits including the umbilical artery, middle cerebral artery, and ductus venosus have been evaluated as diagnostic tools for fetal well-being (Chap. 44, Prevention). Maternal uterine artery Doppler velocimetry has also been assessed as a modality to predict placental dysfunction, with the goal to balance stillbirth against the risks of preterm delivery (Ghidini, 2007). Even the effects of sildenafil in pregnant sheep have been evaluated using Doppler velocimetry (Alanne, 2017). The rationale is that sildenafil would improve placental blood flow in the presence of placental insufficiency. This proved untrue, as sildenafil was associated with detrimental effects on fetal cardiovascular dynamics.

Doppler Blood Flow Velocity

Waveforms were first studied in the umbilical arteries late in pregnancy, and abnormal waveforms correlated with placental villous hypovascularity. Of the small placental arterial channels, 60 to 70 percent need to be obliterated before the umbilical artery Doppler waveform becomes abnormal. Such extensive placental vascular pathology has a major effect on fetal circulation. According to Trudinger (2007), because more than 40 percent of the combined fetal ventricular output is directed to the placenta, obliteration of placental vascular channel increases afterload and leads to fetal hypoxemia. This in turn leads to ventricular dilation and redistribution of middle cerebral artery blood flow. Ultimately, pressure rises in the ductus venosus due to afterload in the right side of the fetal heart (Baschat, 2004). Clinically, abnormal Doppler waveforms in the ductus venosus are a late finding in the progression of fetal deterioration due to chronic hypoxemia.

Umbilical Artery Velocimetry

The umbilical artery systolic-diastolic (S/D) ratio is considered abnormal if it is >95th percentile for gestational age or if diastolic flow is either absent or reversed (Chap. 10, Doppler). Absent or reversed end-diastolic flow signifies greater impedance to umbilical artery blood flow (Fig. 44-8). It is reported to result from poorly vascularized placental villi and is seen in extreme cases of fetal-growth restriction (Todros, 1999). According to Zelop and colleagues (1996), the perinatal mortality rate for absent end-diastolic flow was about 10 percent, and for reversed end-diastolic flow, it approximated 33 percent.

Spinillo and associates (2005) studied neurodevelopmental outcome at 2 years of age in 266 growth-restricted fetuses delivered between 24 and 35 weeks' gestation. Of infants who had shown absent or reversed umbilical artery flow, 8 percent had evidence of cerebral palsy compared with 1 percent of those in whom Doppler flow had been normal.

Doppler ultrasound of the umbilical artery has been subjected to more extensive assessment with randomized controlled trials than has any previous test of fetal health. Williams and colleagues (2003) randomized 1360 high-risk women to either nonstress testing or Doppler velocimetry. They found a significantly higher incidence of cesarean delivery for fetal distress in the nonstress test group compared with that for those tested with Doppler velocimetry—8.7 versus 4.6 percent, respectively. One interpretation of this finding is that the nonstress test more frequently identified fetuses in jeopardy. Conversely, Gonzalez and associates (2007) found that abnormal umbilical artery Doppler findings in a cohort of growth-restricted fetuses were the best predictors of perinatal outcomes.

The utility of umbilical artery Doppler velocimetry was reviewed by the American College of Obstetricians and Gynecologists (2016). They concluded that no benefit has been demonstrated other than in pregnancies with suspected fetal-growth restriction. Similarly, velocimetry has not proved valuable as a screening test for fetal compromise in the general obstetrical population.

Various other fetal-maternal Doppler indices have been studied, including the fetal middle cerebral artery and ductus venosus and the uterine arteries. The American College of Obstetricians and Gynecologists (2016) concluded that Doppler investigations of other blood vessels besides the umbilical artery have not been shown to improve perinatal outcome.

Middle Cerebral Artery

As discussed, at this time, Doppler velocimetry interrogation of the middle cerebral artery (MCA) to detect fetal compromise is not recommended. Still, the technology has received particular attention because of observations that the hypoxic fetus attempts *brain sparing* by reducing cerebrovascular impedance and thus increasing blood flow. Such brain sparing in growth-restricted fetuses has been documented to undergo reversal (Konje, 2001). Investigators reported that 8 of 17 fetuses with this reversal died. Ott and coworkers (1998) randomized 665 women undergoing modified biophysical profile evaluation to either the profile alone or combined with middle cerebral and umbilical artery velocity flow assessment. Pregnancy outcomes between these two study groups did not differ significantly.

Middle cerebral artery Doppler velocimetry has proven valuable to detect severe fetal anemia in 165 fetuses with d-antigen alloimmunization. Oepkes and colleagues (2006) prospectively compared serial amniocentesis for measurement of bilirubin levels with Doppler measurement of peak systolic velocity in the middle cerebral artery. These investigators concluded that Doppler could safely replace amniocentesis in the management of alloimmunized pregnancies. And as discussed in Chapter 15 (Management of the Alloimmunized Pregnancy), this technique has been reported to be useful for detection and management of fetal anemia of any cause (Moise, 2008).

Ductus Venosus

Doppler ultrasound has also been used to assess the fetal venous circulation. Bilardo and colleagues (2004) prospectively studied umbilical artery and ductus venosus Doppler velocimetry in 70 growth-restricted fetuses at 26 to 33 weeks' gestation. They concluded that ductus venosus velocimetry was the best predictor of perinatal outcome. Importantly, negative or reversed flow in the ductus venosus was a late finding because these fetuses had already sustained irreversible multiorgan damage due to hypoxemia. Also, gestational age at delivery was a major determinant of perinatal outcome independent of ductus venosus flow. Specifically, 36 percent of growth-restricted fetuses delivered between 26 and 29 weeks' gestation succumbed compared with only 5 percent delivered from 30 to 33 weeks.

Baschat and coworkers (2007) studied 604 growth-restricted fetuses using umbilical artery, middle cerebral artery, and ductus venosus Doppler velocimetry and reached similar conclusions. Specifically, absent or reversed flow in the ductus venosus was associated with profound generalized fetal metabolic collapse. They too reported that gestational age was a powerful cofactor in ultimate perinatal outcome for growth-restricted fetuses delivered before 30 weeks. Put another way, by the time severely abnormal flow is seen in the ductus venosus, it is too late because the fetus is already near death. Conversely, earlier delivery puts the fetus at risk for death due to preterm delivery. Ghidini (2007) concluded that these reports do not support routine use of ductus venosus Doppler in the monitoring of growth-restricted fetuses and recommended further study.

Uterine Artery

Vascular resistance in the uterine circulation normally decreases in the first half of pregnancy due to invasion of maternal uterine vessels by trophoblastic tissue (Chap. 5, Endometrial Cycle). This process can be detected using Doppler flow velocimetry, and uterine artery Doppler may be most helpful in assessing pregnancies at high risk of uteroplacental insufficiency (Abramowicz, 2008). Persistence or development of high-resistance patterns has been linked to various pregnancy complications (Lees, 2001; Yu, 2005). In a study of 30,519 unselected British women, Smith and colleagues (2007) assessed uterine artery velocimetry at 22 to 24 weeks' gestation. The risk of fetal death before 32 weeks, when associated with abruption, preeclampsia, or fetal-growth restriction, was significantly linked to high-resistance flow. This has led to suggestions for continued research of uterine artery Doppler velocimetry as a screening tool to detect pregnancies at risk for stillbirth (Reddy, 2008). Sciscione and Hayes (2009) reviewed the use of uterine artery Doppler flow studies in obstetrical practice. Because standards for the study technique and criteria for an abnormal test are lacking, they noted that uterine artery Doppler studies should not be considered standard practice in either low- or high-risk populations.

ANTENATAL TESTING SUMMARY

Antenatal forecasts of fetal health have clearly been the focus of intense interest, and several themes emerge. First, despite a continuous evolution of testing options, the precision or efficacy of any given method is limited. Second, the wide range of normal biological fetal variation makes interpretation of test results challenging. Last, despite the invention of increasingly complex testing methods, abnormal results are seldom reliable, prompting many clinicians to use antenatal testing to forecast fetal *wellness* rather than *illness.*

Platt and coworkers (1987) reviewed the efficacy of antenatal testing between 1971 and 1985 at Los Angeles County Hospital. During this 15-year period, more than 200,000 pregnancies were managed, and nearly 17,000 of these women underwent antepartum testing of various types. Fetal surveillance rose from <1 percent of pregnancies in the early 1970s to 15 percent in the mid-1980s. These authors concluded that such testing was clearly beneficial because the fetal death rate was significantly less in the tested high-risk pregnancies compared with the rate in those not tested. The study, however, did not consider other innovations incorporated into practice during those 15 years. Preliminary results from Ghana suggest that nonstress testing may be beneficial in low-resource countries (Lawrence, 2016). In an observational study of 316 pregnancies complicated by gestational hypertension, women undergoing nonstress testing had a nonsignificant decreased risk for stillbirth compared with those not tested—3.6 versus 9.2 percent, respectively.

The benefits of antenatal fetal testing have not been sufficiently evaluated in randomized controlled trials according to Thacker and Berkelman (1986). This was concluded after reviewing 600 reports, which included only four randomized trials that were not powered to permit detection of important benefits. From their review, Enkin and colleagues (2000) concluded that "despite their widespread use, most tests of fetal well-being should be considered of experimental value only rather than validated clinical tools."

Another important and unanswered question is whether antepartum fetal surveillance identifies fetal asphyxia early enough to prevent brain damage. Manning and coworkers (1998) studied the incidence of cerebral palsy in 26,290 high-risk pregnancies managed with serial biophysical profile testing. These outcomes were compared with those of 58,657 low-risk pregnancies in which antepartum testing was not performed. The rate of cerebral palsy was 1.3 per 1000 in tested pregnancies compared with 4.7 per 1000 in untested women. Todd and coworkers (1992) attempted to correlate cognitive development in infants up to age 2 years following either abnormal umbilical artery Doppler velocimetry or nonstress test results. Only abnormal nonstress tests were associated with marginally poorer cognitive outcomes. These investigators concluded that by the time fetal compromise is diagnosed with antenatal testing, fetal damage has already been sustained. Low and associates (2003) reached a similar conclusion.

According to the American College of Obstetricians and Gynecologists (2016), a *normal* antepartum fetal test result is highly reassuring that a stillbirth will not occur within 1 week. This conclusion was reached after an analysis of reports of stillbirth rates associated with the various antepartum fetal heart rate tests (Table 17-4). Note that these results are corrected to remove lethal anomalies and unpredictable catastrophes such as placental abruption or cord accidents. The most important consideration in deciding when to begin antepartum testing is the prognosis for neonatal survival.

The severity of maternal disease is another. In general, with most high-risk pregnancies, testing begins by 32 to 34 weeks' gestation. Pregnancies with severe complications might require testing as early as 26 to 28 weeks. The frequency for repeating tests has been arbitrarily set at 7 days, but more frequent testing is often done.

TABLE 17-4

Stillbirth Rates within 1 Week of a Normal Antepartum Fetal Surveillance Test

Antepartum Fetal Test	Stillbirth[a] Rate/1000	Number
Nonstress test	1.9	5861
Contraction stress test	0.3	12,656
Biophysical profile	0.8	44,828
Modified biophysical profile	0.8	54,617

[a]Corrected for lethal anomalies and unpredictable causes of fetal death such as abruption or cord accident.

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CHAPTER 18: Abortion

In the early months of pregnancy spontaneous expulsion of the ovum is nearly always preceded by the death of the foetus. For this reason the consideration of the aetiology of abortion practically resolves itself into determining the cause of foetal death. In the later months, on the other hand, the foetus is frequently born alive, and other factors must be looked for to explain its expulsion.

—J. Whitridge Williams (1903)

INTRODUCTION

In early pregnancy, miscarriage is a common event. Most early losses stem from genetic abnormalities or yet unidentified reasons. Thus, the opportunity for prevention is currently small. Women with later miscarriage or with recurrent miscarriage more likely have a repetitive cause that may be modified. In contrast to these spontaneous losses, pregnancy termination may be elected. For both induced abortion and miscarriage, management has evolved to include surgical or medical options, and providers should have an understanding of these techniques and their potential complications.

NOMENCLATURE

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability. It thus is appropriate that miscarriage and abortion are terms used interchangeably. However, popular use of *abortion* by laypersons implies intended pregnancy termination, and many prefer *miscarriage* for spontaneous loss. In contrast, *induced abortion* describes surgical or medical termination of a live fetus that has not reached viability.

Terms used to define fetal viability and thus an abortus vary among authoritative organizations. The National Center for Health Statistics, the Centers for Disease Control and Prevention, and the World Health Organization all define *abortion* as pregnancy termination or loss before 20 weeks' gestation or with a fetus delivered weighing <500 g. These criteria, however, are somewhat contradictory because the mean birthweight of a 20-week fetus is 320 g, whereas 500 g is the mean for 22 to 23 weeks (Moore, 1977). Further confusion may derive from criteria set by state laws that define abortion even more widely.

Technological developments have added to current abortion terminology. For example, precise measurement of serum human chorionic gonadotropin (hCG) concentrations can identify extremely early pregnancies. Also, transvaginal sonography allows greater inspection of failed pregnancies, but recommendations vary as to terms for: (1) early conceptions in which no products are seen sonographically, (2) pregnancies that display a gestational sac but no embryo, and (3) those in which a dead embryo is seen (Kolte, 2015; Silver, 2011). Further, incongruity exists for the term *early pregnancy loss* itself. Currently, the American College of Obstetricians and Gynecologists (2017c) defines this as a nonviable, intrauterine pregnancy (IUP) with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first $12^{6/7}$ weeks of gestation. Of other clinical terms, *spontaneous abortion* includes threatened, inevitable, incomplete, complete, and missed abortion. Septic abortion is used to further classify any of these that are complicated further by infection. *Recurrent pregnancy loss* is variably defined but is meant to identify women with repetitive miscarriage.

Other definitions help distinguish intrauterine from ectopic gestations. The term *pregnancy of unknown location (PUL)* describes a pregnancy identified by hCG testing but without a confirmed sonographic location. In this context, five categories are proposed for early pregnancies: definite ectopic pregnancy, probable ectopic, PUL, probable IUP, and definite IUP (Barnhart, 2011). Diagnostic and management options for ectopic gestation are described in Chapter 19 (Multimodality Diagnosis).

FIRST-TRIMESTER SPONTANEOUS ABORTION

Pathogenesis

More than 80 percent of spontaneous abortions occur within the first 12 weeks of gestation. With first-trimester losses, demise of the embryo or fetus nearly always precedes spontaneous expulsion. Death is usually accompanied by hemorrhage into the decidua basalis. This is followed by adjacent tissue necrosis that stimulates uterine contractions and expulsion. An intact gestational sac is usually filled with fluid. An *anembryonic miscarriage* contains no identifiable embryonic elements. Less accurately, the term blighted ovum may be used (Silver, 2011). The others are *embryonic miscarriages*, which often display a developmental abnormality of the embryo, fetus, yolk sac, and, at times, the placenta. In contrast, in later pregnancy losses, the fetus usually does not die before expulsion, and other sources for abortion are sought.

Incidence

Rates for miscarriage vary according to the study population. In pregnancies aged 5 to 20 weeks' gestation, the incidence ranges from 11 to 22 percent and is higher in earlier weeks (Ammon Avalos, 2012). To evaluate rates starting at conception, Wilcox and colleagues (1988) studied 221 healthy women trying to conceive through 707 menstrual cycles and found a miscarriage rate of 31 percent. This study found that two thirds of these losses are early and *clinically silent*. Currently, certain factors are known to influence *clinically apparent* miscarriage. However, it is unknown if these same factors also affect clinically silent pregnancy loss.

Fetal Factors

Of all miscarriages, approximately half are *euploid abortions,* that is, carrying a normal chromosomal complement. The other half has a chromosomal abnormality. Initially determined by tissue karyotyping, this percentage appears to persist even when implementing newer cytogenetic techniques (Jenderny, 2014). Notably, the American College of Obstetricians and Gynecologists (2016d) does not recommend routine use of chromosomal microarray testing of first-trimester fetal tissues. However, these organizations, and the American Society for Reproductive Medicine (2012), recognize its value if cytogenetic analysis alters future care.

Both abortion and chromosomal anomaly rates decline with advancing gestational age (Ammon Avalos, 2012; Eiben, 1990). Kajii and associates (1980) noted that 75 percent of chromosomally abnormal abortions occurred by 8 weeks' gestation. Of chromosomal abnormalities, 95 percent are caused by maternal gametogenesis errors, and 5 percent by paternal errors (Jacobs, 1980). Most common abnormalities are trisomy, found in 50 to 60 percent; monosomy X, in 9 to 13 percent; and triploidy, in 11 to 12 percent (Eiben, 1980; Jenderny, 2014).

Trisomies typically result from isolated nondisjunction, rates of which rise with maternal age (Boué, 1975). Trisomies of chromosomes 13, 16, 18, 21, and 22 are most common. In contrast, balanced structural chromosomal rearrangements may originate from either parent and are found in 2 to 4 percent of couples with recurrent pregnancy loss.

Monosomy X (45,X) is the single most frequent specific chromosomal abnormality. This is *Turner syndrome*, which usually results in abortion, but liveborn females are described in Chapter 13 (Polyploidy). Conversely, *autosomal monosomy* is rare and incompatible with life.

Triploidy is often associated with hydropic or molar placental degeneration (Chap. 20, Epidemiology and Risk Factors). The fetus within a partial hydatidiform mole frequently aborts early, and the few carried longer are all grossly deformed. Advanced maternal and paternal ages do not increase the incidence of triploidy. *Tetraploid* fetuses most often abort early in gestation, and they are rarely liveborn.

Maternal Factors

In chromosomally normal pregnancy losses, maternal influences play a role. The causes of euploid abortions are poorly understood, but various medical disorders, environmental conditions, and developmental abnormalities have been implicated.

Euploid pregnancies abort later than aneuploid ones. Specifically, the rate of euploid abortion peaks at approximately 13 weeks (Kajii, 1980). In addition, the incidence of euploid abortion rises dramatically after maternal age exceeds 35 years (Stein, 1980).

Infections

Some common viruses, bacteria, and parasites that invade the normal human can infect the fetoplacental unit by blood-borne transmission. Others may infect locally through genitourinary infection or colonization. However, despite the numerous infections acquired in pregnancy and discussed in Chapters 64 and 65, these uncommonly cause early abortion.

Medical Disorders

Some disorders are possibly linked with higher rates of early pregnancy loss and are discussed in their respective chapters. Prominent risks are associated with poorly controlled diabetes mellitus, obesity, thyroid disease, and systemic lupus erythematosus. In these and others, inflammatory mediators may be an underlying theme (Kalagiri, 2016; Sjaarda, 2017). Although thrombophilias were initially linked to various pregnancy outcomes, most putative associations have been refuted (American College of Obstetricians and Gynecologists (2017e).

Cancer

Therapeutic doses of radiation are undeniably abortifacient. Doses that cause abortion are not precisely known, but suggested parameters are found in Chapter 46 (X-Ray Dosimetry). Similarly, the effects of chemotherapy exposure in causing abortion are not well defined (Chap. 12, Antimicrobial Drugs). Particularly worrisome are women with an ongoing pregnancy after early exposure to methotrexate, described later (Medical Abortion). Of cancer survivors, those who were treated with abdominopelvic radiotherapy or chemotherapy may later be at greater risk for miscarriage, as discussed in Chapter 63 (Reproductive Tract Neoplasms).

Surgical Procedures

The risk of miscarriage caused by surgery is not well studied. But, as discussed in Chapter 46 (Medications and Surgeries), *uncomplicated* surgical procedures performed during early pregnancy are unlikely to increase the abortion risk (Mazze, 1989). Of indications, ovarian tumors can generally be resected without inciting miscarriage. An important exception involves early removal of the corpus luteum or the ovary in which it resides. If performed before 10 weeks' gestation, supplemental progesterone should be given, and supplementation is enumerated in Chapter 63 (Diagnosis).

Trauma seldom causes first-trimester miscarriage, and although Parkland Hospital is a busy trauma center, this is an infrequent association. Major trauma—especially abdominal—can cause fetal loss, but is more likely as pregnancy advances (Chap. 47, Trauma).

Nutrition

Sole deficiency of one nutrient or moderate deficiency of all does not appear to increase risks for abortion. Even in extreme cases—for example, hyperemesis gravidarum—abortion is rare. Dietary quality may play a role, as miscarriage risk may be reduced in women who consume a diet rich in fruits, vegetables, whole grains, vegetable oils, and fish (Gaskins, 2015). With regard to maternal weight, underweight is not associated with a greater miscarriage risk (Balsells, 2016). However, as noted in Chapter 48 (Pregnancy and Obesity), obesity does raise pregnancy loss rates.

Social and Behavioral Factors

Lifestyle choices reputed to be associated with a higher miscarriage risk are most often related to chronic and especially heavy use of *legal* substances. The most commonly used is alcohol, with its potent teratogenic effects discussed in Chapter 12 (Known and Suspected Teratogens). That said, an increased miscarriage risk is only seen with regular or heavy use (Avalos, 2014; Feodor Nilsson, 2014).

Approximately 10 percent of pregnant women admit to cigarette smoking (Centers for Disease Control and Prevention, 2016). It seems intuitive that cigarettes could cause early pregnancy loss (Pineles, 2014). Adverse effects of illicit drugs are discussed in Chapter 12 (Tobacco).

Excessive caffeine consumption—not well defined—has been associated with a higher abortion risk. Reports link heavy intake of approximately five cups of coffee per day—about 500 mg of caffeine—with a slightly greater abortion risk (Cnattingius, 2000; Klebanoff, 1999). Studies of "moderate" intake—less than 200 mg daily—did not indicate increased risk (Savitz, 2008; Weng, 2008). In contrast, in one prospective cohort of more than 5100 gravidas, caffeine was linked to miscarriage but not in a dose-response relationship (Hahn, 2015). Currently, the American College of Obstetricians and Gynecologists (2016e) has concluded that moderate consumption likely is not a major abortion risk and that any associated risk with higher intake is unsettled.

Occupational and Environmental Factors

Environmental toxins suggested to have a possible link to miscarriage include bisphenol A, phthalates, polychlorinated biphenyls, and dichlorodiphenyltrichloroethane (DDT) (Krieg, 2016). Even fewer studies implicate occupational exposures. In a follow-up of the Nurses Health Study II, Lawson and associates (2012) reported slightly increased miscarriage risks in nurses exposed to sterilizing agents, x-rays, and antineoplastic drugs. Also, a higher miscarriage risk was found for dental assistants exposed to more than 3 hours of nitrous oxide daily if there was no gas-scavenging equipment (Boivin, 1997).

Paternal Factors

Increasing paternal age is significantly associated with an greater risk for abortion (de La Rochebrochard, 2003). In the Jerusalem Perinatal Study, this risk was lowest before age 25 years, after which it progressively increased at 5-year intervals (Kleinhaus, 2006). The etiology of this association is not well studied, but chromosomal abnormalities in spermatozoa likely play a role (Sartorius, 2010).

Spontaneous Abortion Clinical Classification

Threatened Abortion

This diagnosis is presumed when bloody vaginal discharge or bleeding appears through a closed cervical os during the first 20 weeks. This bleeding in early pregnancy must be differentiated from that with implantation, which some women have at the time of their expected menses. Aside from this, almost one fourth of women develop bleeding during early gestation that may persist for days or weeks. It may be accompanied by suprapubic discomfort, mild cramps, pelvic pressure, or persistent low backache. Of symptoms, bleeding is by far the most predictive risk factor for pregnancy loss.

Even if miscarriage does not follow threatened abortion, rates of later adverse pregnancy outcomes are increased as shown in Table 18-1. Of these, highest risks are for preterm delivery. Weiss and coworkers (2004) noted greater risks for adverse outcomes in later pregnancy if early bleeding was heavy rather than light. Compared with those without bleeding, women with first-trimester bleeding in an initial pregnancy have higher recurrence rates in their second (Lykke, 2010).

TABLE 18-1

Adverse Outcomes That Are Increased in Women with Threatened Abortion

Maternal	Perinatal
Placenta previa	Preterm ruptured membranes
Placental abruption	Preterm birth
Manual removal of placenta	Low-birthweight infant
Cesarean delivery	Fetal-growth restriction
	Fetal and neonatal death

From Lykke, 2010; Saraswat, 2010; Weiss, 2004; Wijesiriwardana, 2006.

Every woman with an early pregnancy, vaginal bleeding, and pain should be evaluated. The primary goal is prompt diagnosis of ectopic pregnancy, and serial quantitative serum β-hCG levels and transvaginal sonography are integral tools. Because these are not 100-percent accurate to confirm early embryo death or location, repeat evaluations are often necessary. With a robust uterine pregnancy, serum β-hCG levels should rise at least 53 to 66 percent every 48 hours (Barnhart, 2004c; Kadar, 1982). Although a less-used marker, serum progesterone concentrations <5 ng/mL suggest a dying pregnancy. Values >20 ng/mL support the diagnosis of a healthy one (Daily, 1994).

Transvaginal sonography is used to locate the pregnancy and determine viability. If this cannot be done, then a *PUL* is diagnosed, and serial surveillance is implemented for clinically stable women. The gestational sac—an anechoic fluid collection that represents the exocoelomic cavity—may be seen by 4.5 weeks (Fig. 9-3). At this same time, β-hCG levels generally measure 1500 to 2000 mIU/mL (Barnhart, 1994; Timor-Tritsch, 1988). Connolly and colleagues (2013) observed that this value could be as low as 390 mIU/mL. However, they also noted that a threshold as high as 3500 mIU/mL may be needed to identify the gestational sac in some cases that ultimately yield a viable singleton IUP.

Another caveat is that a gestational sac may appear similar to other intrauterine fluid accumulations—the so-called pseudogestational sac (Fig. 19-4). This pseudosac may be blood derived from a bleeding ectopic pregnancy and is easier to exclude once a yolk sac is seen. Typically, the yolk sac is visible by 5.5 weeks and with a mean gestational-sac diameter of 10 mm. Thus, the diagnosis of an IUP should be made cautiously if the yolk sac is not yet seen (American College of Obstetricians and Gynecologists, 2016h).

For management of threatened abortion, observation is the norm. Acetaminophen-based analgesia will help relieve discomfort from cramping. Bed rest is often recommended but does not improve outcomes. The hematocrit and blood type is determined. If anemia or hypovolemia is significant, then pregnancy evacuation is generally indicated. In cases in which there is a live fetus, some instead may choose transfusion and further observation.

Incomplete Abortion

During abortion, bleeding follows partial or complete placental separation and dilation of the cervical os. Before 10 weeks' gestation, the fetus and the placenta are frequently expelled together, but later, they deliver separately. Thus, tissue may remain entirely within the uterus or partially extrude through the cervix. Products lying loosely within the cervical canal can be easily extracted with ring forceps. In contrast, with incomplete expulsion, three management options include curettage, expectant management, or misoprostol (Cytotec), which is prostaglandin E_1 (PGE_1) (Kim, 2017). The last two are deferred in clinically unstable women or those with uterine infection.

Each option has its own risks and benefits. With all three, infection and need for transfusion are uncommon. However, misoprostol and expectant care are associated with unpredictable bleeding, and some women will undergo unscheduled curettage. Expectant management of spontaneous incomplete abortion has failure rates that approximate 25 percent in randomized trials (Nadarajah, 2014; Nielsen, 1999; Trinder, 2006). Some observational studies have shown failure rates of 10 to 15 percent (Blohm, 2003; Casikar, 2012; Luise, 2002). Medical therapy carries failure rates of 5 to 30 percent (Dao, 2007; Shochet, 2012; Trinder, 2006). In many studies for this, an oral misoprostol dose of 600 µg has been used (American College of Obstetricians and Gynecologists, 2009). Alternatively, an 800-µg vaginal or a 400-µg oral or sublingual misoprostol dose is suitable. Last, curettage usually results in a quick resolution that is 95- to 100-percent successful. However, it is invasive and not necessary for all women.

Complete Abortion

At times, complete expulsion of the entire pregnancy may ensue, and the cervical os subsequently closes. A history of heavy bleeding, cramping, and passage of tissue is typical. Patients are encouraged to bring in passed tissue, in which a complete gestation should be discerned from blood clots or a decidual cast. The latter is a layer of endometrium in the shape of the uterine cavity that when sloughed can appear as a collapsed sac (Fig. 19-2).

If an expelled complete gestational sac is not identified, transvaginal sonography is performed to differentiate a complete abortion from threatened abortion or ectopic pregnancy. Characteristic findings of a complete abortion include a minimally thickened endometrium without a gestational sac. However, this does not guarantee a recent uterine pregnancy. Condous and associates (2005) described 152 women with heavy bleeding, an empty uterus with endometrial thickness <15 mm, and a diagnosis of completed miscarriage. Six percent were subsequently found to have an ectopic pregnancy. Thus, a complete abortion cannot be surely diagnosed unless: (1) true products of conception are seen grossly or (2) unless sonography confidently documents first an intrauterine pregnancy and then later an empty cavity. In unclear settings, serial serum hCG level measurements aid clarification. With complete abortion, these levels drop quickly (Table 18-2).

TABLE 18-2

Percentage Decline of Initial Serum β-hCG Levels Following Complete Spontaneous Abortion

	Percentage Decline[a]		
Initial hCG (mIU/mL)	**by day 2 Expected % (Minimum %)**	**by day 4 Expected % (Minimum %)**	**by day 7 Expected % (Minimum %)**
50	68 (12)	78 (26)	88 (34)
100	68 (16)	80 (35)	90 (47)
300	70 (22)	83 (45)	93 (62)
500	71 (24)	84 (50)	94 (68)
1000	72 (28)	86 (55)	95 (74)
2000	74 (31)	88 (60)	96 (79)
3000	74 (33)	88 (63)	96 (81)
4000	75 (34)	89 (64)	97 (83)
5000	75 (35)	89 (66)	97 (84)

[a]The percentage decline is given as the expected decline. The minimum expected decline in parentheses is the 95th percentile value. Declines less than this minimum may reflect retained either intrauterine or extrauterine trophoblast.

Data from Barnhart, 2004a; Chung, 2006.

Missed Abortion

This describes dead products of conception that have been retained for days or weeks in the uterus with a closed cervical os. Diagnosis is imperative prior to intervention and avoids interruption of a potentially live IUP. Transvaginal sonography is the primary tool.

At 5 to 6 weeks' gestation, a 1- to 2-mm embryo adjacent to the yolk sac can be seen (Daya, 1993). As listed in Table 18-3, absence of an embryo in a sac with a mean sac diameter (MSD) ≥25 mm signifies a dead fetus (Fig. 18-1). Fetal cardiac activity can typically be detected at 6 to 6.5 weeks with a crown-rump length (CRL) of 1 to 5 mm and an MSD of 13 to 18 mm (Goldstein, 1992; Levi, 1990). A threshold CRL ≥7 mm with absent cardiac activity is also used to diagnose nonviability (Doubilet, 2013). Preisler and associates (2015) implemented the guidelines in Table 18-3 and confirmed these CRL and MSD thresholds. However, for cases in which a gestational sac had no embryo or yolk sac and measured <12 mm, they recommended that to diagnose nonviability after 2 weeks, in addition to the lack of an embryo with a heartbeat, the MSD should have failed to double.

TABLE 18-3

Guidelines for Early Pregnancy Loss Diagnosis[a]

Sonographic Findings
CRL ≥ 7 mm and no heartbeat MSD ≥ 25 mm and no embryo An initial US scan shows a gestational sac with yolk sac, and after ≥ 11 days no embryo with a heartbeat is seen An initial US scan shows a gestational sac without a yolk sac, and after ≥ 2 weeks no embryo with a heartbeat is seen
Modalities Transvaginal preferable to transabdominal US M-mode imaging used to document and measure heartbeat Doppler US not used to evaluate a normal early embryo

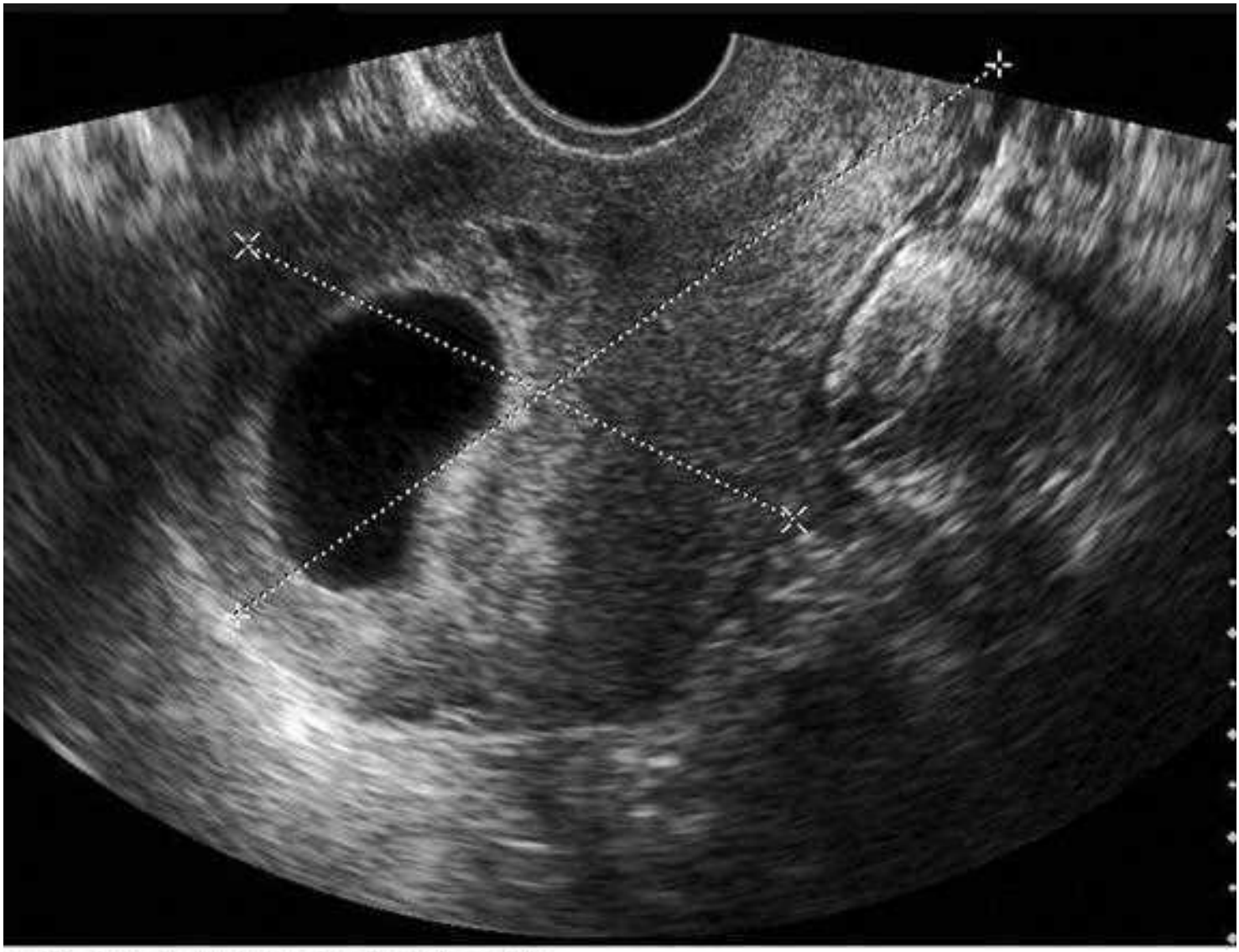
[a]From the Society of Radiologists in Ultrasound ; American College of Radiology.

CRL = crown-rump length; MSD = mean sac diameter; US = ultrasound.

From Doubilet, 2013; Lane, 2013.

FIGURE 18-1

Transvaginal sonogram displays a large anechoic sac consistent with an anembryonic gestation. Calipers measure uterine length and anteroposterior thickness in a sagittal plane.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

During scanning, because of theoretical temperature elevation in tissues exposed to pulsed Doppler beam, this modality is applied only when needed for additional diagnostic purposes. M-mode should be used to document cardiac activity and measure the rate (Lane, 2013). Finding of an IUP and cardiac activity lowers subsequent miscarriage rates (Siddiqi, 1988).

In addition to the diagnostic parameters of Table 18-3, other softer sonographic markers may portend early pregnancy failure. Values for yolk sac diameters (measured inner-to-inner ring) for each gestational week in normal pregnancy have been established. Yolk sac diameters ≥6 mm in pregnancies <10 weeks' gestation are suspicious for pregnancy failure (Berdahl, 2010; Lindsay, 1992). The fetal heart rate in the first trimester rises from 110 to 130 beats per minute (bpm) at 6 weeks' gestation to 160 to 170 bpm at 8 weeks (Achiron, 1991; Rauch, 2009). A slower heart rate is unfavorable, especially those <85 bpm (Laboda, 1989; Stefos, 1998). Even with cardiac activity, fetuses with a small MSD may presage embryonic loss. Specifically, a difference <5 mm between the MSD and CRL values raises concern (Bromley, 1991; Dickey, 1992). Last, subchorionic hematoma, that is, blood collected between the chorion and uterine wall, often accompanies threatened miscarriage. Studies are contradictory as to its association with ultimate pregnancy loss (Pedersen, 1990; Stabile, 1989; Tuuli, 2011). Bennett and associates (1996) noted that miscarriage risk correlated with larger hematoma size, older maternal age, and bleeding at a gestational age ≤8 weeks.

With rapid confirmation of embryonic or fetal death, surgical or medical evacuation or expectant observation is an option. As with induced abortion, nonsurgical options balance their noninvasiveness against heavier procedural bleeding, longer completion times, and lower success rates. Of options, expectant care underperforms medical or surgical options, and failure rates range from 15 to 50 percent (Luise, 2002; Trinder, 2006; Zhang, 2005). Also, weeks may pass between pregnancy failure diagnosis and actual spontaneous miscarriage.

Alternatively, misoprostol can be given to hasten uterine evacuation. A single 800-µg dose vaginally is a common standard (American College of Obstetricians and Gynecologists, 2016c). It may be repeated in 1 to 2 days, and one large trial reported that 22 percent of women required a second dose (Zhang, 2005). Overall, failure rates range from 15 to 40 percent (Petersen, 2014; Trinder, 2006). Unlike induced abortion, adding mifepristone does not add value (Stockheim, 2006). Contraindications mirror those listed in the section describing induced abortion (Medical Abortion).

Confirmation of completion may include a history of heavy bleeding, cramping, and tissue passage followed by ebbing flow; a sonographically thin endometrial thickness; and rapidly dropping serum hCG levels. That said, there is no consensus on an endometrial thickness threshold that mandates additional intervention.

Inevitable Abortion

Preterm premature rupture of membranes (PPROM) at a previable gestational age complicates 0.5 percent of pregnancies (Hunter, 2012). Rupture may be spontaneous or may follow an invasive procedure such as amniocentesis or fetal surgery. Risks for spontaneous rupture at a previable gestation are prior PPROM, prior second-trimester delivery, and tobacco use (Kilpatrick, 2006).

A gush of vaginal fluid that is seen pooling during sterile speculum examination confirms the diagnosis. In suspect cases, amnionic fluid will fern on a microscope slide or will have a pH >7, or oligohydramnios will be seen on sonography (Sugibayashi, 2013). Also, amnionic fluid proteins placental alpha microglobulin-1 and insulin growth factor binding protein-1, described in Chapter 22 (Identification of Labor), can be assayed (Doret, 2013).

In iatrogenic cases, defects are typically higher in the uterus and tend to self seal. Also, an occlusive plug—termed an amniopatch—can be created by intraamnionic instillation of autologous platelets and cryoprecipitate. Considered investigational, it is used to seal some surgical leaks (Richter, 2013).

Spontaneous rupture in the first trimester is nearly always followed by either uterine contractions or infection, and termination is typical. In some second-trimester cases not associated with pain, fever, or bleeding, fluid may have collected previously between the amnion and chorion. If this is documented, then diminished activity with observation is reasonable. After 48 hours, if no additional amnionic fluid has escaped and if there is no bleeding, cramping, or fever, then a woman may resume ambulation and pelvic rest at home.

However, more typically with second-trimester spontaneous PPROM at a previable age, 40 to 50 percent of women will deliver within the first week, and 70 to 80 percent will do so after 2 to 5 weeks (American College of Obstetricians and Gynecologists, 2016f). Average latency is 2 weeks (Hunter, 2012; Kibel, 2016). Significant maternal complications attend previable PPROM and include chorioamnionitis, endometritis, sepsis, placental abruption, and retained placenta (Waters, 2009). With bleeding, cramping, or fever, abortion is considered inevitable, and the uterus is evacuated.

Without these complications, expectant management is an option in the well-counseled patient (American College of Obstetricians and Gynecologists, 2017f). Many will choose termination due to the just-described maternal risks and tenuous neonatal outcomes. In contemporary cohorts with PPROM at <24 weeks' gestation, only approximately 20 percent of fetuses survive until hospital discharge (Esteves, 2016; Everest, 2008; Muris, 2007). Of surviving infants, 50 to 80 percent suffer long-term sequelae (Miyazaki, 2012; Pristauz, 2008). Further stratification of outcomes by gestational age is described in Chapter 42 (Periviable Neonatal Survival). Overall, prognosis is improved if previable PPROM occurred at a later gestation, latency is longer, and oligohydramnios is absent. Neonatal mortality predominantly stems from pulmonary dysfunction, which has higher rates when oligohydramnios persists (Winn, 2000). Fetal deformations may also result from scant amnionic fluid. Amnioinfusion has been investigated but is currently investigational (Roberts, 2014).

If expectant care is elected, management is described in Chapter 42 (Late-Preterm Birth). Antibiotics are considered and given for 7 days to extend latency. Other topics include lung-maturing corticosteroids, magnesium sulfate neuroprophylaxis, group B streptococcus antibiotic prophylaxis, tocolytics, and neonatal resuscitation efforts. After initial hospitalization, the patient may be discharged home, with instruction for careful surveillance for complications until viability, at which time readmission is usual (American College of Obstetricians and Gynecologists, 2016f). In subsequent pregnancies, the risk for recurrent preterm birth is great, and in one cohort study, the rate neared 50 percent (Monson, 2016).

Septic Abortion

With abortion legalization, horrific infections and maternal deaths associated previously with criminal septic abortions are now rare. Still, with spontaneous or induced abortion, organisms may invade myometrial tissues and extend to cause parametritis, peritonitis, and septicemia. Most bacteria causing septic abortion are part of the normal vaginal flora. Particularly worrisome are severe necrotizing infections and toxic shock syndrome caused by group A streptococcus—*S pyogenes* (Daif, 2009).

Rare but severe infections with otherwise low-virulence organisms can complicate medical or spontaneous abortions. Deaths have been reported from toxic shock syndrome due to *Clostridium perfringens* (Centers for Disease Control and Prevention, 2005). Similar infections are caused by *Clostridium sordellii* and have clinical manifestations that begin within a few days after an abortion. Women may be afebrile when first seen with severe endothelial injury, capillary leakage, hemoconcentration, hypotension, and a profound leukocytosis. Maternal deaths from these clostridial species approximate 0.58 per 100,000 medical abortions (Meites, 2010).

Management of clinical infection includes prompt administration of broad-spectrum antibiotics as discussed in Chapter 37 (Pathogenesis and Clinical Course). If there are retained products, then suction curettage is also performed. Most women respond to this treatment within 1 to 2 days and are discharged when afebrile. Follow-up oral antibiotic treatment is likely unnecessary (Savaris, 2011). In a very few women, severe sepsis syndrome develops, and intensive supportive care is essential. Although rare, clinical decline in the patient and widespread peritonitis despite curettage should raise concerns. Imaging that shows free air or air within the uterine wall typically prompts laparotomy (Eschenbach, 2015). If the uterus is necrotic, hysterectomy is indicated.

Anti-D Immunoglobulin

With spontaneous miscarriage, 2 percent of Rh D-negative women will become alloimmunized if not provided passive isoimmunization. With an induced abortion, this rate may reach 5 percent. The American College of Obstetricians and Gynecologists (2017g) recommends anti-Rho (D) immunoglobulin given as 300 µg intramuscularly (IM) for all gestational ages. Doses may also be graduated, with 50 µg given IM for pregnancies ≤12 weeks and 300 µg for ≥13 weeks. This is administered immediately following surgical evacuation. For planned medical or expectant management, the injection is given within 72 hours of pregnancy failure diagnosis.

With threatened abortion, immunoglobulin prophylaxis is controversial because of sparse evidence-based data (Hannafin, 2006). That said, it is reasonable to administer anti-D immunoglobulin for a threatened abortion and a live fetus, and this is our practice.

RECURRENT MISCARRIAGE

Affecting approximately 1 percent of fertile couples, recurrent pregnancy loss (RPL) is classically defined as three or more consecutive pregnancy losses <20 weeks' gestation or with a fetal weight <500 g. Mindful of this threshold, data from two large studies showed the risk for a subsequent miscarriage to be similar whether following two or three prior pregnancy losses (Bhattacharya, 2010; Brigham, 1999). And, the American Society for Reproductive Medicine (2013) now defines RPL as two or more failed pregnancies confirmed by sonographic or histopathological examination. *Primary RPL* refers to multiple losses in a woman who has never delivered a liveborn, and *secondary RPL* refers to multiple pregnancy losses in a patient with a prior live birth. Remarkably, the chances for a successful pregnancy are >50 percent even after five losses (Table 18-4).

TABLE 18-4

Predicted Success Rate of Subsequent Pregnancy According to Age and Number of Previous Miscarriages

No. of Previous Miscarriages at Age (yrs)	2	3	4	5
	Predicted Success of Subsequent Pregnancy (%)			
20	92	90	88	85
25	89	86	82	79
30	84	80	76	71
35	77	73	68	62
40+	69	64	58	52

Data from Brigham, 1999.

Evaluation for RPL addresses the major etiologies, described next (American Society for Reproductive Medicine, 2012). Treatment considerations reach beyond the scope of this book, and interested readers are referred to Chapter 6 in *Williams Gynecology,* 3rd edition (Halvorson, 2016).

Etiology

Three widely accepted causes of RPL are parental chromosomal abnormalities, antiphospholipid antibody syndrome, and structural uterine abnormalities. First-trimester losses in RPL have a significantly lower incidence of genetic abnormalities than sporadic miscarriage (Stephenson, 2002; Sullivan, 2004).

The timing of recurrent loss can offer clues, and in some women, each miscarriage may occur near the same gestational age (Heuser, 2010). Genetic factors usually result in early embryonic losses, whereas autoimmune or uterine anatomical abnormalities more likely cause second-trimester losses (Schust, 2002). Approximately 40 to 50 percent of women have idiopathic RPL (Li, 2002; Stephenson, 1996).

Parental Chromosomal Abnormalities

Although these account for only 2 to 4 percent of RPL cases, karyotyping of both parents is considered by many to be essential. Of abnormalities, reciprocal translocations are most common and followed by robertsonian translocations (Fan, 2016). Their genesis and reproductive sequelae are discussed in Chapter 13 (Chromosomal Translocations).

After thorough genetic counseling, couples with an abnormal karyotype can be offered in vitro fertilization (IVF) followed by preimplantation genetic diagnosis (American Society for Reproductive Medicine, 2012; Society for Assisted Reproductive Technology, 2008). This technique is described in Chapter 14 (Preimplantation Genetic Testing). However, in couples with RPL who are *chromosomally normal,* PGD is not currently recommended.

Anatomical Factors

Several genital tract abnormalities have been implicated in RPL and other adverse pregnancy outcomes (Reichman, 2010). According to Devi Wold and colleagues (2006), 15 percent of women with three or more consecutive miscarriages will be found to have a congenital or acquired uterine anomaly.

Of acquired abnormalities, uterine synechiae—*Asherman syndrome*—usually result from destruction of large areas of endometrium. This can follow uterine curettage, hysteroscopic surgeries, or uterine compression sutures (Conforti, 2013; Rathat, 2011). Characteristic multiple filling defects are seen with hysterosalpingography or saline-infusion sonography. Treatment is hysteroscopic adhesiolysis. In many, this lowers miscarriage rates and improves live birth rates (Yu, 2008).

Uterine leiomyomas are common and may cause miscarriage, especially if located near the placental implantation site. That said, data indicating them to be a significant cause of RPL are not convincing (Saravelos, 2011). Uterine cavity distortion is apparently not requisite for bad outcomes (Sunkara, 2010). But in women undergoing IVF, pregnancy outcomes are adversely affected by submucous but not subserosal or intramural leiomyomas (Jun, 2001; Ramzy, 1998). As discussed in Chapter 63 (Ovary), most agree that excision of submucosal leiomyomas in women with RPL can be considered.

Congenital genital tract anomalies often originate from abnormal müllerian duct formation. These have an overall incidence of approximately 1 in 200 women (Nahum, 1998). Depending on their anatomy, some may raise risks for early miscarriage, whereas others may cause midtrimester abortion or preterm delivery. Unicornuate, bicornuate, and septate uteri are associated with all three types of loss (Reichman, 2010). A fuller discussion of these anatomical abnormalities and their reproductive effects is found in Chapter 3 (Bladder and Perineal Abnormalities).

Immunological Factors

Miscarriages are more common in women with systemic lupus erythematosus (Clowse, 2008). Many of these women, as well as some without lupus, carry *antiphospholipid antibodies*, a family of autoantibodies that bind to phospholipid-binding plasma proteins (Erkan, 2011). Women with RPL have a higher frequency of these antibodies compared with normal controls (Branch, 2010). As shown in Table 18-5, the *antiphospholipid antibody syndrome (APS)* is defined by these antibodies in combination with various forms of reproductive loss and substantively increased risks for venous thromboembolism (American College of Obstetricians and Gynecologists, 2017b,i). Mechanisms that cause pregnancy loss are discussed along with treatment in Chapter 59 (Pregnancy and Antiphospholipid Antibodies).

TABLE 18-5

Clinical and Laboratory Criteria for Diagnosis of Antiphospholipid Antibody Syndrome[a]

Clinical Criteria Obstetric: One or more unexplained deaths of a morphologically normal fetus at or beyond 10 weeks, ***or*** Severe preeclampsia or placental insufficiency necessitating delivery before 34 weeks, ***or*** Three or more unexplained consecutive spontaneous abortions before 10 weeks Vascular: One or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ
Laboratory Criteria[b] Presence of lupus anticoagulant according to guidelines of the International Society on Thrombosis and Hemostasis, ***or*** Medium or high serum levels of IgG or IgM anticardiolipin antibodies, ***or*** Anti-β2 glycoprotein-I IgG or IgM antibody

[a]At least one clinical and one laboratory criteria must be present for diagnosis.

[b]These tests must be positive on two or more occasions at least 12 weeks apart.

IgG = immunoglobulin G; IgM = immunoglobulin M.

Modified from Branch, 2010; Erkan, 2011; Miyakis, 2006.

Regarding alloimmunity, one provocative theory suggests that normal pregnancy requires formation of blocking factors that avert maternal rejection of foreign fetal antigens that are paternally derived (Chap. 5, Fetal–Maternal Interface). Factors that prevent this tolerance may underlie RPL (Berger, 2010). However, proposed therapies using paternal or third-party leukocyte immunization or intravenous immunoglobulin (IVIG) have not proved beneficial in women with idiopathic RPL (Christiansen, 2015; Stephenson, 2010).

Endocrine Factors

According to Arredondo and Noble (2006), 8 to 12 percent of recurrent miscarriages are caused by endocrine factors. Studies to evaluate these have been inconsistent and generally underpowered. Two examples, both controversial, are progesterone deficiency caused by a *luteal-phase defect* and *polycystic ovarian syndrome* (Bukulmez, 2004; Cocksedge, 2008).

In contrast, the well-known abortifacient action of uncontrolled diabetes mellitus is detailed in Chapter 57 (Impact on Pregnancy). Optimal periconceptional glycemic control will mitigate many of these losses.

Likewise, the effects of overt hypothyroidism and severe iodine deficiency on early pregnancy failure are well known and discussed in Chapter 58 (Subclinical Hypothyroidism). Correction with supplementation reverses these actions. Also, the influence of subclinical hypothyroidism and antithyroid antibodies are sporadic, and thus any effects on recurrent miscarriage rates have been debated (Garber, 2012). That said, two metaanalyses reported convincingly positive associations between these antibodies and a greater risk for sporadic and recurrent miscarriages (Chen, 2011; Thangaratinam, 2011). One ongoing randomized trial regarding potential benefits of treatment will help guide future management (Vissenberg, 2015).

MIDTRIMESTER ABORTION

Incidence and Etiology

The timespan that defines a midtrimester fetal loss extends from the end of the first trimester until the fetus weighs <500 g or gestational age reaches 20 weeks. Less than in the first trimester, the spontaneous loss rate in the second ranges from 1.5 to 3 percent and, after 16 weeks, is only 1 percent (Simpson, 2007; Wyatt, 2005). Unlike earlier miscarriages that frequently are caused by chromosomal aneuploidies, these later fetal losses are due to a multitude of causes (Table 18-6). One frequently overlooked factor is that many second-trimester abortions are medically induced because of fetal abnormalities detected by prenatal screening programs for chromosome aneuploidy and structural defects.

TABLE 18-6

Some Causes of Midtrimester Spontaneous Pregnancy Losses

Fetal Anomalies
Chromosomal
Structural
Uterine Defects
Congenital
Leiomyomas
Incompetent cervix
Placental Causes
Abruption, previa
Defective spiral artery transformation
Chorioamnionitis
Maternal Disorders
Autoimmune
Infections
Metabolic

Management

Midtrimester abortions are classified similarly to first-trimester miscarriages (Paternal Factors). Management is similar in many regards to that used for second-trimester induced abortion, described later (Second-Trimester Abortion Methods). One exception is cervical cerclage, which may be employed for cervical insufficiency.

Cervical Insufficiency

Also known as incompetent cervix, this is a discrete obstetrical entity characterized classically by painless cervical dilatation in the second trimester. It can be followed by prolapse and ballooning of membranes into the vagina, and ultimately, expulsion of an immature fetus. This sequence often repeats in

future pregnancies.

Although the cause of insufficiency is obscure, previous cervical trauma has been implicated. One Norwegian cohort study of more than 15,000 women with prior cervical conization found a fourfold risk of pregnancy loss before 24 weeks' gestation (Albrechtsen, 2008). However, cerclage is not beneficial for women solely with this risk and without a preterm birth history (Zeisler, 1997). Of other surgeries, dilation and evacuation carries a 5-percent risk of cervical injury, but neither it nor dilation and extraction raises the likelihood of cervical insufficiency (Chasen, 2005). In other instances, abnormal cervical development, including that following in utero exposure to diethylstilbestrol (DES), may play a role (Hoover, 2011). Last, cervical ripening changes, such as altered hyaluronan or collagen content, discussed in Chapter 21 (Cervical Ripening), may be contributory (Eglinton, 2011; Sundtoft, 2017).

Surgical Indications

For women with an unequivocal history of second-trimester painless delivery, prophylactic cerclage placement is an option and reinforces a weak cervix by an encircling suture. However, some women have a history and clinical findings that make it difficult to verify—*classic* cervical insufficiency. In one randomized trial of almost 1300 women with an atypical history, cerclage was found to be only marginally beneficial—13 versus 17 percent—to prolong pregnancy past 33 weeks (MacNaughton, 1993). It seems likely that many of these women instead had preterm labor.

In addition to history, the physical finding of early dilation of the internal cervical os may be an indicator of insufficiency. In a systematic review, cerclages that were placed based on this finding provided superior perinatal outcomes compared with expectant management (Ehsanipoor, 2015).

Transvaginal sonography is yet another tool, and cervical length and the presence of *funneling* are sought. The latter is ballooning of the membranes into a dilated internal os, but with a closed external os. In women with these findings, early randomized trials were inconclusive in proving the clinical value of cerclage to prevent preterm birth (Rust, 2001; To, 2004). A multicenter randomized trial of 302 high-risk women with cervical length <25 mm reported that cerclage prevented birth before viability but not birth before 34 weeks (Owen, 2009). Subsequently, however, Berghella and coworkers (2011) included five trials in a metaanalysis and showed that cerclage for these high-risk women significantly reduced preterm birth before 24, 28, 32, 35, and 37 weeks.

Cervical length screening is now recommended by both the American College of Obstetricians and Gynecologists (2016b) and the Society for Maternal-Fetal Medicine (2015) for women with prior preterm birth. Between 16 and 24 weeks' gestation, sonographic cervical measurement is completed every 2 weeks. If an initial or subsequent cervical length is 25 to 29 mm, then a weekly interval is considered. If the cervical length measures <25 mm, cerclage is offered to this group of women. Notably, for women *without* a history of preterm birth but with a short cervix incidentally identified sonographically, progesterone therapy is offered instead of cerclage.

With twin gestations, one retrospective analysis found no improved outcomes in women with a cervical length <25 mm (Stoval, 2013). The College (2016b) does not recommend the use of cerclage in twin pregnancies.

Presurgical Preparation

Contraindications to cerclage usually include bleeding, contractions, or ruptured membranes, which substantially raises the likelihood of failure. Thus, prophylactic cerclage before dilatation is preferable. Surgery between 12 and 14 weeks' gestation allows this early intervention yet avoids surgery in a woman with a first-trimester pregnancy destined for spontaneous loss.

Preoperatively, screening for aneuploidy and obvious malformation is completed. Cervical secretions are tested for gonorrhea and chlamydial infection. These and obvious cervical infections are treated.

At times, the cervix instead is found to be dilated, effaced, or both, and an emergent *rescue cerclage* is performed. However, there is debate as to how late this should be performed. The conundrum is that the more advanced the pregnancy, the greater the risk that surgical intervention will stimulate preterm labor or membrane rupture. At Parkland Hospital, cerclage procedures are generally not done once supposed fetal viability is reached after 23 to 24 weeks. Others, however, recommend placement later than this (Caruso, 2000; Terkildsen, 2003).

When outcomes of cerclage are evaluated, women with similar clinical presentations are ideally compared. For example, in the study of elective cerclage by Owen and associates (2009), approximately a third of women delivered before 35 weeks, and complications were few. By contrast, in a 10-year review of 75 women undergoing rescue cerclage procedures, Chasen and Silverman (1998) reported that only half were delivered after 36 weeks. Importantly, only 44 percent of those with bulging membranes at the time of cerclage reached 28 weeks. Terkildsen and associates (2003) had similar experiences. Caruso and coworkers (2000) described rescue cerclage done in 23 women with a dilated cervix and protruding membranes from 17 to 27 weeks' gestation. There were 11 liveborn neonates, and these researchers concluded that success was unpredictable. Our experiences at Parkland Hospital are that rescue cerclages have a high failure rate, and women are counseled accordingly.

If the clinical indication for cerclage is questionable, a woman may instead be observed. Most undergo cervical examinations weekly or every 2 weeks to assess effacement and dilatation. Unfortunately, rapid effacement and dilation can develop despite such precautions (Witter, 1984).

Vaginal Cerclage

Of the two vaginal cerclage operations, most use the simpler procedure developed by McDonald (1963) and shown in Figure 18-2. The more complicated operation is a modification of the procedure described by Shirodkar (1955) and shown in Figure 18-3. When either technique is performed prophylactically, women with a classic history of cervical incompetence have excellent outcomes (Caspi, 1990; Kuhn, 1977). For either vaginal or abdominal cerclage, there is insufficient evidence to recommend perioperative antibiotic prophylaxis (American College of Obstetricians and

Gynecologist, 2016b,i). Thomason and coworkers (1982) found that perioperative tocolytics failed to arrest most labor. Regional analgesia is suitable and preferred. After this, the woman is placed in standard dorsal lithotomy position. The vagina and perineum are surgically prepared, and the bladder is drained. Some operators do not use potentially irritating antiseptic solution on the exposed amnionic membranes and instead use warm saline (Pelosi, 1990). Although steps are described subsequently, a thorough and illustrated review of cerclage technique is provided by Hawkins (2017).

FIGURE 18-2

McDonald cerclage procedure for incompetent cervix. **A.** Start of the cerclage procedure with a no. 2 monofilament suture being placed in the body of the cervix very near the level of the internal os. **B.** Continuation of suture placement in the body of the cervix so as to encircle the os. **C.** Encirclement completed. **D.** The suture is tightened around the cervical canal sufficiently to reduce the diameter of the canal to 5 to 10 mm, and then the suture is tied. The effect of the suture placement on the cervical canal is apparent. A second suture placed somewhat higher may be of value if the first is not in close proximity to the internal os.

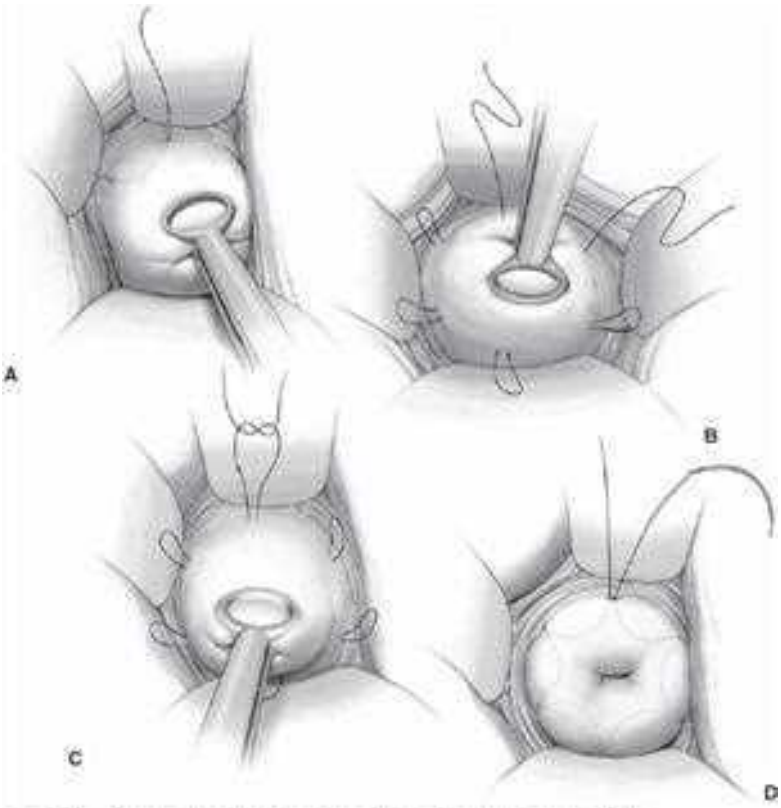
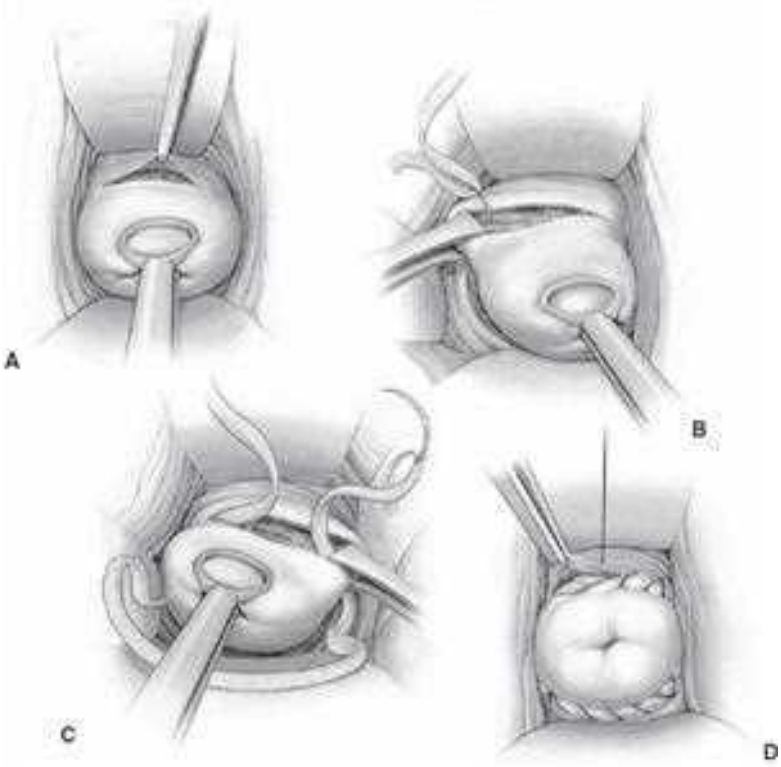


FIGURE 18-3

Modified Shirodkar cerclage for incompetent cervix. **A.** A transverse incision is made in the mucosa overlying the anterior cervix, and the bladder is pushed cephalad. **B.** A 5-mm Mersilene tape on a swaged-on or Mayo needle is passed anterior to posterior. **C.** The tape is then directed posterior to anterior on the other side of the cervix. Allis clamps are placed so as to bunch the cervical tissue. This diminishes the distance that the needle must travel submucosally and aids tape placement. **D.** The tape is snugly tied anteriorly, after ensuring that all slack has been taken up. The cervical mucosa is then closed with continuous stitches of chromic suture.



For suturing, options include a no. 1 or 2 nylon or polypropylene monofilament suture or 5-mm Mersilene tape. During placement, the suture is placed as high as possible and into the dense cervical stroma. Two cerclage sutures do not appear more effective than one (Giraldo-Isaza, 2013).

Rescue cerclage with a thinned dilated cervix is more difficult and risks tissue tearing and membrane puncture. Replacement of the prolapsed amnionic sac back into the uterus will usually aid suturing (Locatelli, 1999). Options include steep Trendelenburg or filling the bladder with 600 mL of saline through an indwelling Foley catheter. However, these steps may carry the cervix cephalad and away from the operating field. Membrane reduction can also be achieved by pressure from a wide moist swab or by placing a Foley catheter through the cervix and inflating the 30-mL balloon to deflect the amnionic sac cephalad. The balloon is then deflated gradually as the cerclage suture is tightened around the catheter tubing, which is then removed. Simultaneous outward traction created by ring forceps placed on the cervical edges may be helpful. In some women with bulging membranes, transabdominal amnionic fluid aspiration to decompress the sac may be considered. If this is done, bacterial cultures of the fluid should be obtained.

For uncomplicated pregnancies without labor, the cerclage is usually cut and removed at 37 weeks' gestation. This balances the risk of preterm birth against that of cervical laceration from a cerclage in place with labor contractions. Transvaginally placed cerclages are typically removed even with cesarean delivery to avoid rare long-term foreign-body complications (Hawkins, 2014). With scheduled cesarean delivery, the cerclage may be removed at 37 weeks or deferred until the time of regional analgesia and delivery. Again, the risk of labor ensuing before delivery must be considered. During extraction, particularly with a Shirodkar cerclage or a cerclage using Mersilene tape, analgesia helps ensure patient comfort and adequate visualization.

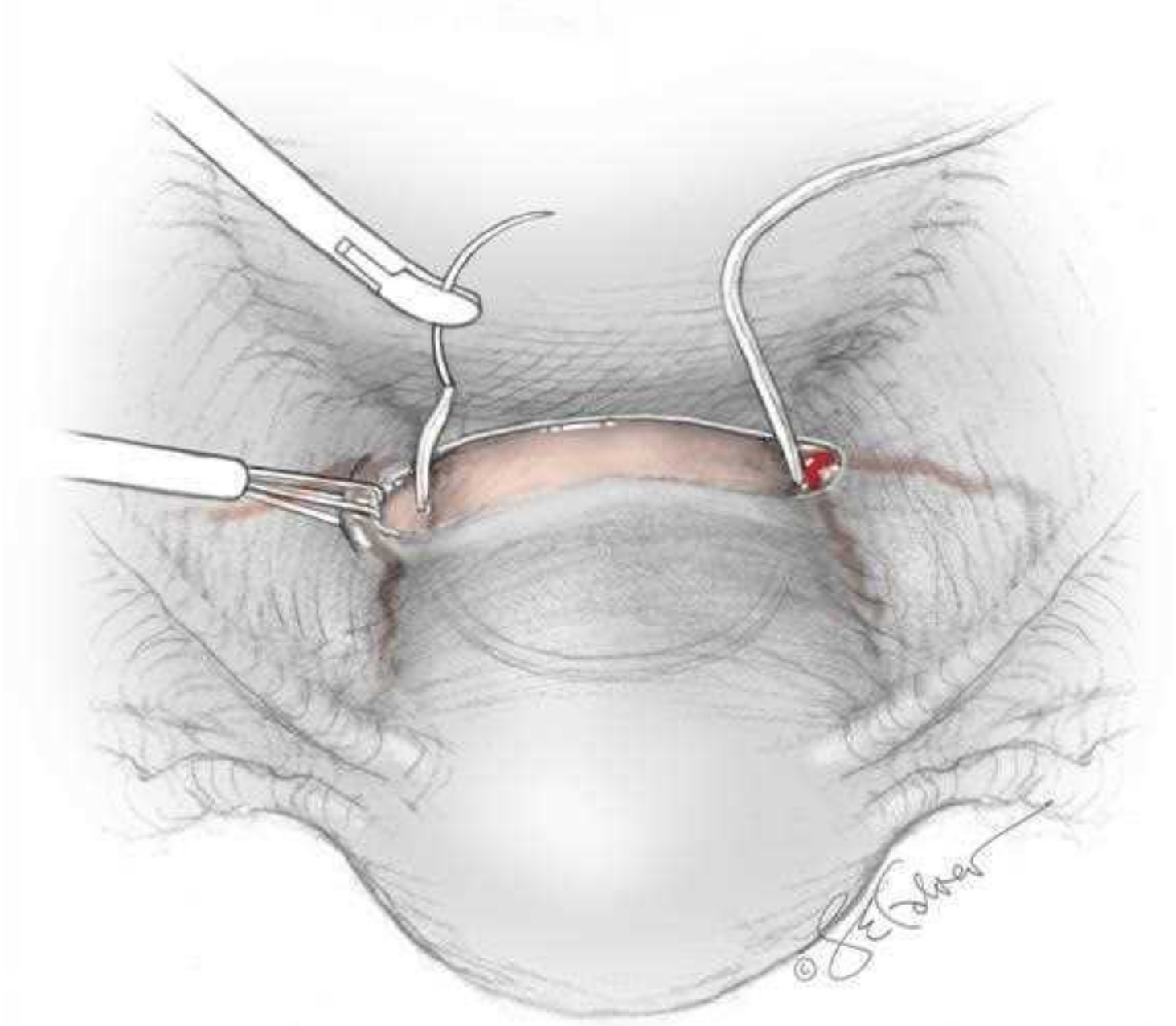
Transabdominal Cerclage

At times, suture placed at the uterine isthmus can be used and left until completion of childbearing. Because of significantly greater risks of bleeding and complications during placement, this approach is reserved for selected instances of severe cervical anatomical defects or prior transvaginal cerclage failure.

Placement of a cervicoisthmic cerclage was originally described using laparotomy, but several reports additionally detail laparoscopic or robotically assisted cervicoisthmic cerclages. Steps are summarized in Figure 18-4. Tulandi and coworkers (2014) evaluated 16 studies involving 678 pregnancies. Placement before pregnancy and during pregnancy was similar, whether performed laparoscopically or by laparotomy.

FIGURE 18-4

Transabdominal cervicoisthmic cerclage. Following incision and sharp dissection in the vesicouterine space, the bladder is mobilized caudally. At the level of the internal os, a window is made in free space medial to the uterine vessels. This avoids vessel compression by the tightened cerclage. Care is also taken to avoid the ureter, which is lateral and posterior. The suture is passed anterior to posterior or vice versa. In this case, the knot is tied anteriorly, and the vesicouterine peritoneum is closed with absorbable suture in a running fashion. (Reproduced with permission from Hawkins JS: Lower genital tract procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Zaveri and associates (2002) reviewed 14 observational studies in which a prior transvaginal cerclage had failed to prevent preterm delivery. The risk of perinatal death or delivery before 24 weeks' gestation was only slightly lower following transabdominal cerclage compared with the risk following repeat transvaginal cerclage—6 versus 13 percent, respectively. Importantly, 3 percent of women who underwent transabdominal cerclage had serious operative complications, whereas there were none in the transvaginal group. Whittle and coworkers (2009) described 31 women in whom transabdominal cervicoisthmic cerclage was done laparoscopically between 10 and 16 weeks. The procedure was converted to laparotomy in 25 percent, and there were four failures due to chorioamnionitis. Overall, fetal survival rate approximated 80 percent.

Complications

Principal among these are membrane rupture, preterm labor, hemorrhage, infection, or combinations thereof. All are uncommon with prophylactic cerclage. In the multicenter study by Owen and colleagues (2009), of 138 procedures, there was one instance each of ruptured membranes and bleeding. In the trial by MacNaughton and associates (1993), membrane rupture complicated only 1 of more than 600 procedures done before 19 weeks. In our view, clinical infection mandates immediate removal of the suture with labor induced or augmented. Similarly, with imminent abortion or delivery, the suture should be removed at once because uterine contractions can tear through the uterus or cervix.

Following cerclage, if subsequent cervical thinning is detected by sonographic assessment, then some consider a reinforcement cerclage. In one retrospective study, however, reinforcing cerclage sutures placed later did not significantly prolong pregnancy (Contag, 2016).

Membrane rupture during suture placement or within the first 48 hours following surgery is considered by some to be an indication for cerclage removal because of the likelihood of serious fetal or maternal infection (Kuhn, 1977). That said, the range of management options includes observation, removal of the cerclage and observation, or removal of the cerclage and labor induction (O'Connor, 1999).

INDUCED ABORTION

The term *induced abortion* is defined as the medical or surgical termination of pregnancy before the time of fetal viability. Definitions used to evaluate these statistically include: (1) *abortion ratio*—the number of abortions per 1000 live births, and (2) *abortion rate*—the number of abortions per 1000 women aged 15 to 44 years. Overall, abortions most likely are underreported in the United States because clinics inconsistently list medically induced abortions. For example, the Guttmacher Institute found that 926,000 procedures were performed in 2014 (Jones, 2017). But for 2013, only about 664,400 elective abortions were reported to the Centers for Disease Control and Prevention (Jatlaoui, 2016). Of these, 66 percent were pregnancies aged ≤8 weeks' gestation, and 92 percent of abortions were completed before ≤13 weeks. The abortion ratio was 200 per 1000 live births, and the abortion rate was 12.5 per 1000 women.

Classification

Therapeutic abortion refers to termination of pregnancy for medical indications. Inclusive medical and surgical disorders are diverse and discussed throughout this text. In cases of rape or incest, many consider termination. The most frequent indication currently is to prevent birth of a fetus with a significant anatomical, metabolic, or mental deformity.

The term *elective abortion* or *voluntary abortion* describes the interruption of pregnancy before viability at the request of the woman, but not for medical reasons. Most abortions done today are elective, and thus, it is one of the most frequently performed medical procedures.

Abortion in the United States

Legal Influence

The legality of elective abortion was established by the United States Supreme Court in the case of *Roe v. Wade.* The Court defined the extent to which states might regulate abortion and ruled that first-trimester procedures must be left to the medical judgment of the physician. After this, the state could regulate abortion procedures in ways reasonably related to maternal health. Finally, subsequent to viability, the state could promote its interest in the potential of human life and regulate and even proscribe abortion, except for preservation of the life or health of the mother.

Other legislation soon followed. The 1976 Hyde Amendment forbids use of federal funds to provide abortion services except in case of rape, incest, or life-threatening circumstances. The Supreme Court in 1992 reviewed *Planned Parenthood v. Casey* and upheld the fundamental right to abortion, but established that regulations before viability are constitutional as long as they do not impose an "undue burden" on the woman. Subsequently, many states introduced counseling requirements, waiting periods, parental consent for minors, facility requirements, and funding restrictions. Such limits are often called targeted regulation of abortion providers (TRAP) laws. One major choice-limiting decision was the 2007 Supreme Court decision that reviewed *Gonzales v. Carhart* and upheld the 2003 Partial-Birth Abortion Ban Act. This was problematic because there is no medically approved definition of partial-birth abortion according to the American College of Obstetricians and Gynecologists (2014a). In 2016, some TRAP laws were dialed back by the Supreme Court ruling in the case of *Whole Woman's Health v. Hellerstedt*. With this, the justices noted that abortion laws must confer health safety benefits that outweigh burdens on access.

Provider Availability

The American College of Obstetricians and Gynecologists (2014a, 2017d) supports the legal right of women to obtain an abortion prior to fetal viability and advocates for improved access. The College also (2017a) supports abortion training, and the Accreditation Council for Graduate Medical Education mandates that obstetrics and gynecology residency education must include access to experience with induced abortion. The Kenneth J. Ryan Residency Training Program was established in 1999 to work with residency programs to improve abortion and contraceptive training. Moreover, postresidency training in these techniques is available in formal 2-year Family Planning fellowships.

Other residency programs are less codified, but teach residents technical aspects through their management of early spontaneous abortions and pregnancy interruption for fetal death, severe fetal anomalies, and life-threatening medical or surgical disorders.

The College (2016g) respects the need and responsibility of health-care providers to determine their individual positions on induced abortion. It also advocates for counseling and timely referral if providers have individual beliefs that preclude pregnancy termination. Three basic choices available to a woman considering an abortion are: (1) continued pregnancy with its risks and parental responsibilities; (2) continued pregnancy with arranged adoption; or (3) termination of pregnancy with its risks. Knowledgeable and compassionate counseling should objectively describe and provide information regarding these choices to permit informed decision-making (Templeton, 2011).

FIRST-TRIMESTER ABORTION METHODS

Pregnancy termination can be performed either medically or surgically by several methods. In the absence of serious maternal medical disorders, abortion procedures do not require hospitalization (Guiahi, 2012). However, outpatient surgical facilities should have the ability to provide emergency resuscitation and immediate transfer to a hospital (American College of Obstetricians and Gynecologists, 2014b).

Surgical Abortion

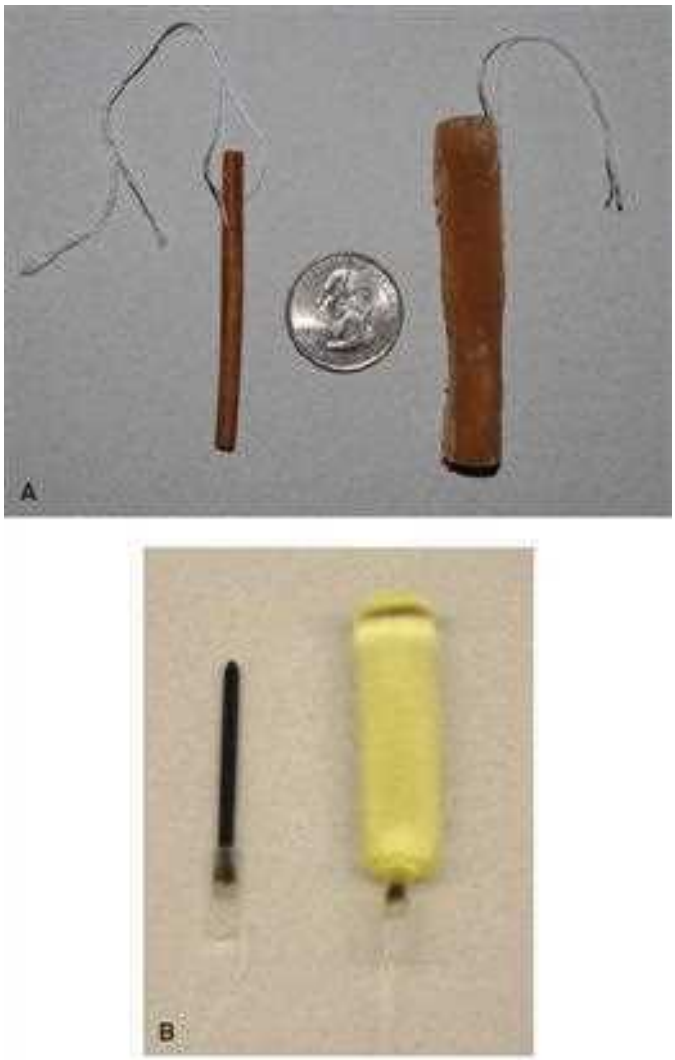
Preoperative Preparation

Surgical evacuation is performed transvaginally through an appropriately dilated cervix. For this, preoperative cervical ripening is favored by many and is typically associated with less manual intraoperative cervical dilation, a technically easier procedure, less pain, and shorter operative times (Kapp, 2010; Webber, 2015). On balance, cervical preparation adds a surgical delay and potential side effects. In a selective approach, some recommend cervical priming for first-trimester suction curettage only for those at greater risk of complications from intraoperative cervical dilation, such as those with cervical stenosis and adolescents (Allen, 2016). Of note, surgical steps presented here apply to both induced abortion and miscarriage, discussed earlier (First-Trimester Spontaneous Abortion).

For ripening, hygroscopic dilators, also called osmotic dilators, are devices that draw water from surrounding tissues and expand to gradually dilate the endocervical canal. One type is derived from various species of *Laminaria* algae that are harvested from the ocean floor (Fig. 18-5). These come in different diameters, which allow the number of inserted devices, also called tents, to be customized to a given cervix. Another device is *Dilapan-S,* which is composed of an acrylic-based gel. Each type expands to an ultimate diameter three to four times that of its dry state. However, Dilapan-S achieves this in 4 to 6 hours, which is faster than the 12 to 24 hours needed for laminaria (Fox, 2014).

FIGURE 18-5

Hygroscopic dilators. With each type, the dry unit (*left*) expands exponentially when exposed to water (*right*) as in the endocervical canal. **A.** Laminaria. **B.** Dilapan-S.



With hygroscopic dilators, shallow insertion yields insufficient internal os dilation or tent expulsion, but deep placement risks dislodgement into the uterine cavity (Fig. 18-6). Accordingly, the numbers of sponges and dilators inserted are carefully counted and recorded in the patient's chart. Once tents

are inserted, several gauze sponges at the external os help prevent spontaneous tent expulsion. Patients can ambulate, void, or stool without limitation.

FIGURE 18-6
Insertion of laminaria before dilatation and curettage. **A.** Laminaria immediately after being appropriately placed with its upper end just through the internal os. **B.** Several hours later the laminaria is now swollen, and the cervix is dilated and softened. **C.** Laminaria inserted too far through the internal os; the laminaria may rupture the membranes.

Schneider and associates (1991) described 21 cases in which women who had a hygroscopic dilator placed changed their minds. Of 17 women who chose to continue their pregnancy, there were 14 term deliveries, two preterm deliveries, and one miscarriage 2 weeks later. None suffered infection-related morbidity, including three untreated women with cervical cultures positive for *Chlamydia trachomatis*. In similar circumstances with four second-trimester terminations, Siedhoff and Cremer (2009) described two preterm and two term deliveries.

Instead of hygroscopic dilators, misoprostol is often used for cervical ripening. The typical dose is 400 µg administered sublingually, buccally, or placed into the posterior vaginal fornix 3 to 4 hours prior to surgery. Instead, oral administration proves less effective and may take longer (Allen, 2016). Another effective cervical-ripening agent is the antiprogestin mifepristone, 200 mg given orally 24 to 48 hours before surgery (Ashok, 2000). Its cost and greater delay to the procedure, however, typically favor misoprostol use instead.

In comparing hygroscopic dilators and misoprostol for ripening, randomized studies show equal or slightly greater dilation with hygroscopic dilators. Other surgical parameters do not vary significantly (Bartz, 2013; Burnett, 2005; MacIsaac, 1999). Hygroscopic dilators extend procedure time and can be uncomfortable, whereas misoprostol introduces fever, bleeding, and gastrointestinal side effects.

If not done as part of early prenatal care, hemoglobin level and Rh status are assessed. Screening for gonorrhea, for syphilis, and for human immunodeficiency virus, hepatitis B, and chlamydial infections is also completed. Obvious cervical infections are treated and resolved before elective procedures. To prevent postabortal infection after a first- or second-trimester surgical evacuation, prophylactic doxycycline, 100 mg orally 1 hour before and then 200 mg orally after, is provided (Achilles, 2011; American College of Obstetricians and Gynecologists, 2016a). Prophylaxis specifically for infective endocarditis prevention in those with valvular heart disease is not required in the absence of active infection (Nishimura, 2017). No recommendations specifically address venous thromboembolism prophylaxis for suction curettage in low-risk gravidas. At our hospital, we encourage early ambulation.

Vacuum Aspiration

Also called *suction dilation and curettage* or *suction curettage*, vacuum aspiration is a transcervical approach to surgical abortion. The cervix is first dilated and then products of conception are evacuated. For this, a rigid cannula is attached either to an electric-powered vacuum source or to a handheld 60-mL syringe for its vacuum source. These are *electric vacuum aspiration (EVA)* or *manual vacuum aspiration (MVA)*, respectively. *Sharp dilation and curettage (D & C)* in which contents are mechanically scraped out *solely* by a sharp curette is currently not recommended for pregnancy evacuation due to greater blood loss, pain, and procedural time (National Abortion Federation, 2016; World Health Organization, 2012). Importantly, this practice is distinguished from brief sharp curettage following initial aspiration. In one survey, this combination is employed by nearly 50 percent of abortion providers (O'Connell, 2009).

After bimanual examination is performed to determine uterine size and orientation, a speculum is inserted, and the cervix is swabbed with povidone-iodine or equivalent solution. The anterior cervical lip is grasped with a toothed tenaculum. The cervix, vagina, and uterus are richly supplied by nerves of Frankenhäuser plexus, which lies within connective tissue lateral to the uterosacral and cardinal ligaments. Thus, vacuum aspiration at minimum requires intravenously or orally administered sedatives or analgesics, and some add a paracervical or intracervical blockade with lidocaine (Allen, 2009; Renner, 2012). For local blocks, 5 mL of 1- or 2-percent lidocaine is most effective if placed immediately lateral to the insertion of the uterosacral ligaments into the uterus at 4 and 8 o'clock. An intracervical block with 5-mL aliquots of 1-percent lidocaine injected at 12, 3, 6, and 9 o'clock was reported to be equally effective (Mankowski, 2009). Alternatively, general or regional anesthesia may be elected.

Uterine sounding measures the depth and inclination of the cavity before other instrument insertion. If required, the cervix is further dilated with Hegar, Hank, or Pratt dilators until a suction cannula of the appropriate diameter can be inserted. The degree of required cervical dilation roughly approximates gestational age. Hegar sizes reflect their diameter in millimeters. Pratt and Hank dilators are sized in French units, which can be converted to millimeters by dividing the French number by three.

With dilation, the fourth and fifth fingers of the hand introducing the dilator should rest on the perineum and buttocks as the instrument is pushed through the internal os (Fig. 18-7). This technique minimizes forceful expansion and provides a safeguard against uterine perforation.

FIGURE 18-7
Dilatation of cervix with a Hegar dilator. Note that the fourth and fifth fingers rest against the perineum and buttocks, lateral to the vagina. This maneuver is an important safety measure because if the cervix relaxes abruptly, these fingers prevent a sudden and uncontrolled thrust of the dilator, a common cause of uterine perforation.

Following dilation, for most first-trimester aspiration procedures, an 8- to 12-mm Karman cannula is appropriate. Small cannulas carry the risk of leaving retained intrauterine tissue postoperatively, whereas large cannulas risk cervical injury and more discomfort. To begin, the cannula is slowly moved toward the fundus until resistance is met. Suction is then activated. The cannula is gradually pulled back toward the os and is slowly turned circumferentially to cover the entire surface of the uterine cavity (Fig. 18-8). This is repeated until no more tissue is aspirated. A gentle sharp curettage can

follow to remove any remaining tissue fragments (Fig. 18-9). Strong and consistent evidence supports high efficacy, safety, and patient acceptability for both MVA and EVA (Lichtenberg, 2013).

FIGURE 18-8

A suction curette has been placed through the cervix into the uterus. The figure shows the rotary motion used to aspirate the contents. (Reproduced with permission from: Hoffman BL, Corton MM: Surgeries for benign gynecologic disorders. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

FIGURE 18-9

A sharp curette is advanced into the uterine cavity while the instrument is held with the thumb and forefinger as shown in Figure 18-7. In the movement of the curette, only the strength of these two fingers should be used. (Reproduced with permission from: Hoffman BL, Corton MM: Surgeries for benign gynecologic disorders. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

For abortion done at ≤6 weeks' gestation, a distinct drawback is that the pregnancy may be small and missed by the curette. To identify placenta, the aspirated contents are rinsed in a strainer to remove blood, and then placed in a clear plastic container with saline and examined with back lighting (MacIsaac, 2000). Placental tissue macroscopically appears soft, fluffy, and feathery. A magnifying lens, colposcope, or microscope can augment visualization. With gestations ≤7 weeks, the failed abortion rate approximates 2 percent (Kaunitz, 1985; Paul, 2002). Thus, if products are not clearly identified, serial serum hCG levels can be informative (Dean, 2015).

Abortion Complications

In women undergoing abortion, complication rates rise with gestational age. Of these, uterine perforation and lower-genital-tract laceration are uncommon but potentially serious. In one systematic review of first-trimester abortion, the uterine perforation rate was ≤1 percent, as was the cervical or vaginal laceration rate (White, 2015). Perforation is usually recognized when the instrument passes without resistance deep into the pelvis. Risk factors include operator inexperience, prior cervical surgery or anomaly, adolescence, multiparity, and advanced gestational age (Allen, 2016; Grimes, 1984). If the uterine perforation is small and fundal, as when produced by a uterine sound or narrow dilator, observation of vital signs and for uterine bleeding is usually sufficient.

If a suction cannula or sharp curette passes into the peritoneal cavity, considerable intraabdominal damage can ensue. In these cases, laparotomy or laparoscopy to thoroughly examine the abdominal contents is often the safest course. Uterine perforation is not a contraindication to completing the curettage under direct guidance during laparoscopy or laparotomy (Owen, 2017).

Following curettage, uterine synechiae may form, and the risk of synechiae increases with the number of procedures. Most cases are mild and of unclear reproductive significance (Hooker, 2014). However, of Asherman syndrome cases, one series found that two thirds were linked to first-trimester curettage (Schenker, 1982).

Other first-trimester abortion complications are hemorrhage, incomplete removal of products, and postoperative infections, and these are germane to both surgical and medical abortion techniques. Hemorrhage with abortion is variably defined. One supported by the Society for Family Planning is bleeding that prompts a clinical response or bleeding in excess of 500 mL (Kerns, 2013). For first-trimester surgical abortions, hemorrhage complicates ≤1 percent (White, 2015). Atony, abnormal placentation, and coagulopathy are frequent sources, whereas surgical trauma is a rare cause. With medical abortion, bleeding is more common. In one study of more than 42,000 Finnish women undergoing pregnancy termination with pregnancies less 63 days, hemorrhage complicated 15 percent of medical abortion but only 2 percent of surgical cases (Niinimäki, 2009).

Infection is another risk. One review of surgical abortion found a cumulative rate of 0.5 percent in those given prophylaxis compared with 2.6 percent in those given placebo (Achilles, 2011). In another review of nearly 46,000 first-trimester abortions, the postoperative infection rate was <0.3 percent for either surgical or medical methods (Upadhyay, 2015).

Incomplete abortion may require reevacuation. For medical abortion, this neared 5 percent in one systematic review (Raymond, 2013). Reaspiration rates following surgical abortion are typically <2 percent (Ireland, 2015; Niinimaki, 2009).

In sum, first-trimester surgical abortion offers higher efficacy rates (96 to 100 percent) than medical abortion (83 to 98 percent). Medical abortion also carries a greater cumulative risk of complications, although differences are small (Lichtenberg, 2013). These are balanced against the greater privacy of medical abortion and the more invasive steps of curettage.

Medical Abortion

Agents Used

In appropriately selected women, outpatient medical abortion is an acceptable option for pregnancies with a menstrual age <63 days (American College of Obstetricians and Gynecologists (2016c). Although suitable at later gestational ages, success rates are lower.

Among legally induced abortions performed at ≤8 weeks' gestation, one third are completed medically in the United States (Jatlaoui, 2016). Three medications are used alone or in combination: mifepristone, methotrexate, and misoprostol. Of these, mifepristone augments uterine contractility by reversing progesterone-induced myometrial quiescence, whereas misoprostol directly stimulates the myometrium. Both also ripen the cervix (Mahajan,

1997; Tang, 2007). Methotrexate acts on trophoblast and halts implantation. It is used less frequently now due to current availability of the more effective mifepristone.

Contraindications to medical abortion have evolved from exclusion criteria that were used in initial clinical trials. Cautions include current intrauterine device; severe anemia, coagulopathy, or anticoagulant use; long-term systemic corticosteroid therapy; chronic adrenal failure; inherited porphyria; severe liver, renal, pulmonary, or cardiovascular disease; or uncontrolled hypertension (Guiahi, 2012). Of note, misoprostol is suitable for early pregnancy failure in those with prior uterine surgery (Chen, 2008).

Methotrexate and misoprostol are both teratogens. Thus there must be a commitment to completing the abortion once these drugs are given (Auffret, 2016; Hyoun, 2012; Kozma, 2011). With mifepristone, for women who choose to continue their pregnancies after exposure, the ongoing pregnancy rate ranges from 10 to 46 percent (Grossman, 2015). The associated major malformation rate was 5 percent in one series of 46 exposed pregnancies (Bernard, 2013).

Administration

Several dosing schemes are effective, and some are shown in Table 18-7. Because of its greater efficacy, mifepristone/misoprostol combinations are favored. Presently, for gestations up to 63 days, the most widely accepted regimen is mifepristone, 200 mg given orally on day 0 and followed in 24 to 48 hours by misoprostol 800 µg, administered by a vaginal, buccal, or sublingual route (American College of Obstetricians and Gynecologists, 2016c). Another earlier regimen used a 600-mg oral mifepristone dose followed in 48 hours by a 400-µg oral misoprostol dose (Spitz, 1998). If desired, mifepristone and misoprostol may be self-administered at home (Chong, 2015). At Planned Parenthood clinics, for first-trimester medical abortion, doxycycline 100 mg is taken orally daily for 7 days and begins with abortifacient administration (Fjerstad, 2009). The woman is then discharged home and appointed to return in 1 to 2 weeks.

TABLE 18-7

Various Regimens for Medical Termination of Pregnancy

First Trimester
Mifepristone/Misoprostol [a]Mifepristone, 200–600 mg orally; followed in 24–48 hr by: [b]Misoprostol, 200–600 µg orally *or* 400–800 µg vaginally, buccally, or sublingually
Misoprostol Alone [c]800 µg vaginally or sublingually every 3 hr for 3 doses
Methotrexate/Misoprostol [d]Methotrexate, 50 mg/m^2 BSA intramuscularly or orally; followed in 3–7 days by: [e]Misoprostol, 800 µg vaginally. Repeat if needed 1 week after methotrexate initially given
Second Trimester
Mifepristone/Misoprostol Mifepristone, 200 mg orally; followed in 24–48 hr by: Misoprostol, 400 µg vaginally or buccally every 3 hr up to 5 doses
Misoprostol Alone Misoprostol, 600–800 µg vaginally; followed by 400 µg vaginally or buccally every 3 hr up to 5 doses
Dinoprostone 20 mg vaginal suppository every 4 hr
Concentrated Oxytocin 50 units oxytocin in 500 mL of normal saline infused during 3 hr; then 1-hr diuresis (no oxytocin); then escalate sequentially in a similar fashion through 150, 200, 250, and finally 300 units oxytocin each in 500 mL normal saline

[a]Doses of 200 versus 600 mg similarly effective.

[b]Oral route may be less effective and have more nausea and diarrhea. Sublingual route has more side effects than vaginal route.

[c]Intervals 3–12 hours given vaginally; 3–4 hours given sublingually.

[d]Efficacy similar for routes of administration.

[e]Similar efficacy when given on day 3 versus day 5.

BSA = body surface area.

Pymar, 2001; Raghavan, 2009; Schaff, 2000; Shannon, 2006; von Hertzen, 2003, 2007, 2009, 2010; Winikoff, 2008.

Symptoms following misoprostol are common within 3 hours and include vomiting, diarrhea, fever, and chills. Bleeding and cramping with medical termination typically is significantly worse than with menses. Thus, adequate analgesia, usually including a narcotic, is provided. If bleeding soaks two or more pads per hour for at least 2 hours, the woman is instructed to contact her provider to determine whether she needs to be seen.

At the follow-up appointment, routine postabortal sonographic examination is typically unnecessary (Clark, 2010). Instead, assessment of the clinical course along with bimanual pelvic examination is recommended. If sonography is indicated due to concern for failed abortion or for bleeding, unnecessary surgery can be avoided if scans are interpreted appropriately. Specifically, if no gestational sac is seen and there is no heavy bleeding, then intervention is unnecessary. This is true even when, as is common, the uterus contains sonographically evident debris (Paul, 2000). Measurements <15 mm and <30 mm have been used as thresholds to signal evacuation success (Nielsen, 1999; Zhang, 2005). Another study reported that a multilayered sonographic pattern indicated a successful abortion (Tzeng, 2013). Last, hCG values may be informative. Compared with preprocedural levels, Barnhart and coworkers (2004b) found declines of 88 percent at day 3 and 82 percent at day 8 following misoprostol administration correlated with a 95-percent rate of successful abortion completion.

SECOND-TRIMESTER ABORTION METHODS

In the second trimester, fetal anomaly or death, maternal health complications, inevitable abortion, or desired termination may be indications for uterine evacuation. As in the first trimester, available options are medical or surgical. But, in the second trimester, *dilation and evacuation (D & E)* rather than suction D & C is dictated because of fetal size and bony structure.

Of options, D & E is a common means of second-trimester induced abortion in the United States. Of legally obtained abortions in 2013, 9 percent were performed by D & E at gestational ages >13 weeks (Jatlaoui, 2016). Many of the surgical and medical steps for second-trimester abortion mirror those in the first trimester, and differences are emphasized here.

Dilation and Evacuation

Preparation

With D & E, wide mechanical cervical dilation precedes evacuation of fetal parts. The degree needed rises with fetal gestational age, and inadequate dilatation risks cervical trauma, uterine perforation, or tissue retention (Peterson, 1983). Thus, presurgical cervical preparation is advised, and main options include hygroscopic dilators or misoprostol.

With laminaria, overnight preparation offers optimal cervical dilation (Fox, 2014). Uncommonly, laminaria may fail to adequately dilate the cervix, and serial laminaria insertion with an increasing number of tents over several days is one option (Stubblefield, 1982). Supplementing laminaria with misoprostol or mifepristone is another choice (Ben-Ami, 2015).

Dilapan-S is also suitable for cervical preparation. It may be preferable for same-day procedures as this device achieves its maximal effect in 4 to 6 hours (Newmann, 2014).

Misoprostol can be used instead of hydroscopic dilators for cervical preparation. The typical dose is 400 µg given vaginally or buccally 3 to 4 hours prior to D & E. Randomized trials vary regarding the ability of misoprostol to achieve results equal to that with hydroscopic dilators (Bartz, 2013; Goldberg, 2005; Sagiv, 2015). Misoprostol *added* to laminaria offers small increases in dilation but also greater side effects (Edelman, 2006).

Fewer studies have evaluated mifepristone for cervical ripening. In one, mifepristone alone provided less dilation than hydroscopic dilators (Borgatta, 2012). In another trial, mifepristone added 48 hours before misoprostol created greater cervical dilation compared with misoprostol alone (Carbonell, 2007). Last, Goldberg and associates (2015) compared hygroscopic dilation with or without added mifepristone. They found no differences for gestations <19 weeks, but the combination aided procedures for later ages.

In sum, hygroscopic dilators are consistently effective for cervical preparation before D & E. For those desiring same-day procedures, Dilapan-S alone or misoprostol alone may offer advantages. Layering agents may be most helpful for later gestations or for an inadequate response from initial hygroscopic dilators alone. Yet, layering adds cost and potential side effects (Shaw, 2016).

With elective abortion, some choose to induce fetal demise prior to D & E to avert a live birth or to avoid violating the Partial Birth Abortion Ban Act, cited later (Diedrich, 2010). For this, an intracardiac potassium chloride injection or a 1-mg intraamnionic or intrafetal digoxin injection is frequently used prior to cervical ripening (Sfakianaki, 2014; White, 2016).

Technique

During D & E, sonography can be used as an adjunct in all cases or selectively in more challenging ones. Perioperative antibiotic prophylaxis mirrors that for first-trimester procedures (Vacuum Aspiration). To reduce postprocedure bleeding, vasopressin, 2 to 4 units in 20 mL of saline or anesthetic, can be injected intracervically or as part of a paracervical block (Kerns, 2013; Schulz, 1985). Once adequate cervical dilation is achieved, the initial surgical step drains amnionic fluid with an 11- to 16-mm suction cannula or with amniotomy and gravity. This reduces the risk of amnionic fluid embolism and brings the fetus into the lower uterine segment for removal (Owen, 2017; Prager, 2009).

For pregnancies beyond 16 weeks, the fetus is extracted, usually in parts, using Sopher forceps or other destructive instruments. With complete removal of the fetus, a large-bore vacuum curette is used to remove the placenta and remaining tissue.

Major complications are infrequent with D & E, and rates range from 0.2 to 2 percent in large series (Cates, 1982; Lederle, 2015; Peterson, 1983). These include uterine perforation, cervical laceration, uterine bleeding, and postabortal infection. Rare complications include disseminated intravascular coagulopathy or amnionic fluid embolism (Ray, 2004; York, 2012).

Abnormal Placentation

Placenta previa or the accrete syndromes can raise D & E risks. Once diagnosed, *placenta accreta* typically prompts hysterectomy (Matsuzaki, 2015). For *placenta previa,* D & E is preferred to quickly evacuate the placenta, but the ability to transfuse blood products and perform possible hysterectomy must be present (American College of Obstetricians and Gynecologists, 2017h; Perriera, 2017). Medical induction may be elected, but the risk for transfusion is greater than with D & E (Nakayama, 2007; Ruano, 2004). Data are few, but predelivery uterine artery embolization may lower bleeding risks (Pei, 2017).

Prior *cesarean delivery* is not a contraindication for D & E and may be preferred over prostaglandins for those with multiple prior hysterotomies (Ben-Ami, 2009; Schneider, 1994). During medical abortion, the uterine rupture rate is 0.4 percent with one prior cesarean delivery (Berghella, 2009). From fewer data, the rate may reach 2.5 percent with two or more prior cesarean deliveries (Andrikopoulou, 2016). If a medical agent is elected in those with prior cesarean hysterotomy, misoprostol is an option. Prostaglandin E^2 (PGE^2) appears to pose similar risk (le Roux, 2001; Reichman, 2007).

Other Surgical Options

Of these, *dilation and extraction (D & X)* is similar to D & E except that a suction cannula is used to evacuate the intracranial contents after delivery of the fetal body through the dilated cervix. This aids extraction and minimizes uterine or cervical injury from large instruments or fetal bones. D & X is also called an *intact D & E*. In political parlance, this procedure has been termed *partial birth abortion*.

In some women with second-trimester pregnancies who desire sterilization, hysterotomy with tubal ligation is reasonable. If there is significant uterine disease, then hysterectomy may provide ideal treatment. In some cases of a failed second-trimester medical induction, either of these may be considered.

Medical Abortion

Principal among noninvasive methods is a mifepristone plus misoprostol regimen or misoprostol alone (see Table 18-7). Of these two options, the combined regimen yields a shorter termination duration (Kapp, 2007; Ngoc, 2011). Hygroscopic dilators may speed the time to delivery with this combined regimen (Mazouni, 2009; Vincienne, 2017). In selecting misoprostol routes, oral administration leads to a longer time to delivery compared with vaginal or sublingual routes (Dickinson, 2014). Prophylactic antibiotics are not typically given, and infection surveillance during labor is instead applied (Achilles, 2011).

Another induction agent, PGE_2, shows similar efficacy and side effects compared with misoprostol (Jain, 1994; Jansen, 2008). Simultaneous administration of an antiemetic such as metoclopramide (Reglan), an antipyretic such as acetaminophen, and an antidiarrheal such as diphenoxylate/atropine (Lomotil) will help prevent or treat symptoms. Dinoprostone (Prostin) is an available PGE_2 in the United States. However, its greater cost and poor pharmacologic stability at room temperature may make it less attractive than misoprostol.

Of other agents, high-dose intravenous oxytocin in saline will result in second-trimester abortion in 80 to 90 percent of cases (see Table 18-7). However, by comparison, misoprostol leads to higher successful induction rates and faster delivery times (Alavi, 2013).

Rarely used, ethacridine lactate is an organic antiseptic that activates myometrial mast cells to release prostaglandins (Olund, 1980). Placed extraovularly, that is, extraamnionically, it is associated with longer times to delivery and greater complication rates compared with misoprostol (Boza, 2008).

Fetal and Placental Evaluation

For second-trimester gestations, D & E or medical induction is suitable clinically and psychologically. Thus, patient input and clinical indication guide selection (Burgoine, 2005; Kerns, 2012). Once delivered, viewing and holding the fetus may or may not be desired by the patient (Sloan, 2008).

Evaluation of a stillborn fetus is described in Chapter 35 (Risk Factors). One component is autopsy, which can also be valuable for second-trimester losses or terminations due to anomaly. For example, in a study of 486 women of all ages with second-trimester miscarriage, fetal malformations were identified in 13 percent (Joo, 2009). In another, a third of otherwise normal fetuses had associated chorioamnionitis that was judged to have preceded labor (Allanson, 2010). Indeed, according to Srinivas and associates (2008), 95 percent of placentas in midtrimester miscarriages are abnormal. Other abnormalities are vascular thromboses and infarctions.

With either surgical or medical abortion, subsequent autopsy can yield information, but fragmented D & E specimens may provide less information than intact fetuses (Gawron, 2013; Lal, 2014). Karyotyping can be performed on samples from either method (Bernick, 1998).

CONSEQUENCES OF ELECTIVE ABORTION

Legally induced abortion in the United States has a low associated mortality rate, and from 2008 to 2012, the rate was <1 death per 100,000 procedures (Jatlaoui, 2016). Early abortions are safer. For example, Zane and coworkers (2015) found a mortality rate of 0.3 deaths per 100,000 procedures at ≤8 weeks' gestation; a rate of 2.5 at 14 to 17 weeks; and 6.7 at ≥18 weeks. As emphasized by Raymond and Grimes (2012), mortality rates are 14-fold greater for pregnancies that are continued.

Data relating abortion to overall maternal health and to subsequent pregnancy outcome are limited. From studies, there is no evidence for excessive mental disorders (Biggs, 2017; Munk-Olsen, 2011). There are few data regarding subsequent reproductive health, although the rates of infertility or ectopic pregnancy are not increased. Exceptions may stem from postabortal infections, especially those caused by *C trachomatis*. Of subsequent adverse pregnancy outcomes, several studies note an approximate 1.5-fold greater incidence of preterm delivery following surgical evacuation (Lemmers, 2016; Makhlouf, 2014; Saccone, 2016). This risk accrues with the number of terminations (Hardy, 2013; Klemetti, 2012). Subsequent pregnancy outcomes are similar regardless of whether a prior induced abortion was completed medically or surgically (Männistö, 2013; Virk, 2007).

After medical or surgical management of an early pregnancy termination or loss, ovulation may resume as early as 8 days, but the average time is 3 weeks (Lahteenmaki, 1978; Stoddard, 2011). Thus, unless another pregnancy is imminently desired, effective contraception is initiated to help lower the unintended pregnancy rate, which was 45 percent in 2011 in the United States (Finer, 2016). In suitable candidates described in Chapter 38 (Progestin Implants), an intrauterine device can be inserted after the procedure or medical abortion is completed (Bednarek, 2011; Korjamo, 2017). Alternatively, any of the various forms of hormonal contraception can be initiated at this time (Curtis, 2016).

For women who desire another pregnancy, conception need not be delayed. Specifically, Wong and colleagues (2015) found similar live-birth rates in groups conceiving within 3 months of first-trimester pregnancy loss compared with groups with later conception. Others have found similarly reassuring results using an interval-to-conception threshold of 6 months (Kangatharan, 2017; Love, 2010).

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CHAPTER 19: Ectopic Pregnancy

As soon as an unruptured extra-uterine pregnancy is positively diagnosed, its immediate removal by laparotomy is urgently indicated, since rupture may occur at any time and the patient die from haemorrhage before operative aid can be obtained.

—J. Whitridge Williams (1903)

INTRODUCTION

Following fertilization and fallopian tube transit, the blastocyst normally implants in the endometrial lining of the uterine cavity. Implantation elsewhere is considered ectopic and accounts for 0.5 to 1.5 percent of all first-trimester pregnancies in the United States (Hoover, 2011; Stulberg, 2014). This small proportion disparately accounts for 3 percent of all pregnancy-related deaths (Creanga, 2017). Fortunately, urine and serum beta-human chorionic gonadotropin (β-hCG) assays and transvaginal sonography allow earlier diagnosis. As a result, both maternal survival rates and conservation of reproductive capacity are improved.

TUBAL PREGNANCY

Classification

Nearly 95 percent of ectopic pregnancies are implanted in the various segments of the fallopian tube. These segments are shown in Chapter 2 (Fig. 2-14). The ampulla (70 percent) is the most frequent site, followed by isthmic (12 percent), fimbrial (11 percent), and interstitial tubal pregnancies (2 percent) (Bouyer, 2002). The remaining 5 percent of nontubal ectopic pregnancies implant in the ovary, peritoneal cavity, cervix, or prior cesarean scar. Occasionally, a multifetal pregnancy contains one conceptus with normal uterine implantation that coexists with one implanted ectopically. The natural incidence of these *heterotopic pregnancies* approximates 1 per 30,000 pregnancies (Reece, 1983). However, with assisted reproductive technologies (ART), their incidence is 9 in 10,000 pregnancies (Perkins, 2015). Rarely, twin tubal pregnancy with both embryos in the same tube or with one in each tube has been reported (Eze, 2012; Goswami, 2015).

Regardless of location, D-negative women with an ectopic pregnancy who are not sensitized to D-antigen are given IgG anti-D immunoglobulin (American College of Obstetricians and Gynecologists, 2017). In first-trimester pregnancies, a 50-μg or 300-μg dose is appropriate, whereas a standard 300-μg dose is used for later gestations (Chap. 15, Prevention of Anti-D Alloimmunization).

Risks

Abnormal fallopian tube anatomy underlies many cases of tubal ectopic pregnancy. Surgeries for a prior tubal pregnancy, for fertility restoration, or for sterilization confer the highest risk. After one previous ectopic pregnancy, the chance of another is increased fivefold (Bhattacharya, 2012). Prior sexually transmitted disease or other tubal infection, which can distort normal tubal anatomy, is another factor. Specifically, one episode of salpingitis can be followed by a subsequent ectopic pregnancy in up to 9 percent of women (Westrom, 1992). Peritubal adhesions subsequent to salpingitis, appendicitis, or endometriosis can also increase chances. *Salpingitis isthmica nodosa*, which is a condition in which epithelium-lined diverticula extend into a hypertrophied muscularis layer, is another (Bolaji, 2015). Finally, congenital fallopian tube anomalies, especially those secondary to in utero diethylstilbestrol exposure, can predispose (Hoover, 2011).

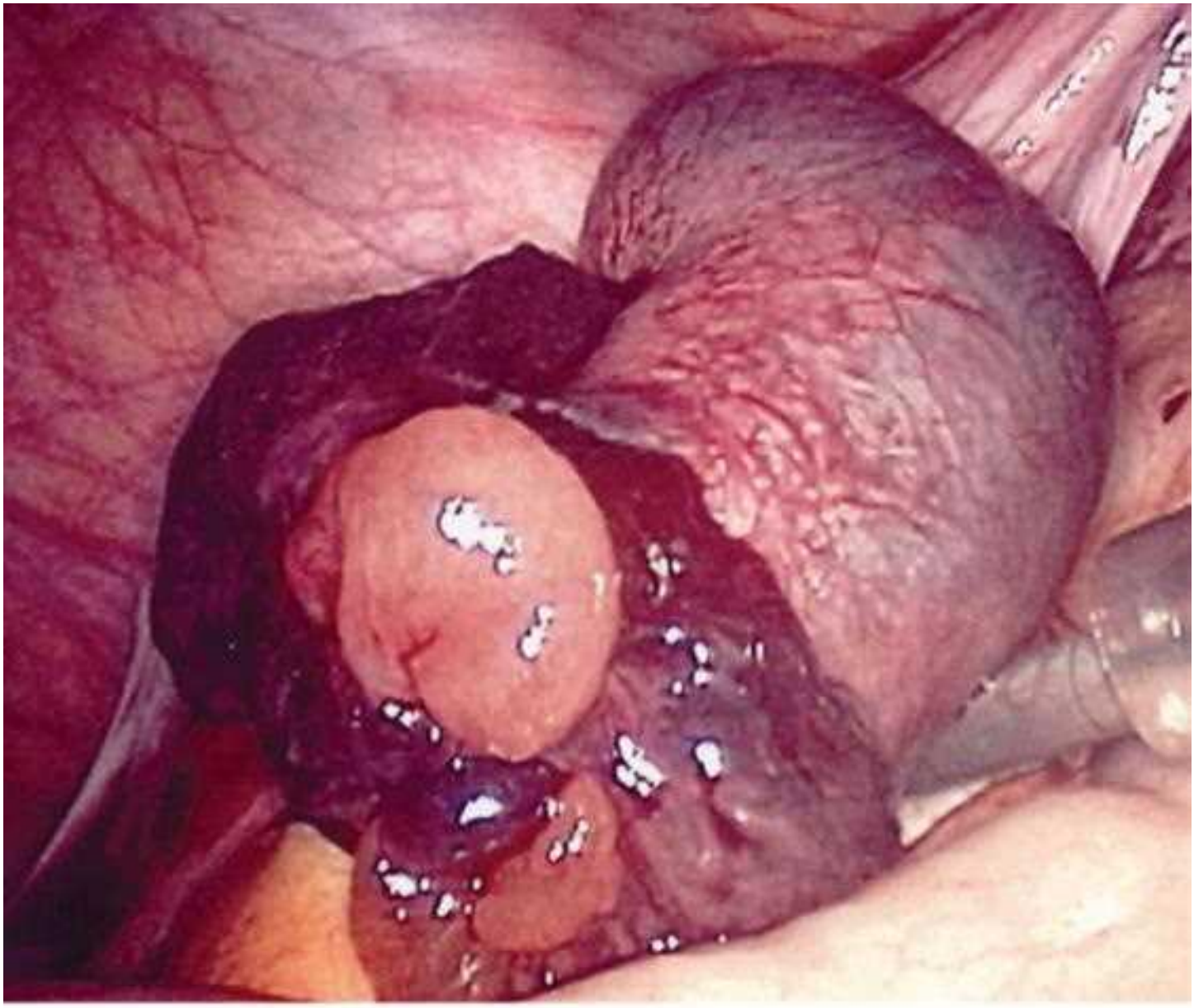
Infertility, as well as the use of ART to overcome it, is linked to substantively increased risks for ectopic pregnancy (Clayton, 2006). With ART, the ectopic pregnancy rate in the United States between 2001 and 2011 was 1.6 percent (Perkins, 2015). And “atypical” implantations—cornual, abdominal, cervical, ovarian, and heterotopic pregnancy—are more frequent. Smoking is another known association, although the underlying mechanism is unclear (Hyland, 2015). Last, with any form of contraception, the absolute number of ectopic pregnancies is decreased because pregnancy occurs less often. However, with some contraceptive method failures, the relative number of ectopic pregnancies is increased. Examples include tubal sterilization, copper and progestin-releasing intrauterine devices (IUDs), and progestin-only contraceptives (Chap. 38).

Evolution and Potential Outcomes

With tubal pregnancy, because the fallopian tube lacks a submucosal layer, the fertilized ovum promptly burrows through the epithelium. The zygote comes to lie near or within the muscularis, which is invaded by rapidly proliferating trophoblast. The embryo or fetus in an ectopic pregnancy is often absent or stunted.

Outcomes of ectopic pregnancy include tubal rupture, tubal abortion, or pregnancy failure with resolution. With rupture, the invading expanding conceptus and associated hemorrhage can tear rents in the fallopian tube (Fig. 19-1). Tubal ectopic pregnancies usually burst spontaneously but may occasionally rupture following coitus or bimanual examination.

FIGURE 19-1
Ruptured ampullary early tubal pregnancy. (Used with permission from Dr. Togas Tulandi.)



Alternatively, the pregnancy may pass out the distal fallopian tube. Tubal abortion frequency depends in part on the initial implantation site, and distal implantations are favored. Subsequently, hemorrhage may cease and symptoms eventually disappear. But bleeding can persist as long as products remain in the tube. Blood slowly trickles from the tubal fimbria into the peritoneal cavity and typically pools in the rectouterine cul-de-sac. If the fimbriated extremity is occluded, the fallopian tube may gradually become distended by blood, forming a hematosalpinx. Uncommonly, an aborted fetus will implant on a peritoneal surface and become an abdominal pregnancy, which is discussed in Abdominal Pregnancy.

Last, an unknown number of ectopic pregnancies spontaneously fail and are reabsorbed. This may be documented now more regularly with the advent of sensitive β-hCG assays.

Distinctions between “acute” ectopic pregnancy just described and “chronic” ectopic pregnancy can be drawn. The more common acute ectopic pregnancies are those with a high serum β-hCG level and rapid growth, leading to a timely diagnosis. These carry a higher risk of tubal rupture (Barnhart, 2003c). With chronic ectopic pregnancy, abnormal trophoblast dies early, and thus negative or low, static serum β-hCG levels are found (Brennan, 2000). Chronic ectopic pregnancies typically rupture late, if at all, but commonly form a complex pelvic mass, which often is the reason prompting diagnostic surgery (Cole, 1982; Uğur, 1996).

Clinical Manifestations

Earlier patient presentation and more precise diagnostic technology typically allow identification before rupture. In these cases, symptoms and signs of ectopic pregnancy are often subtle or even absent. The woman does not suspect tubal pregnancy and assumes that she has a normal early pregnancy or is having a miscarriage.

With later diagnosis, the classic triad is delayed menstruation, pain, and vaginal bleeding or spotting. With tubal rupture, lower abdominal and pelvic pain is usually severe and frequently described as sharp, stabbing, or tearing. Abdominal palpation elicits tenderness. Bimanual pelvic examination, especially cervical motion,

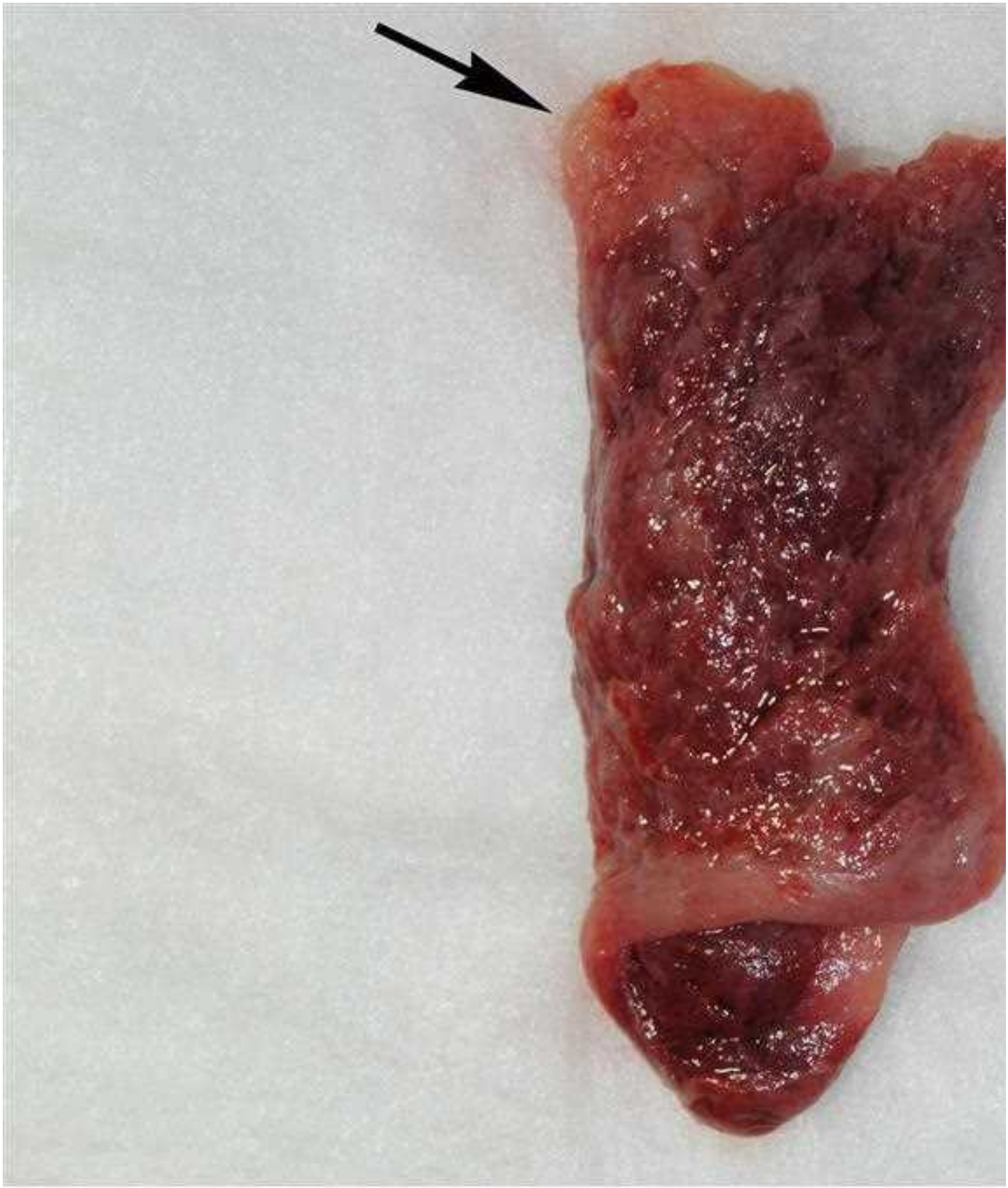
causes exquisite pain. The posterior vaginal fornix may bulge from blood in the rectouterine cul-de-sac, or a tender, boggy mass may be felt beside the uterus. The uterus can also be slightly enlarged due to hormonal stimulation. Symptoms of diaphragmatic irritation, characterized by neck or shoulder pain, especially on inspiration, develop in perhaps half of women with sizable hemoperitoneum.

Some degree of vaginal spotting or bleeding is reported by 60 to 80 percent of women with tubal pregnancy. Although profuse vaginal bleeding suggests an incomplete abortion, such bleeding occasionally is seen with tubal gestations. Moreover, tubal pregnancy can lead to significant intraabdominal hemorrhage. Responses to moderate bleeding include no change in vital signs, a slight rise in blood pressure, or a vasovagal response with bradycardia and hypotension. Blood pressure will fall and pulse will rise only if bleeding continues and hypovolemia becomes significant. Vasomotor disturbances develop, ranging from vertigo to syncope.

Even after substantive hemorrhage, hemoglobin or hematocrit readings may at first show only a slight reduction. Hence, after an acute hemorrhage, a trending decline in hemoglobin or hematocrit levels over several hours is a more valuable index of blood loss than is the initial level. In approximately half of women with a ruptured ectopic pregnancy, varying degrees of leukocytosis up to 30,000/μL may be documented.

Decidua is endometrium that is hormonally prepared for pregnancy, and the degree to which the endometrium is converted with ectopic pregnancy is variable. Thus, in addition to bleeding, women with ectopic tubal pregnancy may pass a *decidual cast.* This is the entire sloughed endometrium that takes the form of the endometrial cavity (Fig. 19-2). Importantly, decidual sloughing may also occur with uterine abortion. Thus, tissue is carefully evaluated visually by the provider and then histologically for evidence of a conceptus. If no clear gestational sac is seen or if no villi are identified histologically within the cast, then the possibility of ectopic pregnancy must still be considered.

FIGURE 19-2
This decidual cast was passed by a patient with a tubal ectopic pregnancy. The cast mirrors the shape of the endometrial cavity, and each arrow marks the portion of decidua that lined the cornua.



Multimodality Diagnosis

The differential diagnosis for abdominal pain coexistent with pregnancy is extensive. Pain may derive from uterine conditions such as miscarriage, infection, degenerating or enlarging leiomyomas, or round-ligament pain. Adnexal disease may include ectopic pregnancy; hemorrhagic, ruptured, or torsed ovarian masses;

salpingitis; or tuboovarian abscess. Last, appendicitis, cystitis, renal stone, and gastroenteritis are more common nongynecological sources of lower abdominal pain in early pregnancy.

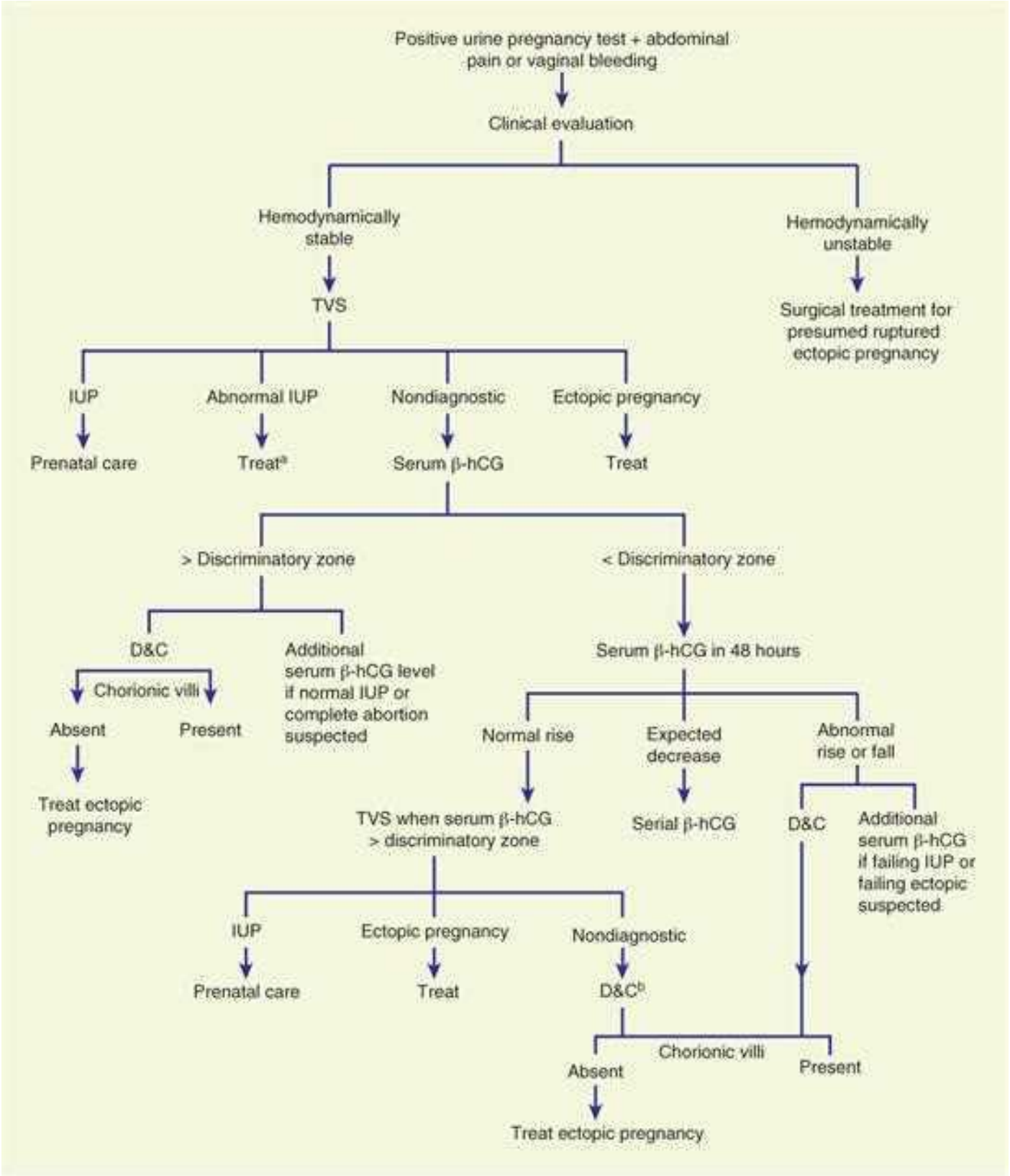
Several algorithms have been proposed to identify ectopic pregnancy. Most include these key components: physical findings, transvaginal sonography (TVS), serum β-hCG level measurement—both the initial and the subsequent pattern of rise or decline, and diagnostic surgery, which includes dilation and curettage (D&C), laparoscopy, and occasionally, laparotomy (Fig. 19-3). Algorithm use applies only to hemodynamically stable women, and those with presumed rupture undergo prompt surgical therapy. For a suspected unruptured ectopic pregnancy, all diagnostic strategies involve trade-offs. Strategies that maximize detection of ectopic pregnancy may result in termination of a normal intrauterine pregnancy (IUP). Conversely, those that reduce the potential for normal pregnancy interruption will delay ectopic pregnancy diagnosis. Patient desires for the index pregnancy are also discussed and may influence these trade-offs.

FIGURE 19-3
One suggested algorithm for evaluation of a woman with a suspected ectopic pregnancy.

[a]Expectant management, D&C, or medical regimens are suitable options.

[b]May consider repeat β-hCG level if normal IUP suspected.

β-hCG = beta human chorionic gonadotropin; D&C = dilatation and curettage; IUP = intrauterine pregnancy; TVS = transvaginal sonography.



Beta-Human Chorionic Gonadotropin

Rapid and accurate determination of pregnancy is essential to identify an ectopic pregnancy. Current pregnancy tests use enzyme-linked immunosorbent assays (ELISAs) for the beta subunit of hCG. With these assays, lower limits of detection are 20 to 25 mIU/mL for urine and ≤5 mIU/mL for serum (Greene, 2015).

With bleeding or pain and a positive pregnancy test result, an initial TVS is typically performed to identify gestation location. If a yolk sac, embryo, or fetus is identified within the uterus or the adnexa, then a diagnosis can be made. In many cases, however, TVS is nondiagnostic, and tubal pregnancy is still a possibility. In

these cases in which neither intrauterine nor extrauterine pregnancy is identified, the term *pregnancy of unknown location (PUL)* is used until additional clinical information allows determination of pregnancy location.

Levels above the Discriminatory Zone

Several investigators have described discriminatory β-hCG levels above which failure to visualize a uterine pregnancy indicates that the pregnancy either is not alive or is ectopic (Barnhart, 1994). Some institutions set their discriminatory threshold at ≥1500 mIU/mL, whereas others use ≥2000 mIU/mL. Connolly and associates (2013) suggested an even higher threshold. They noted that with live uterine pregnancies, a gestational sac was seen 99 percent of the time with a discriminatory level of >3510 mIU/mL.

If the initial β-hCG level exceeds the set discriminatory level and no evidence for an IUP is seen with TVS, then ectopic pregnancy is a concern. The diagnosis is narrowed in most cases to a failing IUP, a recent complete abortion, or an ectopic pregnancy. Early multifetal gestation also remains a possibility. Without clear evidence for ectopic pregnancy, serial β-hCG level assessment is reasonable, and a level is checked 48 hours later. This averts unnecessary methotrexate administration and avoids harming an early normal multifetal pregnancy. With greater concern for an ectopic gestation, D&C is another option to distinguish an ectopic from a failing IUP. Importantly, patient factors greatly influence these decisions.

Levels below the Discriminatory Zone

If the initial β-hCG level is below the set discriminatory value, pregnancy location is often not technically discernible with TVS. With these PULs, serial β-hCG level assays are done to identify patterns that indicate either a growing or failing IUP. Levels that rise or fall outside these expected parameters increase the concern for ectopic pregnancy. Thus, appropriately selected women with a possible ectopic pregnancy, but whose initial β-hCG level is below the discriminatory threshold, are seen 2 days later for further evaluation. Trends in levels aid diagnosis.

With early normal progressing IUPs, Barnhart and coworkers (2004b) reported a 53-percent 48-hour minimum rise with a 24-hour minimum rise of 24 percent. Seeber and associates (2006) found an even more conservative minimal 35-percent 48-hour rise in normal IUPs. With multifetal gestation, this same anticipated rate of rise is expected (Chung, 2006). Despite these guidelines, Silva and colleagues (2006) caution that a third of women with an ectopic pregnancy will have a 53-percent rise at 48 hours. They further reported that no single pattern characterizes ectopic pregnancy and that approximately half of ectopic pregnancies will show decreasing β-hCG levels, whereas the other half will have increasing levels. Also, despite a declining β-hCG level, a resolving ectopic pregnancy may rupture.

With a failing IUP, patterned rates of β-hCG level decline can also be anticipated. Following spontaneous abortion, rates decline by 21 to 35 percent at 48 hours and 68 to 84 percent at 7 days. Of note, these ranges reflect that β-hCG percentages drop faster if the initial β-hCG level is higher (Barnhart, 2004a). With resolving PULs, Butts and coworkers (2013) found greater rates of decline that ranged from 35 to 50 percent at 48 hours and 66 to 87 percent at 7 days for starting hCG values between 250 and 5000 mIU/mL.

In pregnancies without these expected rises or falls in β-hCG levels, distinction between a nonliving IUP and an ectopic pregnancy may be aided by additional β-hCG levels (Zee, 2014). Again delay is balanced against the risk from rupture. D&C is an option and provides a quicker diagnosis balanced against normal pregnancy interruption. Before curettage, a second TVS examination may be indicated and may display new informative findings.

Serum Progesterone

A single serum progesterone measurement may clarify the diagnosis in a few cases (Stovall, 1989, 1992). A value exceeding 25 ng/mL excludes ectopic pregnancy with 92-percent sensitivity (Lipscomb, 1999a; Pisarska, 1998). Conversely, values <5 ng/mL are found in only 0.3 percent of normal progressing IUPs (Mol, 1998; Verhaegen, 2012). Thus, values <5 ng/mL suggest either a nonliving IUP or an ectopic pregnancy. Because in most ectopic pregnancies, progesterone levels range between 10 and 25 ng/mL, the clinical utility of this practice is limited. One caveat is that pregnancy achieved with assisted reproductive technology may be associated with higher than usual progesterone levels (Perkins, 2000).

Transvaginal Sonography

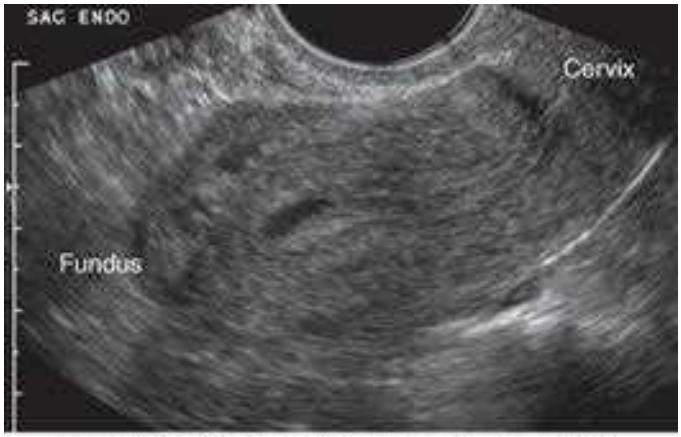
Endometrial Findings

In a woman in whom ectopic pregnancy is suspected, TVS is performed to look for findings indicative of uterine or ectopic pregnancy. During endometrial cavity evaluation, an intrauterine gestational sac is usually visible between 4½ and 5 weeks. The yolk sac appears between 5 and 6 weeks, and a fetal pole with cardiac activity is first detected at 5½ to 6 weeks (Fig. 9-3). With transabdominal sonography, these structures are visualized slightly later.

In contrast, with ectopic pregnancy, a trilaminar endometrial pattern can be diagnostic (Fig. 19-4). Its specificity is 94 percent, but with a sensitivity of only 38 percent (Hammoud, 2005). In addition, Moschos and Twickler (2008b) determined in women with a pregnancy of unknown location at presentation that no normal IUPs had a stripe thickness <8 mm.

FIGURE 19–4

Transvaginal sonography of a pseudogestational sac within the endometrial cavity. Its cavity-conforming shape and central location are characteristic of these anechoic fluid collections. Distal to this fluid, the endometrial stripe has a trilaminar pattern, which is a common finding with ectopic pregnancy. (Reproduced with permission from Gala RB: Ectopic pregnancy. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education; 2016. Photo contributor: Dr. Elysia Moschos.)



Anechoic fluid collections, which might normally suggest an early intrauterine gestational sac, may also be seen with ectopic pregnancy. These include pseudogestational sac and decidual cyst. First, a pseudosac is a fluid collection between the endometrial layers and conforms to the cavity shape (see Fig. 19-4). If a pseudosac is noted, the risk of ectopic pregnancy is increased (Hill, 1990; Nyberg, 1987). Second, a decidual cyst is identified as an anechoic area lying within the endometrium but remote from the canal and often at the endometrial-myometrial border. Ackerman and colleagues (1993b) suggested that this finding represents early decidual breakdown and precedes decidual cast formation.

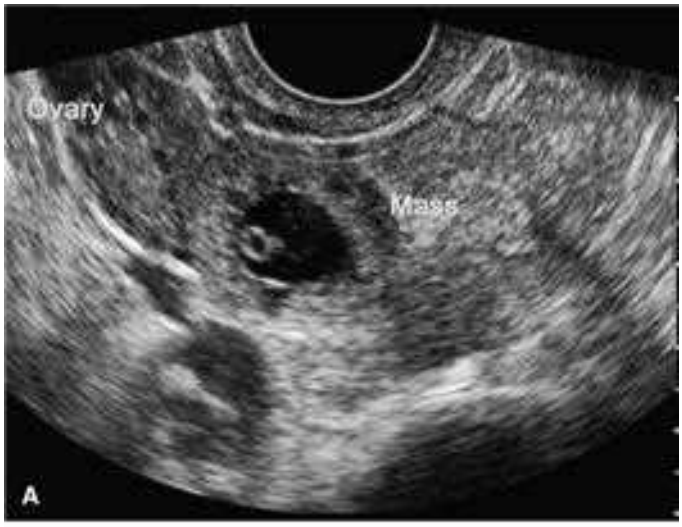
These two findings contrast with the intradecidual sign seen with uterine pregnancies. With this, an early gestational sac is seen as an anechoic sac eccentrically located within one of the endometrial stripe layers (Dashefsky, 1988). The American College of Obstetricians and Gynecologists (2016) advises caution in diagnosing an IUP in the absence of a definite yolk sac or embryo.

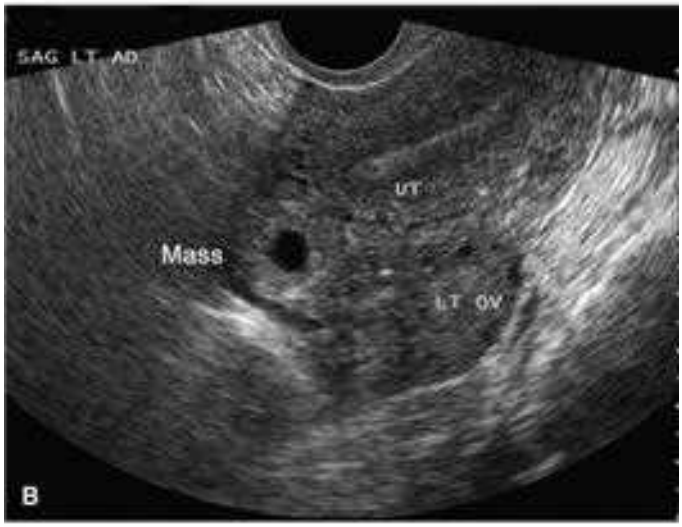
Adnexal Findings

The sonographic diagnosis of ectopic pregnancy rests on visualization of an adnexal mass separate from the ovary (Fig. 19-5). If fallopian tubes and ovaries are visualized and an extrauterine yolk sac, embryo, or fetus is identified, then an ectopic pregnancy is confirmed. In other cases, a hyperechoic halo or tubal ring surrounding an anechoic sac is seen (Nadim, 2017). Alternatively, an inhomogeneous adnexal mass is usually caused by hemorrhage within the ectopic sac. Overall, approximately 60 percent of ectopic pregnancies are seen as an inhomogeneous mass adjacent to the ovary; 20 percent appear as a hyperechoic ring; and 13 percent have an obvious gestational sac with a fetal pole (Condous, 2005). Importantly, not all adnexal masses represent an ectopic pregnancy, and integration of sonographic findings with other clinical information is necessary.

FIGURE 19-5

Various transvaginal sonographic findings with ectopic tubal pregnancies. For sonographic diagnosis, an ectopic mass should be seen in the adnexa separate from the ovary and may be seen as: **(A)** a yolk sac (shown here) and/or fetal pole with or without cardiac activity within an extrauterine sac, **(B)** an empty extrauterine sac with a hyperechoic ring, or **(C)** an inhomogeneous adnexal mass. In this last image, color Doppler shows a classic “ring of fire,” which reflects increased vascularity typical of ectopic pregnancies. LT OV = left ovary; SAG LT AD = sagittal left adnexa; UT = uterus.





Placental blood flow within the periphery of the complex adnexal mass—the *ring of fire*—can be seen with transvaginal color Doppler imaging. Although this can aid diagnosis, this finding can also be seen with a corpus luteum cyst, and differentiation can be challenging.

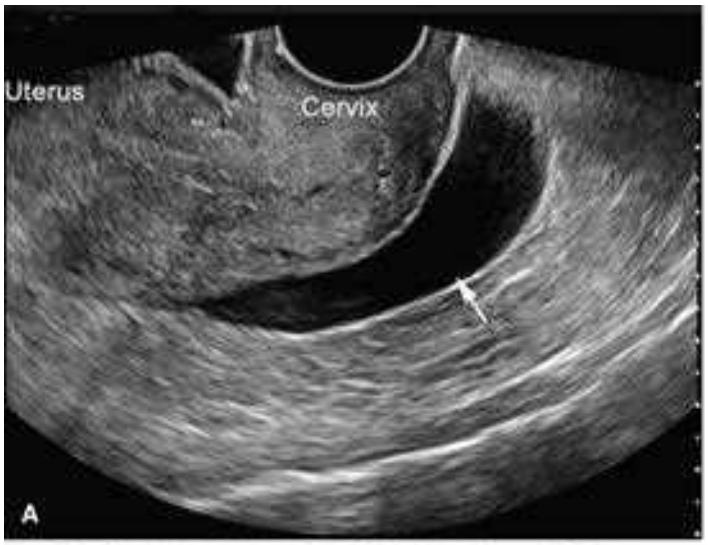
Hemoperitoneum

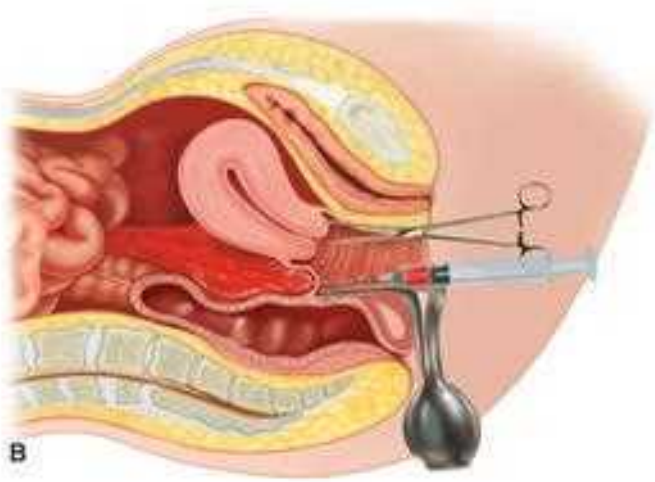
In affected women, blood in the peritoneal cavity is most often identified using sonography, but assessment can also be made by culdocentesis (Fig. 19-6). Sonographically, anechoic or hypoechoic fluid initially collects in the dependent retrouterine cul-de-sac, and then additionally surrounds the uterus as it fills the pelvis. As much as 50 mL of blood can be seen in the cul-de-sac using TVS, and transabdominal imaging then is used to assess the hemoperitoneum extent. Importantly, however, a small amount of peritoneal fluid is physiologically normal. With significant intraabdominal hemorrhage, blood will track up the pericolic gutters to fill Morison pouch near the liver. Free fluid in this pouch typically is not seen until accumulated volumes reach 400 to 700 mL (Branney, 1995; Rodgerson,

2001; Rose, 2004). Diagnostically, peritoneal fluid in conjunction with an adnexal mass is highly predictive of ectopic pregnancy (Nyberg, 1991). Ascites from ovarian or other cancer is a notable mimic.

FIGURE 19-6

Techniques to identify hemoperitoneum. **A.** Transvaginal sonography of an anechoic fluid collection (*arrow*) in the retrouterine cul-de-sac. **B.** Culdocentesis: with a 16- to 18-gauge spinal needle attached to a syringe, the cul-de-sac is entered through the posterior vaginal fornix as upward traction is applied to the cervix with a tenaculum. (B, Reproduced with permission from Gala RB: Ectopic pregnancy. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)





Culdocentesis is a simple technique used commonly in the past. The cervix is pulled outward and upward toward the symphysis with a tenaculum, and a long 18-gauge needle is inserted through the posterior vaginal fornix into the retrouterine cul-de-sac. If present, fluid can be aspirated. However, a failure to do so is interpreted only as unsatisfactory entry into the cul-de-sac. Fluid containing fragments of old clots or bloody fluid that does not clot suggests hemoperitoneum. In contrast, if the blood sample clots, it may have been obtained from an adjacent blood vessel or from a briskly bleeding ectopic pregnancy. Several studies have challenged its usefulness, and culdocentesis has been largely replaced by TVS (Glezerman, 1992; Vermesh, 1990).

Endometrial Sampling

Several endometrial changes accompany ectopic pregnancy, and all lack coexistent trophoblast. Decidual reaction is found in 42 percent of samples, secretory endometrium in 22 percent, and proliferative endometrium in 12 percent (Lopez, 1994). Some recommend that the absence of trophoblastic tissue be confirmed by D&C before methotrexate treatment is given (Chung, 2011; Shaunik, 2011). Investigators found that the presumptive diagnosis of ectopic pregnancy is inaccurate in nearly 40 percent of cases without histological exclusion of a spontaneous pregnancy loss. Nevertheless, the risks of D&C are weighed against the limited maternal risks of methotrexate.

Endometrial biopsy with a Pipelle catheter was studied as an alternative to D&C and found inferior (Barnhart, 2003b; Ries, 2000). By comparison, frozen section of curettage fragments to identify products of conception is accurate in more than 90 percent of cases (Barak, 2005; Li, 2014b).

Laparoscopy

Direct visualization of the fallopian tubes and pelvis by laparoscopy offers a reliable diagnosis in most cases of suspected ectopic pregnancy. This also permits a ready transition to definitive operative therapy, which is discussed in Surgical Management.

Medical Management

Regimen Options

Medical therapy traditionally involves the antimetabolite methotrexate (MTX). This drug is a folic acid antagonist. It tightly binds to dihydrofolate reductase, blocking the reduction of dihydrofolate to tetrahydrofolate, which is the active form of folic acid. As a result, de novo purine and pyrimidine synthesis is halted, which leads to arrested DNA, RNA, and protein synthesis. Thus, MTX is highly effective against rapidly proliferating tissue such as trophoblast. Overall, ectopic tubal pregnancy resolution rates approximate 90 percent with its use. The drawbacks, however, are that bone marrow, gastrointestinal mucosa, and respiratory epithelium can also be harmed. It is directly toxic to hepatocytes and is renally excreted. MTX is also a potent teratogen, and MTX embryopathy is notable for craniofacial and skeletal abnormalities and fetal-growth restriction (Nurmohamed, 2011). In addition, MTX is excreted into breast milk and may accumulate in neonatal tissues and interfere with neonatal cellular metabolism (American Academy of Pediatrics, 2001; Briggs, 2015). Based on all these findings, a list of contraindications and pretherapy laboratory testing is found in Table 19-1.

TABLE 19-1

Medical Treatment Protocols for Ectopic Pregnancy

	Single Dose	Multidose
Dosing	One dose; repeat if necessary	Up to four doses of both drugs until serum β-hCG declines by 15%
Medication dosage Methotrexate Leucovorin	 50 mg/m^2 BSA (day 1) NA	 1 mg/kg, days 1, 3, 5, and 7 0.1 mg/kg days 2, 4, 6, and 8
Serum β-hCG level	Days 1 (baseline), 4, and 7	Days 1 (baseline), 3, 5, and 7
Indication for additional dose	If serum β-hCG level does not decline by 15% from day 4 to day 7 Less than 15% decline during weekly surveillance	If serum β-hCG level declines <15%, give additional dose; repeat serum β-hCG in 48 hours and compare with previous value; maximum four doses
Surveillance	Once 15% decline achieved, then weekly serum β-hCG levels until undetectable	
Methotrexate Contraindications		
Sensitivity to MTX Tubal rupture Breastfeeding	Intrauterine pregnancy Peptic ulcer disease Active pulmonary disease	

BSA = body surface area; β-hCG =β-human chorionic gonadotropin; MTX = methotrexate; NA = not applicable.

Data from American Society for Reproductive Medicine, 2013.

Of precautions, MTX is bound primarily to albumin, and its displacement by other medications such as phenytoin, tetracyclines, salicylates, and sulfonamides can increase MTX serum drug levels. Moreover, renal clearance of MTX may be impaired by nonsteroidal antiinflammatory drugs including aspirin, probenecid, or penicillins (Stika, 2012). Last, vitamins containing folic acid may lower MTX efficacy.

For ease and efficacy, intramuscular MTX administration is used most often for ectopic pregnancy medical resolution, and single-dose and multidose MTX protocols are available (see Table 19-1). As noted, MTX can lead to bone marrow depression. This toxicity can be blunted by early administration of leucovorin, which is *folinic acid* and has activity equivalent to folic acid. Thus, leucovorin, which is given within the multidose protocol, allows for some purine and pyrimidine synthesis to buffer side effects.

In comparing these two protocols, trade-offs are recognized. For example, single-dose therapy offers simplicity, less expense, and less intensive posttherapy monitoring and does not require leucovorin rescue. However, some but not all studies report a higher success rate for the multidose regimen (Alleyassin, 2006; Barnhart, 2003a; Lipscomb, 2005). At our institution, we use single-dose MTX.

Patient Selection

The best candidate for medical therapy is the woman who is asymptomatic, motivated, and compliant. With medical therapy, some classic predictors of success include a low initial serum β-hCG level, small ectopic pregnancy size, and absent fetal cardiac activity. Of these, initial serum β-hCG level is the single best prognostic indicator of successful treatment with single-dose MTX. Specifically, reported failure rates are 1.5 percent if the initial serum β-hCG concentration is <1000 mIU/mL; 5.6 percent at 1000 to 2000 mIU/mL; 3.8 percent at 2000 to 5000 mIU/mL; and 14.3 percent when levels range between 5000 and 10,000 mIU/mL (Menon, 2007). Interestingly, the initial serum β-hCG value is not a valid indicator of the number of doses needed for successful resolution (Nowak-Markwitz, 2009).

Many early trials also used “large size” as an exclusion criterion, although these data are less precise. Lipscomb and colleagues (1998) reported a 93-percent success rate with single-dose MTX when the ectopic mass was <3.5 cm. This compared with success rates between 87 and 90 percent when the mass was >3.5 cm. Last, failure rates rise if cardiac activity is seen, with an 87-percent success rate in such cases.

Treatment Side Effects

These regimens are associated with minimal laboratory changes and symptoms, although occasional toxicity may be severe. Kooi and Kock (1992) reviewed 16 studies and reported that adverse effects resolved by 3 to 4 days after MTX was discontinued. The most common were liver involvement—12 percent; stomatitis— 6 percent; and gastroenteritis—1 percent. One woman had bone marrow depression. Fortunately, MTX treatment does not diminish ovarian reserve (Boots, 2016; Uyar, 2013). Moreover, conceptions within the first 6 months after MTX treatment for this indication are not associated with elevated rates of miscarriage or fetal malformations and growth restriction (Svirsky, 2009).

Importantly, 65 to 75 percent of women initially given MTX will have increasing pain beginning several days after therapy. Thought to reflect separation of the ectopic pregnancy from the tubal wall, this "separation pain" generally is mild and relieved by analgesics. In a series of 258 MTX-treated women by Lipscomb and colleagues (1999b), 20 percent had pain that merited evaluation in a clinic or emergency room. Ultimately, 10 of these 53 underwent surgical exploration. Said another way, 20 percent of women given single-dose MTX will have significant pain, and about 20 percent of these will require laparoscopy.

Monitoring Therapy Efficacy

As shown in Table 19-1, monitoring single-dose therapy calls for serum β-hCG determinations at days 4 and 7 following initial injection on day 1. After single-dose MTX, mean serum β-hCG levels may rise or fall during the first 4 days and then gradually decline. If the level fails to drop more than 15 percent between days 4 and 7, then a second dose of MTX is required. This is necessary in 15 to 20 percent of women treated with single-dose therapy (Cohen, 2014a; Kirk, 2007).

With multidose MTX, levels are measured at 48-hour intervals until they fall more than 15 percent. Up to four doses may be given to one patient if required (Stovall, 1991).

Once appropriately dropping levels are achieved in either regimen, serum β-hCG determinations are then measured weekly until undetectable. Outpatient monitoring is preferred, but if patient safety or compliance is questioned, the woman is hospitalized during initial surveillance. Lipscomb and colleagues (1998) used single-dose MTX to successfully treat 287 women and reported that the average time to resolution—defined as a serum β-hCG level <15 mIU/mL, was 34 days. Importantly, the longest time was 109 days.

Failure is judged when the β-hCG level plateaus or rises or the tube ruptures. Importantly, tubal rupture can occur even with declining β-hCG levels. Lipscomb and associates (1998) described a 14-day mean time to rupture, but one woman had tubal rupture 32 days after single-dose MTX.

From one metaanalysis, the overall success rate for treatment with MTX is 89 percent. The success for the multidose regiment is 92.7 percent, whereas that for single-dose is 88.1 percent (Barnhart, 2003a). Despite this difference, the single dose is more frequently used because of its simplicity and convenience.

Surgical Management

Studies have compared laparotomy with laparoscopic surgery for ectopic pregnancy (Lundorff, 1991; Murphy, 1992; Vermesh, 1989). Overall, tubal patency and number of subsequent uterine pregnancies do not differ between these routes. Thus, laparoscopy is the preferred surgical treatment for ectopic pregnancy unless a woman is hemodynamically unstable. As experience has accrued, cases previously managed by laparotomy—for example, ruptured tubal pregnancies with hemoperitoneum—can safely be managed laparoscopically by those with suitable expertise (Cohen, 2013; Sagiv, 2001). That said, the lowered venous return and cardiac output associated with the pneumoperitoneum of laparoscopy must be factored into the decision to select minimally invasive surgery for hypovolemic women.

Before surgery, future fertility desires are discussed. In women desiring permanent sterilization, the unaffected tube can be ligated or removed concurrently with salpingectomy for the affected fallopian tube.

Two procedures—salpingostomy or salpingectomy—are options. Two multicenter, randomized controlled trials have compared laparoscopic outcomes between the two procedures in women with a normal contralateral fallopian tube. The European Surgery in Ectopic Pregnancy (ESEP) study randomized 231 women to salpingectomy and 215 to salpingostomy. After surgery, subsequent rates of ongoing pregnancy by natural conception did not differ significantly between groups—56 versus 61 percent, respectively (Mol, 2014). Again, in the DEMETER trial, the subsequent 2-year rate for achieving a uterine pregnancy did not differ between groups—64 versus 70 percent, respectively (Fernandez, 2013). In women with an abnormal-appearing contralateral tube, salpingostomy is a conservative option for fertility preservation.

Salpingostomy

This procedure is typically used to remove a small unruptured pregnancy. A 10- to 15-mm linear incision is made on the antimesenteric border of the fallopian tube over the pregnancy. The products usually will extrude from the incision. These can be carefully removed or flushed out using high-pressure irrigation that more thoroughly removes the trophoblastic tissue (Al-Sunaidi, 2007). Small bleeding sites are controlled with needlepoint electrocoagulation, and the incision is left unsutured to heal by secondary intention. Serum β-hCG levels are used to monitor response to both medical and surgical therapy. After linear salpingostomy, serum β-hCG levels decline rapidly over days and then more gradually, with a mean resolution time of approximately 20 days.

Seldom performed today, salpingotomy is essentially the same procedure except that the incision is closed with delayed-absorbable suture. According to Tulandi and Guralnick (1991), prognosis does not differ with or without suturing, and laparoscopic suturing adds surgical time.

Salpingectomy

Tubal resection may be used for both ruptured and unruptured ectopic pregnancies. To minimize the rare recurrence of pregnancy in the tubal stump, complete excision of the fallopian tube is advised. With one laparoscopic technique, the affected fallopian tube is lifted and held with atraumatic grasping forceps (Thompson, 2016). One of several suitable bipolar grasping devices is placed across the fallopian tube at the uterotubal junction. Once desiccated, the tube is cut. The bipolar device is then advanced across the most proximal portion of mesosalpinx. Similarly, current is applied, and the desiccated tissue cut. This process moves serially from the proximal mesosalpinx to its distal extent under the tubal ampulla. Alternatively, an endoscopic suture loop can be used to encircle and ligate the knuckle of involved fallopian tube and its underlying vascular supply within the mesosalpinx. Two consecutive suture loops are placed, and the tube distal to these ligatures is then cut free with scissors. Salpingectomy during laparotomy is shown in Chapter 39 (Nonpuerperal Tubal Sterilization).

Most tubal ectopic pregnancies are small and pliant. Accordingly, they can be held firmly by grasping forceps and drawn up into one of the accessory site cannulas. Larger tubal ectopic pregnancies may be placed in an endoscopic sac to prevent fragmentation as they are removed through the laparoscopic port site. Importantly, to remove all trophoblastic tissue, the pelvis and abdomen should be irrigated and suctioned free of blood and tissue debris. Slow and systematic movement of the patient from Trendelenburg to reverse Trendelenburg positioning during irrigation can also assist in dislodging stray tissue and fluid. These should be suctioned and removed from the peritoneal cavity.

Persistent Trophoblast

After surgery, β-hCG levels usually fall quickly and approximate 10 percent of preoperative values by day 12 (Hajenius, 1995; Vermesh, 1988). Persistent trophoblast is rare following salpingectomy, but complicates 5 to 15 percent of salpingostomies (Kayatas, 2014; Pouly, 1986; Seifer, 1993). Rates are lower for laparotomy versus laparoscopic procedures (Hajenius, 1995). Other risk factors are debatable but may include greater serum β-hCG levels and smaller ectopic size (Rabischong, 2010; Seifer, 1997). Bleeding caused by retained trophoblast is the most serious complication.

Incomplete removal of trophoblast can be identified by stable or rising β-hCG levels. Monitoring approaches are not codified. One scheme measures serum β-hCG levels on postoperative day 1, and values dropping <50 percent of the preoperative value reflect risk for persistent trophoblast (Spandorfer, 1997). Another measures weekly levels (Mol, 2008). With stable or increasing β-hCG levels, additional surgical or medical therapy is necessary. Without evidence for tubal rupture, standard therapy for this is single-dose MTX, 50 mg/m^2 × body surface area (BSA). Rupture and bleeding require surgical intervention.

Medical versus Surgical Therapy

Several randomized trials have compared methotrexate treatment with laparoscopic surgery. One multicenter trial compared a multidose MTX protocol with laparoscopic salpingostomy and found no differences for tubal preservation and primary treatment success (Hajenius, 1997). In this same study group, however, health-related quality-of-life factors such as pain, posttherapy depression, and decreased perception of health were significantly impaired after systemic MTX compared with laparoscopic salpingostomy (Nieuwkerk, 1998). In their randomized controlled trial, Fernandez and coworkers (2013) compared multidose medical therapy against salpingostomy and found that medical and conservative surgery provided similar 2-year rates of attaining a uterine pregnancy.

Evidence is conflicting when single-dose MTX is compared with surgical intervention. In two separate studies, single-dose MTX was overall less successful in resolving pregnancy than laparoscopic salpingostomy, although tubal patency and subsequent uterine pregnancy rates were similar between both groups (Fernandez, 1998; Sowter, 2001). Women treated with MTX had significantly better physical functioning immediately following therapy, but there were no differences in psychological functioning. Krag Moeller and associates (2009) reported the results from their randomized trial that had a median surveillance period of 8.6 years during which future pregnancy rates were evaluated. Ectopic-resolution success rates were not significantly different between those managed surgically and those treated with MTX. Moreover, cumulative spontaneous uterine pregnancy rates were not different between the MTX group (73 percent) and the surgical group (62 percent).

Based on these studies, we conclude that women who are hemodynamically stable and in whom there is a small tubal diameter, no fetal cardiac activity, and serum β-hCG concentrations <5000 mIU/mL have similar outcomes with medical or surgical management. Despite lower success rates with medical therapy for women with larger tubal size, higher serum β-hCG levels, and fetal cardiac activity, medical management can be offered to the motivated woman who understands the risks.

Expectant Management

In select cases, it is reasonable to observe very early tubal pregnancies that are associated with stable or falling serum β-hCG levels. Mavrelos and coworkers (2013) noted that almost one third of 333 tubal ectopic pregnancies measuring <3 cm and with β-hCG levels <1500 mIU/mL resolved without intervention. Cohen and associates (2014b) similarly followed 674 women with declining β-hCG levels to successful resolution. These findings have been supported by smaller randomized trials (Jurkovic, 2017; van Mello, 2013).

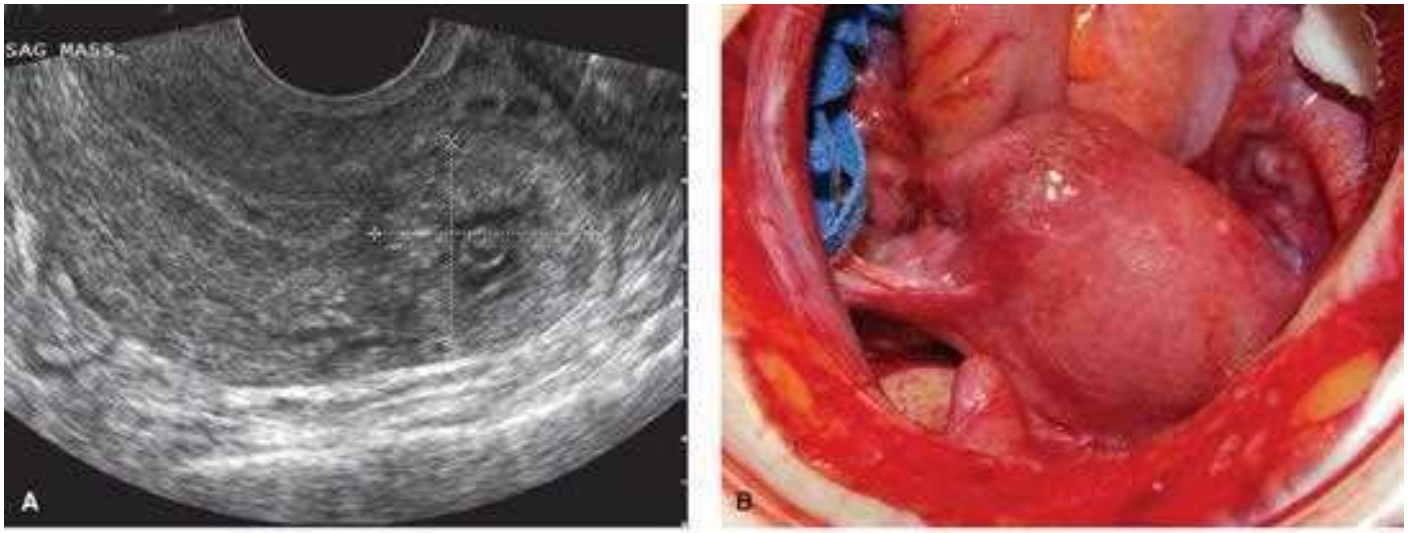
With expectant management, subsequent rates of tubal patency and intrauterine pregnancy are comparable with surgical or medical management. That said, compared with the established safety of medical and surgical therapy, the prolonged surveillance and risks of tubal rupture support the practice of expectant therapy only in appropriately selected and counseled women.

INTERSTITIAL PREGNANCY

Diagnosis

An interstitial pregnancy is one that implants within the proximal tubal segment that lies within the muscular uterine wall (Fig. 19-7). Incorrectly, they may be called cornual pregnancies, but this term describes a conception that develops in the rudimentary horn of a uterus with a müllerian anomaly (Moawad, 2010). Risk factors are similar to others discussed for tubal ectopic pregnancy, although previous ipsilateral salpingectomy is a specific risk factor for interstitial pregnancy (Lau, 1999). Undiagnosed interstitial pregnancies usually rupture following 8 to 16 weeks of amenorrhea, which is later than for more distal pregnancies. This is due to greater distensibility of the myometrium covering the interstitial fallopian tube segment. Because of the proximity of these pregnancies to the uterine and ovarian arteries, hemorrhage can be severe and associated with mortality rates as high as 2.5 percent (Tulandi, 2004).

FIGURE 19-7
Interstitial ectopic pregnancy. **A.** This parasagittal view using transvaginal sonography shows an empty uterine cavity and a mass that is cephalad and lateral to the uterine fundus (*calipers*). **B.** Intraoperative photograph during laparotomy and before cornual resection of the same ectopic pregnancy. In this frontal view, the bulging right-sided interstitial ectopic pregnancy is lateral to the round ligament insertion and medial to the isthmic portion of the fallopian tube. (Used with permission from Drs. David Rogers and Elaine Duryea.)



With transvaginal sonography and serum β-hCG assays, interstitial pregnancy can now be diagnosed early in many cases, but diagnosis can be challenging. These pregnancies sonographically can appear similar to an eccentrically implanted uterine pregnancy, especially in a uterus with a müllerian anomaly. Criteria that may aid differentiation include: an empty uterus, a gestational sac seen separate from the endometrium and >1 cm away from the most lateral edge of the uterine cavity, and a thin, <5-mm myometrial mantle surrounding the sac (Timor-Tritsch, 1992). Moreover, an echogenic line, known as the "interstitial line sign," extending from the gestational sac to the endometrial cavity most likely represents the interstitial portion of the fallopian tube and is highly sensitive and specific (Ackerman, 1993a). In unclear cases, three-dimensional (3-D) sonography, magnetic resonance (MR) imaging, or diagnostic laparoscopy can help clarify anatomy (Parker, 2012; Tanaka, 2014). Laparoscopically, an enlarged protuberance is found lying outside the round ligament and coexistent with a normal distal fallopian tube and ovary.

Management

Surgical management with either cornual resection or cornuostomy may be performed via laparotomy or laparoscopy, depending on patient hemodynamic stability and surgeon expertise (Hoffman, 2016; Zuo, 2012). With either approach, intraoperative intramyometrial vasopressin injection may limit surgical blood loss, and β-hCG levels should be monitored postoperatively to exclude remnant trophoblast. Cornual resection removes the gestational sac and surrounding cornual myometrium by means of a wedge excision (Fig. 19-8). Alternatively, cornuostomy involves incision of the cornua and suction or instrument extraction of the pregnancy. Both instances require myometrial closure.

FIGURE 19-8
During cornual resection, the pregnancy, surrounding myometrium, and ipsilateral fallopian tube are excised en bloc. The incision is angled inward as it is deepened. This creates a wedge shape into the myometrium, which is then closed in layers with delayed-absorbable suture. The serosa is closed with subcuticular style suturing. (Reproduced with permission from Hoffman BL, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

With early diagnosis, medical management may be considered. But because of the low incidence, consensus regarding methotrexate regimens is lacking. In their small series, Jermy and associates (2004) reported a 94-percent success with systemic MTX using a dose of 50 mg/m^2 × BSA. Others have described direct MTX injection into the gestational sac (Framarino-dei-Malatesta, 2014). Importantly, because these women typically have higher initial serum β-hCG levels, longer surveillance is usually needed.

The risk of uterine rupture with subsequent pregnancies following either medical or surgical management is unclear. Thus, careful observation of these women during pregnancy, along with strong consideration of elective cesarean delivery, is warranted.

Distinct from interstitial pregnancy, the term *angular pregnancy* describes implantation within the endometrial cavity but at one cornu and medial to the uterotubal junction and round ligament. An angular pregnancy displaces the round ligament upward and outward, whereas an interstitial tubal pregnancy does not shift it (Arleo, 2014). This distinction is important because angular pregnancies can sometimes be carried to term but with increased risk of abnormal placentation and its consequences (Jansen, 1981).

CESAREAN SCAR PREGNANCY

Diagnosis

This term describes implantation within the myometrium of a prior cesarean delivery scar. Its incidence approximates 1 in 2000 normal pregnancies and has increased along with the cesarean delivery rate (Ash, 2007; Rotas, 2006). The pathogenesis of cesarean scar pregnancy (CSP) has been likened to that for placenta accreta and carries similar risk for serious hemorrhage (Timor-Tritsch, 2014a,b). It is unknown if the incidence increases with multiple cesarean deliveries or if it is affected by either one- or two-layer uterine incision closure during cesarean.

Women with CSP usually present early, and pain and bleeding are common. Still, up to 40 percent of women are asymptomatic, and the diagnosis is made during routine sonographic examination (Rotas, 2006). Sonographically, differentiating between a cervicoisthmic intrauterine pregnancy and CSP can be difficult (Moschos, 2008a; Timor-Tritsch, 2016). According to Godin (1997), four sonographic criteria should be satisfied for the diagnosis and are described in Figure 19-9. Although TVS is the typical first-line imaging tool, MR imaging is useful when sonography is inconclusive (Huang, 2014; Osborn, 2012).

FIGURE 19-9

Cesarean scar pregnancy. **A.** Transvaginal sonogram of a uterus with a cesarean scar pregnancy (CSP) in a sagittal plane. An empty uterine cavity is identified by a bright hyperechoic endometrial stripe (*long, white arrow*). An empty cervical canal is similarly identified (*short, white arrow*). Last, an intrauterine mass is seen in the anterior part of the uterine isthmus (*red arrows*). Myometrium between the bladder and gestational sac is absent or thinned (1 to 3 mm). Photo contributor: Dr. Elysia Moschos.) **B.** Hysterectomy specimen containing a cesarean scar pregnancy. **C.** This same hysterectomy specimen is transversely sectioned at the level of the uterine isthmus and through the gestational sac. The uterine body lies to the left, and the cervix is on the right. A metal probe is placed through the endocervical canal to show the eccentric development of this gestation. Only a thin layer of myometrium overlies this pregnancy, which pushes anteriorly through the uterine wall. (Reproduced with permission from Gala RB: Ectopic pregnancy. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education; 2016. Photo contributors: Drs. Sunil Balgobin, Manisha Sharma, and Rebecca Stone.)

Management

Treatment standards are lacking, and several options are available. Expected management is an option, and live birth rates were 57 percent in one review (Maheux-Lacroix, 2017). However, hemorrhage, placenta accreta, and uterine rupture are risks. Thus, hysterectomy is an acceptable initial choice in those desiring sterilization. It is sometimes necessary with heavy uncontrolled bleeding. Fertility-preserving options include systemic or locally injected methotrexate, either alone or combined with conservative surgery (Birch Petersen, 2016; Cheung, 2015). Surgical procedures include visually guided suction curettage, hysteroscopic removal, or isthmic excision done abdominally or vaginally. These are completed solely or with adjunctive MTX (Jurkovic, 2016; Li, 2014a; Wang, 2014; Yang, 2009). Often uterine artery embolization (UAE) is used preoperatively to minimize hemorrhage risk (Zhang, 2012; Zhuang, 2009). Foley balloon catheter placement can be another option for procedure-associated bleeding (Timor-Tritsch, 2015a).

Following conservative treatment, subsequent pregnancies have good outcomes, but placenta accreta and recurrent CSP are risks (Gao, 2016; Wang, 2015). Uterine arteriovenous malformations are a potential long-term complication (Timor-Tritsch, 2015b).

CERVICAL PREGNANCY

Diagnosis

This rare ectopic pregnancy is defined by cervical glands noted histologically opposite the placental attachment site and by all or part of the placenta found below the entrance of the uterine vessels or below the peritoneal reflection on the anterior uterus. In a typical case, the endocervix is eroded by trophoblast, and the pregnancy develops in the fibrous cervical wall. Predisposing risks include ART and prior uterine curettage (Ginsburg, 1994; Jeng, 2007).

Painless vaginal bleeding is reported by 90 percent of women with a cervical pregnancy—a third of these have massive hemorrhage (Ushakov, 1997). As pregnancy progresses, a distended, thin-walled cervix with a partially dilated external os may be evident. Above the cervical mass, a slightly enlarged uterine fundus can be felt. Identification of cervical pregnancy is based on speculum examination, palpation, and TVS. Sonographic findings typical of cervical pregnancy are shown and described in Figure 19-10. MR imaging and 3-D sonography have also been used to confirm the diagnosis (Jung, 2001; Sherer, 2008).

FIGURE 19-10

Cervical pregnancy. Transvaginal sonographic findings may include: (1) an hourglass uterine shape and ballooned cervical canal; (2) gestational tissue at the level of the cervix (*black arrow*); (3) absent intrauterine gestational tissue (*white arrows*); and (4) a portion of the endocervical canal seen interposed between the gestation and the endometrial canal. (Used with permission from Dr. Elysia Moschos.)

Management

Cervical pregnancy may be treated medically or surgically. Conservative management strives to minimize hemorrhage, resolve the pregnancy, and preserve fertility. In many centers, including ours, methotrexate has become the first-line therapy in stable women, and administration follows protocols listed in Table 19-1 (Verma, 2011; Zakaria, 2011). The drug has also been injected directly into the gestational sac, alone or with systemic doses (Jeng, 2007; Murji, 2015). Others describe MTX infusion combined with uterine artery embolization—"chemoembolization" (Xiaolin, 2010).

With MTX regimens, resolution and uterine preservation are achieved for gestations <12 weeks in 91 percent of cases (Kung, 1997). In selecting appropriate candidates, Hung and colleagues (1996) noted higher risks of systemic MTX treatment failure in those with a gestational age >9 weeks, β-hCG levels >10,000 mIU/mL, crown-rump length >10 mm, and fetal cardiac activity. For this reason, many induce fetal death with intracardiac or intrathoracic injection of potassium chloride. With a single-dose intramuscular protocol, an MTX dose between 50 and 75 mg/m^2 × BSA is typical. To resolve fetal cardiac activity, a sonographically guided fetal intracardiac injection of 2 mL (2 mEq/mL) potassium chloride solution can be given (Verma, 2009). Song and associates (2009) described management of 50 cases and observed that sonographic resolution lagged far behind serum β-hCG regression.

As an adjunct to medical or surgical therapy, uterine artery embolization has been described either as a response to bleeding or as a preprocedural preventive tool (Hirakawa, 2009; Zakaria, 2011). Also, in the event of hemorrhage, a 26F Foley catheter with a 30-mL balloon can be placed intracervically and inflated to effect

hemostasis by vessel tamponade and to monitor uterine drainage. The balloon remains inflated for 24 to 48 hours and is gradually decompressed over a few days (Ushakov, 1997).

Although conservative management is feasible for many women with cervical pregnancies, suction curettage or hysterectomy may be selected. Moreover, hysterectomy may be required with bleeding uncontrolled by conservative methods. Because of the close proximity of the ureters to the ballooned cervix, urinary tract injury rates are a concern during hysterectomy.

If cervical curettage is planned, intraoperative bleeding may be lessened by preoperative UAE, by intracervical vasopressin injection, or by a cerclage placed at the internal cervical os to compress feeding vessels (Chen, 2015; Fylstra, 2014; Wang, 2011). Also, cervical branches of the uterine artery can effectively be ligated with vaginal placement of hemostatic cervical sutures on the lateral aspects of the cervix at 3 and 9 o'clock (Bianchi, 2011). Following curettage, a Foley balloon can be placed to tamponade bleeding and is managed as described earlier. Suction curettage may be especially favored in rare cases of a heterotopic pregnancy composed of a cervical and a desired uterine pregnancy (Tsakos, 2015).

ABDOMINAL PREGNANCY

Diagnosis

These rare ectopic pregnancies are defined as an implantation in the peritoneal cavity exclusive of tubal, ovarian, or intraligamentous implantations. Although a zygote can traverse the tube and implant primarily in the peritoneal cavity, most abdominal pregnancies are thought to follow early tubal rupture or abortion with reimplantation. In cases of advanced extrauterine pregnancy, it is not unusual for the placenta to be still at least partially attached to the uterus or adnexa.

Diagnosis may be difficult. First, symptoms may be absent or vague. Laboratory tests are typically uninformative, although maternal serum alpha-fetoprotein levels can be elevated. Clinically, abnormal fetal positions may be palpated, or the cervix is displaced (Zeck, 2007). Sonographically, the diagnosis is often missed (Costa, 1991). Oligohydramnios is common but nonspecific. Other clues include a fetus seen separate from the uterus or eccentrically positioned within the pelvis; lack of myometrium between the fetus and the maternal anterior abdominal wall or bladder; extrauterine placental tissue; or bowel loops surrounding the gestational sac (Allibone, 1981; Chukus, 2015). If additional anatomical information is needed, MR imaging can help confirm the diagnosis and provide maximal information concerning placental implantation (Bertrand, 2009; Mittal, 2012).

Management

Treatment of an abdominal pregnancy depends on the gestational age at diagnosis. Conservative management carries a maternal risk for sudden and dangerous hemorrhage. Moreover, Stevens (1993) reported fetal malformations and deformations in 20 percent. Thus, we believe that termination generally is indicated when the diagnosis is made. Certainly, before 24 weeks, conservative treatment rarely is justified. Despite this, some have described waiting until fetal viability with close surveillance (Kim, 2013; Marcellin, 2014).

Once placental implantation has been assessed, several options to control intraoperative hemorrhage mimic those used for placenta accrete syndrome (Chap. 41, Adjunctive Surgical Procedures). The principal surgical objectives involve delivery of the fetus and careful assessment of placental implantation without provoking hemorrhage. Unnecessary exploration is avoided because the anatomy is commonly distorted and surrounding areas are extremely vascular. Importantly, placental removal may precipitate torrential hemorrhage because the normal hemostatic mechanism of myometrial contraction to constrict hypertrophied blood vessels is lacking. If it is obvious that the placenta can be safely removed or if there is already hemorrhage from its implantation site, then removal begins immediately. When possible, blood vessels supplying the placenta should be ligated first.

Some advocate leaving the placenta in place as the lesser of two evils. It decreases the chance of immediate life-threatening hemorrhage, but at the expense of long-term sequelae. If left in the abdominal cavity, the placenta commonly becomes infected, with subsequent formation of abscesses, adhesions, intestinal or ureteral obstruction, and wound dehiscence (Bergstrom, 1998; Martin, 1988). In many of these cases, surgical removal becomes inevitable. If the placenta is left, its involution may be monitored using sonography and serum β-hCG levels (France, 1980; Martin, 1990). Color Doppler sonography can be used to assess changes in blood flow. In some cases, and usually depending on its size, placental function rapidly declines, and the placenta is resorbed. But placental resorption may take years (Roberts, 2005; Valenzano, 2003).

If the placenta is left in place, postoperative methotrexate use is controversial. It has been recommended to hasten involution but has been reported to cause accelerated placental destruction with accumulation of necrotic tissue and infection with abscess formation (Rahman, 1982). It is difficult to envision a supporting role for the use of an antimetabolite for a senescent organ (Worley, 2008).

OVARIAN PREGNANCY

Ectopic implantation of the fertilized egg in the ovary is rare and is diagnosed if four clinical criteria are met. These were outlined by Spiegelberg (1878): (1) the ipsilateral tube is intact and distinct from the ovary; (2) the ectopic pregnancy occupies the ovary; (3) the ectopic pregnancy is connected by the uteroovarian ligament to the uterus; and (4) ovarian tissue can be demonstrated histologically amid the placental tissue. Risk factors are similar to those for tubal pregnancies, but ART or IUD failure seems to be disproportionately associated (Zhu, 2014). Presenting complaints and findings mirror those for tubal ectopic pregnancy. Although the ovary can accommodate the expanding pregnancy more easily than the fallopian tube, rupture at an early stage is the usual consequence (Melcer, 2016).

Transvaginal sonography use has resulted in a more frequent diagnosis of unruptured ovarian pregnancies. Sonographically, an internal anechoic area is surrounded by a wide echogenic ring, which in turn is surrounded by ovarian cortex (Comstock, 2005). In their review of 49 cases, Choi and associates (2011) noted that the

diagnosis may not be made until surgery, as many cases are presumed tubal ectopic pregnancy. Moreover, at surgery, an early ovarian pregnancy may be considered to be a hemorrhagic corpus luteum.

Evidence-based management accrues mainly from case reports (Hassan, 2012; Scutiero, 2012). Classically, management for ovarian pregnancies has been surgical. Small lesions can be managed by ovarian wedge resection or cystectomy, whereas larger lesions require oophorectomy (Elwell, 2015; Melcer, 2015). With conservative surgery, β-hCG levels should be monitored to exclude remnant trophoblast.

OTHER ECTOPIC SITES

Pregnancy implanted toward the mesosalpinx may rupture into a space formed between the broad ligament leaves and become an intraligamentous or broad ligament pregnancy. Rents in prior cesarean scars serve as another conduit (Rudra, 2013). These are rare, and information accrues from case reports. Clinical findings and management mirror those for abdominal pregnancy. Although laparotomy is required in most instances, a few case reports describe laparoscopic excision of early small pregnancies (Apantaku, 2006; Cormio, 2006).

Ectopic placental implantations in less expected sites have been described in case reports and include the omentum, liver, and retroperitoneum, among others (Brouard, 2015; Liang, 2014; Watrowski, 2015). Also, intramural uterine implantations at sites other than a cesarean scar have been noted in women with prior uterine surgeries, ART, or adenomyosis (Memtsa, 2013; Wu, 2013). Although laparotomy is preferred by many for these ectopic sites, laparoscopic excision by those with suitable skills is gaining acceptance.

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CHAPTER 20: Gestational Trophoblastic Disease

> *… the terminal extremities of the chorionic villi are converted into transparent vesicles with clear, viscid contents. These vary in size from minute bodies a few millimetres in diameter to cystic structures the size of hazel-nuts, and hang in clusters from the villous stems, to which they are connected by thin pedicles, giving to the external surface of the chorion a grape-like appearance.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

Gestational trophoblastic disease (GTD) is the term used to encompass a group of tumors typified by abnormal trophoblast proliferation. Trophoblast produces human chorionic gonadotropin (hCG), thus the measurement of this peptide hormone in serum is essential for GTD diagnosis, management, and surveillance. GTD histologically is divided into *hydatidiform moles,* which are characterized by the presence of villi, and into nonmolar trophoblastic malignant neoplasms, which lack villi.

Hydatidiform moles are excessively edematous immature placentas (Benirschke, 2012). These include the benign *complete hydatidiform mole* and *partial hydatidiform mole* and the malignant *invasive mole.* Invasive mole is deemed malignant due to its marked penetration into and destruction of the myometrium and its ability to metastasize.

Nonmolar trophoblastic neoplasms include choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These three are differentiated by the type of trophoblast they contain.

The malignant forms of gestational trophoblastic disease are termed *gestational trophoblastic neoplasia (GTN).* These include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Other terms applied to GTN are *malignant gestational trophoblastic disease* and *persistent gestational trophoblastic disease.* These malignancies develop weeks or years following any type of pregnancy, but frequently follow a hydatidiform mole.

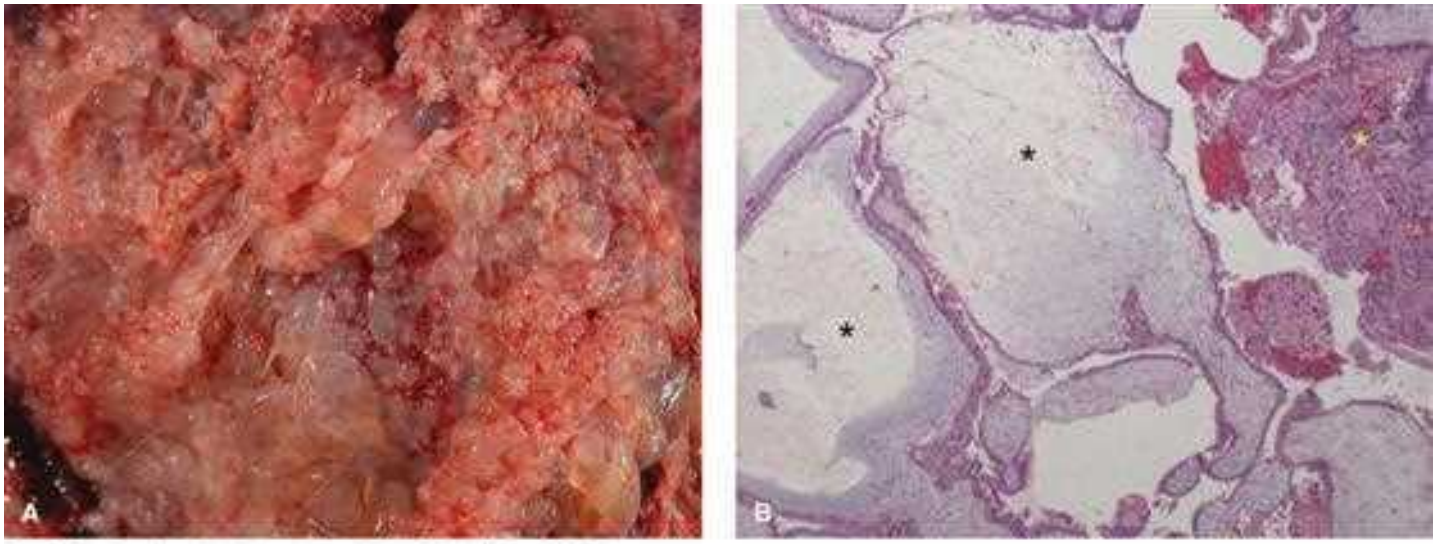
Each of the GTN malignancy types is histologically distinct and varies in its propensity to invade and metastasize. However, histological confirmation is typically not available. Instead, measurement of serum hCG levels combined with clinical findings— rather than a histological specimen—is used to diagnose and treat this malignancy. Accordingly, GTN is often identified and effectively treated as a group.

In the past, these metastatic tumors had a prohibitively high mortality rate. However, with chemotherapy, most tumors currently are highly curable. Early-stage GTN is typically cured with single-agent chemotherapy, whereas later-stage disease usually responds to combination chemotherapy (Ngan, 2015).

HYDATIDIFORM MOLE

The classic histological findings of molar pregnancy include trophoblast proliferation and villi with stromal edema (Fig. 20-1). The degree of histological changes, karyotypic differences, and the absence or presence of embryonic elements are used to classify them as either *complete* or *partial moles.* These two also vary in their associated risks for developing medical comorbidities and postevacuation GTN. Of the two, GTN more frequently follows complete hydatidiform mole.

FIGURE 20-1
Complete hydatidiform mole. **A.** Gross specimen with characteristic vesicles of variable size. (Used with permission from Dr. Brian Levenson.) **B.** Low-magnification photomicrograph shows generalized edema and cistern formation (*black asterisks*) within avascular villi. Haphazard trophoblastic hyperplasia is marked by a yellow asterisk on the right. (Used with permission from Dr. Erika Fong.)



A complete mole has abnormal chorionic villi that grossly appear as a mass of clear vesicles. These vary in size and often hang in clusters from thin pedicles. In contrast, a partial molar pregnancy has focal and less advanced hydatidiform changes and contains some fetal tissue. Both forms of moles usually fill the uterine cavity, but they rarely may be tubal or other forms of ectopic pregnancy (Hassadia, 2012; Sebire, 2005).

Epidemiology and Risk Factors

An ethnic predisposition is seen with hydatidiform mole, which has increased prevalence in Asians, Hispanics, and American Indians (Drake, 2006; Lee, 2011; Smith, 2006). The incidence in the United States and Europe has been relatively constant at 1 to 2 per 1000 deliveries (Eysbouts, 2016; Lee, 2011).

The strongest risk factors are age and a prior hydatidiform mole. Women at both extremes of reproductive age are most vulnerable. Specifically, adolescents and women aged 36 to 40 years have a twofold risk, but those older than 40 have an almost tenfold risk (Altman, 2008; Sebire, 2002a). With a prior complete mole, the risk of another mole is 0.9 percent, and with a previous partial mole, the rate is 0.3 percent. After two prior complete moles, approximately 20 percent of women have a third mole (Eagles, 2015).

Pathogenesis

Molar pregnancies typically arise from chromosomally abnormal fertilizations Figure 20-2. Complete moles most often have a diploid chromosomal composition (Table 20-1). These usually are 46,XX and result from *androgenesis,* meaning both sets of chromosomes are paternal in origin. The chromosomes of the ovum are either absent or inactivated. The ovum is fertilized by a haploid sperm, which then duplicates its own chromosomes after meiosis. Less commonly, the chromosomal pattern may be 46,XY or 46,XX and due to fertilization by two sperm, that is, *dispermic fertilization* or *dispermy* (Lawler, 1991; Lipata, 2010).

TABLE 20-1

Features of Partial and Complete Hydatidiform Moles

Feature	Partial Mole	Complete Mole
Karyotype[a]	69,XXX or 69,XXY	46,XX
Clinical Presentation		
Preliminary diagnosis	Missed abortion	Molar gestation
Uterine size	Small for dates	Large for dates
Theca-lutein cysts	Rare	25–30% of cases
Initial hCG levels	<100,000 mIU/mL	>100,000 mIU/mL
Medical complications[b]	Rare	Uncommon
Rate of subsequent GTN	1–5% of cases	15–20% of cases
Pathology		
Pathology		
Embryo-fetus	Often present	Absent
Amnion, fetal erythrocytes	Often present	Absent
Villous edema	Focal	Widespread
Trophoblastic proliferation	Focal, slight to moderate	Slight to severe
Trophoblast atypia	Mild	Marked
$p57^{KIP2}$ immunostaining	Positive	Negative

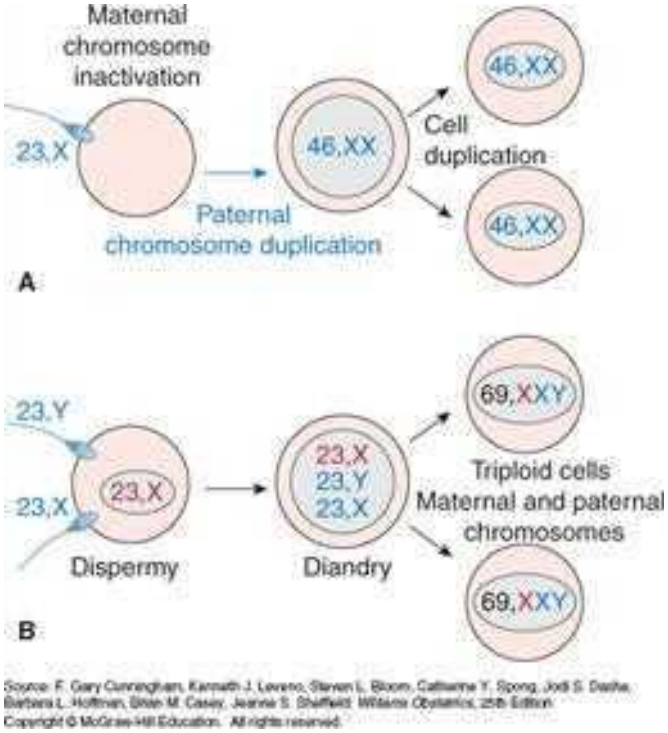
[a]Typical karyotypes.

[b]These include anemia, hyperthyroidism, hyperemesis gravidarum, preeclampsia, and infection.

GTN = gestational trophoblastic neoplasia; hCG = human chorionic gonadotropin.

FIGURE 20-2

Typical pathogenesis of complete and partial moles. **A.** A 46,XX complete mole may be formed if a 23,X-bearing haploid sperm penetrates a 23,X-containing haploid egg whose genes have been "inactivated." Paternal chromosomes then duplicate to create a 46,XX diploid complement solely of paternal origin. **B.** A partial mole may be formed if two sperm—either 23,X- or 23,Y-bearing—both fertilize (dispermy) a 23,X-containing haploid egg whose genes have not been inactivated. The resulting fertilized egg is triploid with two chromosome sets being donated by the father. This paternal contribution is termed diandry..



Partial moles usually have a triploid karyotype—69,XXX, 69,XXY—or much less commonly, 69,XYY. These are each composed of two paternal haploid sets of chromosomes contributed by dispermy and one maternal haploid set (see Fig. 20-2B). Less frequently, a similar haploid egg may be fertilized by an unreduced diploid 46,XY sperm. These triploid zygotes result in some embryonic development, however, it ultimately is a lethal fetal condition (Joergensen, 2014; Lakovschek, 2011). Fetuses that reach advanced ages have severe growth restriction, multiple congenital anomalies, or both.

Twin Pregnancy

Rarely, in some twin pregnancies, one chromosomally normal fetus is paired with a complete diploid molar pregnancy. Importantly, these cases must be distinguished from a single partial molar pregnancy with its associated abnormal fetus. Amniocentesis and fetal karyotyping aid confirmation.

Several unique pregnancy problems complicate such twin pregnancies. And, many women may choose to terminate the gestation, if diagnosed early. In those with continuing pregnancy, survival of the normal fetus varies and depends on associated comorbidity from the molar component. The most worrisome are preeclampsia or hemorrhage, which frequently necessitate preterm delivery. Wee and Jauniaux (2005) reviewed outcomes in 174 women, of whom 82 chose termination. Of the remaining 92 pregnancies, 42 percent either miscarried or had a perinatal death; approximately 60 percent delivered preterm; and only 40 percent delivered at term.

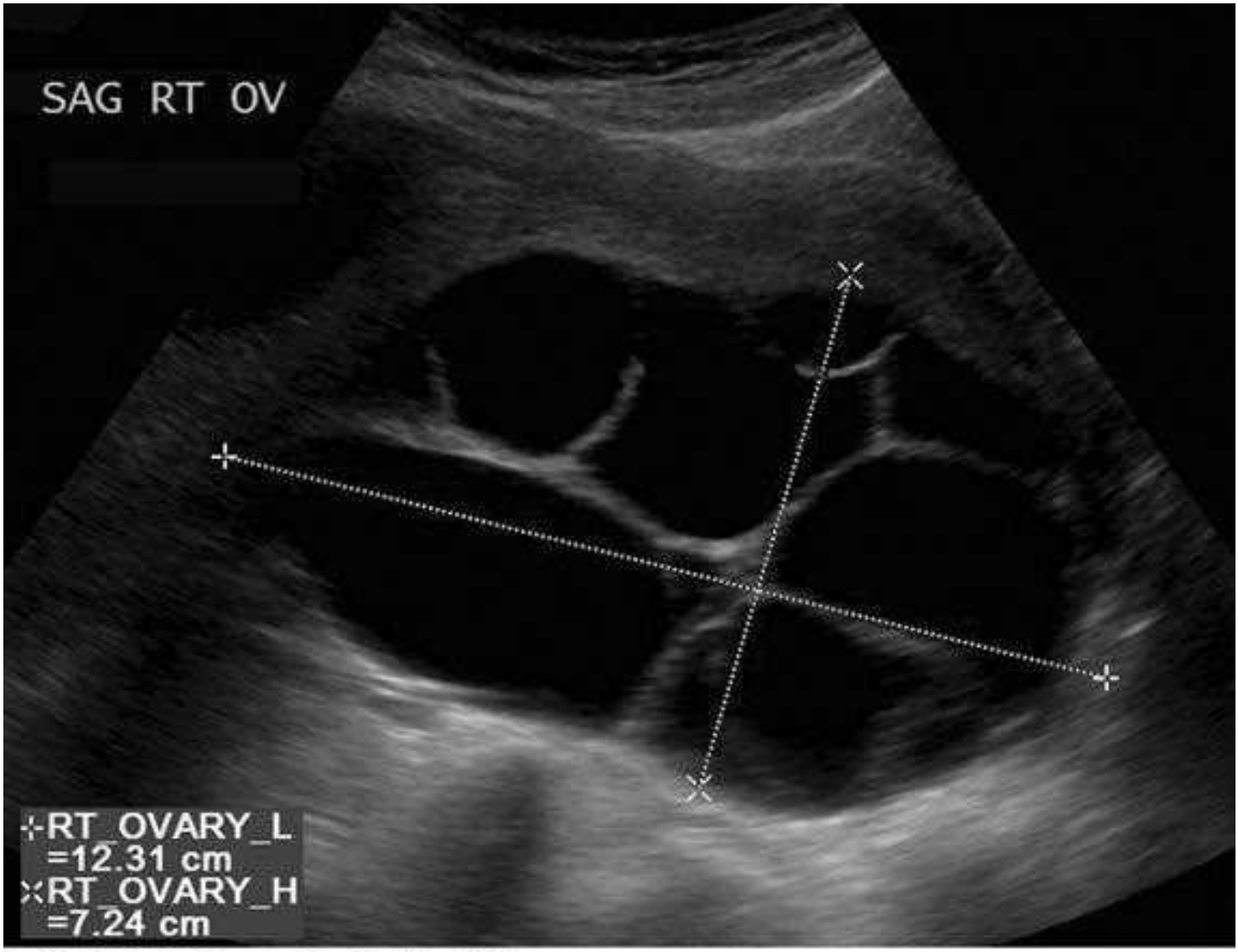
Another concern for those continuing their pregnancy is the risk for developing subsequent GTN. However, most data indicate no significant difference between women who continue or terminate their pregnancy (Massardier, 2009; Sebire, 2002b). Postdelivery surveillance is conducted as for any molar pregnancy (Gestational Trophoblastic Neoplasia).

Clinical Findings

The presentation of women with a molar pregnancy has changed remarkably over the past several decades because prenatal care is sought much earlier and because sonography is virtually universal. Typically, 1 to 2 months of amenorrhea precede the diagnosis. For example, in 194 women with a complete mole, evacuation was completed at a median gestational age of 9 weeks and at 12 weeks for 172 patients with a partial mole (Sun, 2015b). As a result, most molar pregnancies are detected before complications ensue (Kerkmeijer, 2009; Mangili, 2008).

As gestation advances, symptoms tend to be more pronounced with complete compared with partial moles (Niemann, 2007). Untreated molar pregnancies will almost always cause uterine bleeding that varies from spotting to profuse hemorrhage. Bleeding may presage spontaneous molar abortion, but more often, it follows an intermittent course for weeks to months. In more advanced moles with considerable concealed uterine hemorrhage, moderate iron-deficiency anemia develops. Nausea and vomiting may be significant. Of physical findings, many women have uterine growth that is more rapid than expected, and the enlarged uterus is comparatively softer. Fetal heart motion is absent with complete moles. The ovaries can be fuller and cystic from multiple theca-lutein cysts (Fig. 20-3). These are more common with a complete mole and likely result from ovarian overstimulation by excessive hCG levels. Because theca-lutein cysts regress following pregnancy evacuation, expectant management is preferred. Occasionally a larger cyst may undergo torsion, infarction, and hemorrhage. However, oophorectomy is not performed unless extensive infarction persists after untwisting.

FIGURE 20-3
Sonographic image of an ovary with theca-lutein cysts in a woman with a hydatidiform mole.



The thyrotropin-like effects of hCG frequently cause serum free thyroxine (fT_4) levels to be elevated and thyroid-stimulating hormone (TSH) levels to be decreased. Despite this, clinically apparent thyrotoxicosis is unusual and in our experience can be mimicked by bleeding and sepsis from infected products. Moreover, the serum free T_4 levels rapidly normalize after uterine evacuation. Despite this, cases of presumed "thyroid storm" have been reported (Kofinas, 2015).

Severe preeclampsia and eclampsia are relatively common with advanced molar pregnancies. However, these are seldom seen today because of early diagnosis and evacuation. An exception is the case of a normal fetus coexisting with a complete mole, described earlier. In continuing twin gestations, severe preeclampsia frequently mandates preterm delivery.

Diagnosis

Serum β-HCG Measurements

Most women initially have irregular bleeding that almost always prompts pregnancy testing and sonography. Some women will present with spontaneous passage of molar tissue.

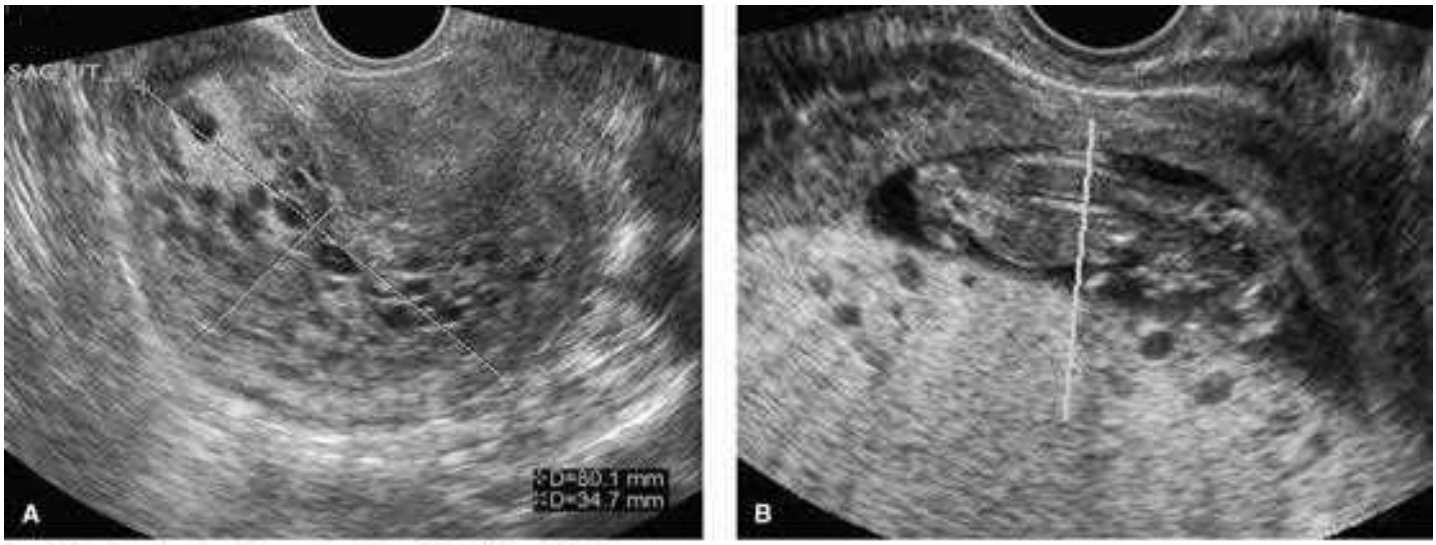
With a complete molar pregnancy, serum β-hCG levels are commonly elevated above those expected for gestational age. With more advanced moles, values in the millions are not unusual. Importantly, these high values can lead to erroneous false-negative *urine* pregnancy test results. Termed a "hook effect," excessive β-hCG hormone levels oversaturate the assay's targeting antibody and create a falsely low reading (Cormano, 2016). In these cases, *serum* β-hCG determinations with or without sample dilution will clarify the conundrum. With a partial mole, β-hCG levels may also be significantly elevated, but more commonly concentrations fall into ranges expected for gestational age.

Sonography

Although this is the mainstay of trophoblastic disease diagnosis, not all cases are confirmed initially. Sonographically, a complete mole appears as an echogenic uterine mass with numerous anechoic cystic spaces but without a fetus or amnionic sac. The appearance is often described as a “snowstorm” (Fig. 20-4). A partial mole has features that include a thickened, multicystic placenta along with a fetus or at least fetal tissue. However, in early pregnancy, these sonographic characteristics are seen in fewer than half of hydatidiform moles. In the largest series of more than 1000 patients with molar pregnancy, the reported sensitivity and specificity of sonography were 44 and 74 percent, respectively (Fowler, 2006). The most common mimics are incomplete or missed abortion. Occasionally, molar pregnancy may be confused for a multifetal pregnancy or a uterine leiomyoma with cystic degeneration.

FIGURE 20-4

Sonograms of hydatidiform moles. **A.** Sagittal view of a uterus with a complete hydatidiform mole. The characteristic “snowstorm” appearance is due to an echogenic uterine mass, marked by calipers, that has numerous anechoic cystic spaces. Notably, a fetus and amnionic sac are absent. **B.** In this image of a partial hydatidiform mole, the fetus is seen above a multicystic placenta. (Used with permission from Dr. Elysia Moschos.)



Pathology

Surveillance for subsequent neoplasia following molar pregnancy is crucial. Thus, moles must be distinguished from other types of pregnancy failure that have hydropic placental degeneration, which can mimic molar villous changes. Some distinguishing histological characteristics are shown in Table 20-1.

In pregnancies before 10 weeks, classic molar changes may not be apparent because villi may not be enlarged and molar stroma may not yet be edematous and avascular. Histopathologic evaluation can be enhanced by immunohistochemical staining for p57 expression and by molecular genotyping (Banet, 2014). $p57^{KIP2}$ is a nuclear protein whose gene is paternally imprinted and maternally expressed. This means that the gene product is produced only in tissues containing a maternal allele. Because complete moles contain only paternal genes, the $p57^{KIP2}$ protein is absent in complete moles, and tissues do not pick up this stain (Merchant, 2005). In contrast, this nuclear protein is strongly expressed in normal placentas, in spontaneous pregnancy losses with hydropic degeneration, and in partial hydatidiform moles (Castrillon, 2001). Accordingly, immunostaining for $p57^{KIP2}$ is an effective means to isolate complete mole from the diagnostic list. For distinction of a partial mole from a nonmolar hydropic abortus, both of which express p57, molecular genotyping can be used. Molecular genotyping determines the parental source of alleles. Thereby, it can distinguish among a diploid diandric genome (complete mole), a triploid diandric-monogynic genome (partial mole), or biparental diploidy (nonmolar abortus).

Management

Maternal deaths from molar pregnancies are rare because of early diagnosis, timely evacuation, and vigilant postevacuation surveillance for GTN. Preoperative evaluation attempts to identify known potential complications such as preeclampsia, hyperthyroidism, anemia, electrolyte depletions from hyperemesis, and metastatic disease (Table 20-2) (Lurain, 2010). Most recommend chest radiography, whereas computed tomography (CT) and magnetic resonance (MR) imaging are not routinely done unless a chest radiograph shows lung lesions or unless other extrauterine disease is suspected.

TABLE 20-2

Some Considerations for Management of Hydatidiform Mole

Preoperative
Laboratory
Hemogram; serum β-hCG, creatinine, electrolyte, and hepatic aminotransferase levels
TSH, free T_4 levels
Type and Rh; group and screen or crossmatch
Chest radiograph
Consider hygroscopic dilators
Intraoperative
Large-bore intravenous catheter(s)
Regional or general anesthesia
Oxytocin (Pitocin): 20 units in 1000 mL Ringer lactate for continuous infusion
One or more other uterotonic agents may be added as needed:
Methylergonovine (Methergine): 0.2 mg = 1 mL = 1 ampule IM every 2 hr prn
Carboprost tromethamine ($PGF_{2\alpha}$) (Hemabate): 250 µg = 1 mL = 1 ampule IM every 15–90 min prn
Misoprostol (PGE_1) (Cytotec): 200 mg tablets for rectal administration, 800–1000 mg once
Karman cannula—size 10 or 14 mm
Consider sonography machine
Postevacuation
Anti-D immune globulin (Rhogam) if Rh D-negative
Initiate effective contraception[a]
Review pathology report
Serum hCG levels: within 48 hours of evacuation, weekly until undetectable, then monthly for 6 months

[a]Intrauterine devices are not suitable during surveillance.

hCG = human chorionic gonadotropin; IM = intramuscular; PG = prostaglandin; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

Molar Pregnancy Termination

Regardless of uterine size, molar evacuation by suction curettage is usually the preferred treatment. Preoperative cervical dilatation with an osmotic dilator is recommended if the cervix is minimally dilated. Intraoperative bleeding can be greater with molar pregnancy than with a comparably sized uterus containing nonmolar products. Thus with large moles, adequate anesthesia, sufficient intravenous access, and blood-banking support is imperative. The cervix is mechanically dilated to preferably allow insertion of a larger suction curette. Depending on uterine size, a 10- to 14-mm diameter is typical. As evacuation is begun, oxytocin is infused to limit bleeding. Intraoperative sonography is often recommended to help ensure complete uterine cavity emptying. When the myometrium has contracted, a thorough but gentle curettage with a sharp large-loop Sims curette is performed. If bleeding continues despite uterine evacuation

and oxytocin infusion, other uterotonic agents are given (see Table 20-2). In rare cases, pelvic arterial embolization or hysterectomy may be necessary (Tse, 2007). Profuse hemorrhage and surgical methods that may be useful for its management are discussed in Chapter 41 (General Considerations).

Some volume of trophoblast is deported into the pelvic venous system during molar evacuation (Hankins, 1987). With large moles, the amount of tissue may be sufficient to produce clinically apparent respiratory insufficiency, pulmonary edema, or even embolism. In our earlier experiences with substantial moles, these and their chest radiographic manifestations clear rapidly without specific treatment. However, fatalities have been described (Delmis, 2000). Because of deportation, there is concern that trophoblastic tissue will thrive within the lung parenchyma to cause persistent disease or even overt malignancy. Fortunately, no evidence suggests that this is a major problem.

Following curettage, anti-D immunoglobulin (Rhogam) is given to Rh D-negative women because fetal tissues with a partial mole may include red cells with D-antigen (Chap. 15, Prevention of Anti-D Alloimmunization). Those with suspected complete mole are similarly treated because a definitive diagnosis of complete versus partial mole may not be confirmed until histological evaluation of the evacuated products.

Following evacuation, the long-term prognosis for women with a hydatidiform mole is not improved with prophylactic chemotherapy. Moreover, chemotherapy toxicity—including death—may be significant, and thus it is not recommended routinely (Gueye, 2014; Wang, 2017).

Methods other than suction curettage can be considered for select cases. Hysterectomy with ovarian preservation may be preferable for women with complete moles who have finished childbearing. Of women aged 40 to 49 years, 30 to 50 percent will subsequently develop GTN, and hysterectomy markedly reduces this likelihood (Bandy, 1984; Elias, 2010, 2012). Theca-lutein cysts seen at the time of hysterectomy do not require removal, and they spontaneously regress following molar termination. Labor induction or hysterotomy is seldom used for molar evacuation in the United States. Both will likely increase blood loss and theoretically may increase the incidence of persistent trophoblastic disease (American College of Obstetricians and Gynecologists, 2016; Tidy, 2000).

Postevacuation Surveillance

Close biochemical surveillance for persistent gestational neoplasia follows each hydatidiform mole evacuation. This monitoring is by serial measurement of serum β-hCG to detect persistent or renewed trophoblastic proliferation. As a glycoprotein, hCG shows structural heterogeneity and exists in different isoforms. Thus for surveillance, an hCG assay that can detect all forms of hCG should be used (Harvey, 2010; Ngan, 2015). These are different from those used for routine pregnancy testing (de Medeiros, 2009). The initial β-hCG level is obtained within 48 hours after evacuation. This serves as the baseline, which is compared with β-hCG quantification done thereafter every 1 to 2 weeks until levels progressively decline to become undetectable.

The median time for such resolution is 7 weeks for partial moles and 9 weeks for complete moles. Once β-hCG is undetectable, this is confirmed with monthly determinations for another 6 months (Lurain, 2010; Sebire, 2007). Concurrently, reliable contraception is imperative to avoid confusion caused by rising β-hCG levels from a new pregnancy. Most recommend combination hormonal contraception, injectable depot medroxyprogesterone acetate, or progestin implant (Dantas, 2017). The latter two are particularly useful if poor patient compliance is anticipated. Intrauterine devices are not used until β-hCG levels are undetectable because of the risk of uterine perforation if there is an invasive mole. Although not recommended, if a woman conceives during surveillance, live-birth rates and risk for congenital anomalies appear to mirror the general population (Tuncer, 1999a,b). After these 6 months, monitoring is discontinued and pregnancy allowed.

Importantly, during β-hCG level surveillance, either increasing or persistently plateaued levels mandate evaluation for trophoblastic neoplasia. If the woman has not become pregnant, then these levels signify increasing trophoblastic proliferation that is most likely malignant. Several factors predispose a patient to trophoblastic neoplasia following molar evacuation. Most important, complete moles have a 15 to 20 percent incidence of malignant sequelae, compared with 1 to 5 percent following partial moles. Surprisingly, with much earlier recognition and evacuation of molar pregnancies, the risk for neoplasia has not been lowered (Schorge, 2000; Sun, 2015a). Other risk factors are older maternal age, β-hCG levels >100,000 mIU/mL, uterine size that is large for gestational age, theca-lutein cysts >6 cm, and slow decline in β-hCG levels (Berkowitz, 2009; Kang, 2012; Wolfberg, 2005).

GESTATIONAL TROPHOBLASTIC NEOPLASIA

This group includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. These tumors almost always develop with or after some form of recognized pregnancy. Half follow hydatidiform mole, a fourth follow miscarriage or tubal pregnancy, and another fourth develop after a preterm or term pregnancy (Goldstein, 2012). Although these four tumor types are histologically distinct, they are usually diagnosed solely by persistently elevated serum β-hCG levels because tissue is infrequently available for study. Criteria to diagnose postmolar GTN are shown in Table 20-3.

TABLE 20-3

Criteria for Diagnosis of Gestational Trophoblastic Neoplasia

1. Plateau of serum β-hCG level (± 10 percent) for four measurements during a period of 3 weeks or longer—days 1, 7, 14, 21
2. Rise of serum β-hCG level >10 percent during three weekly consecutive measurements or longer, during a period of 2 weeks or more—days 1, 7, 14
3. Serum β-hCG level remains detectable for 6 months or more
4. Histological criteria for choriocarcinoma

Clinical Findings

These placental tumors are characterized clinically by their aggressive invasion into the myometrium and propensity to metastasize. The most common finding with GTN is irregular bleeding associated with uterine subinvolution. The bleeding may be continuous or intermittent, with sudden and sometimes massive hemorrhage. Myometrial perforation from trophoblastic growth may cause intraperitoneal hemorrhage. In some women, lower genital tract metastases are evident, whereas in others only distant metastases are found with no trace of uterine tumor.

Diagnosis, Staging, and Prognostic Scoring

Consideration for the possibility of GTN is the most important factor in its recognition. Unusually persistent bleeding after any type of pregnancy should prompt measurement of serum β-hCG levels and consideration for diagnostic curettage if levels are elevated. Uterine size is assessed along with careful examination for lower genital tract metastases, which usually appear as bluish vascular masses (Cagayan, 2010). Tissue diagnosis is unnecessary, thus biopsy is not required and may cause significant bleeding.

Once the diagnosis is verified, in addition to a baseline serum β-hCG level and hemogram, a search for local disease and metastases includes tests of liver and renal function, transvaginal sonography, chest CT scan or radiograph, and brain and abdominopelvic CT scan or MR imaging. Less commonly, positron-emission tomographic (PET) scanning and cerebrospinal fluid β-hCG level determination are used to identify metastases (Lurain, 2011).

GTN is staged clinically using the system of the International Federation of Gynecology and Obstetrics (FIGO) (2009). This includes a modification of the World Health Organization (WHO) (1983) prognostic index score, with which scores of 0 to 4 are given for each of the categories shown in Table 20-4. Women with WHO scores of 0 to 6 are considered to have low-risk disease, whereas those with a score ≥7 are considered in the high-risk group.

TABLE 20-4

International Federation of Gynecology and Obstetrics (FIGO) Staging and Diagnostic Scoring System for Gestational Trophoblastic Neoplasia

Anatomical Staging					
Stage I	Disease confined to the uterus				
Stage II	GTN extends outside of the uterus but is limited to the genital structures (adnexa, vagina, broad ligament)				
Stage III	GTN extends to the lungs, with or without known genital tract involvement				
Stage IV	All other metastatic sites				
Modified World Health Organization (WHO) Prognostic Scoring System[a]					
Scores[b]		**0**	**1**	**2**	**4**
Age (years)		<40	≥40	—	—
Antecedent pregnancy		Mole	Abortion	Term	—
Interval after index pregnancy (mo)		<4	4–6	7–12	>12
Pretreatment serum β-hCG (mIU/mL)		$<10^3$	10^3 to 10^4	10^4 to 10^5	≥10^5
Largest tumor size (including uterus)		<3 cm	3–4 cm	≥5 cm	—
Site of metastases		—	Spleen, kidney	GI	Liver, brain
Number of metastases		—	1–4	5–8	>8
Previous failed chemotherapy drugs			—	1	≥2

[a]Adapted by FIGO.

[b]Low risk = WHO score of 0 to 6; high risk = WHO score of ≥7.

β-hCG = beta human chorionic gonadotropin; GI = gastrointestinal; GTN = gestational trophoblastic neoplasia.

Adapted with permission from FIGO Committee on Gynecologic Oncology: Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia, Int J Gynaecol Obstet 2009 Apr;105(1):3–4.

Histological Classification

Again, it is stressed that the diagnosis of trophoblastic neoplasias is usually made by persistently elevated serum β-hCG levels without confirmation by tissue study. Clinical staging is assigned without regard to histological findings, even if available. Still, there are distinct histological types, described next.

Invasive Mole

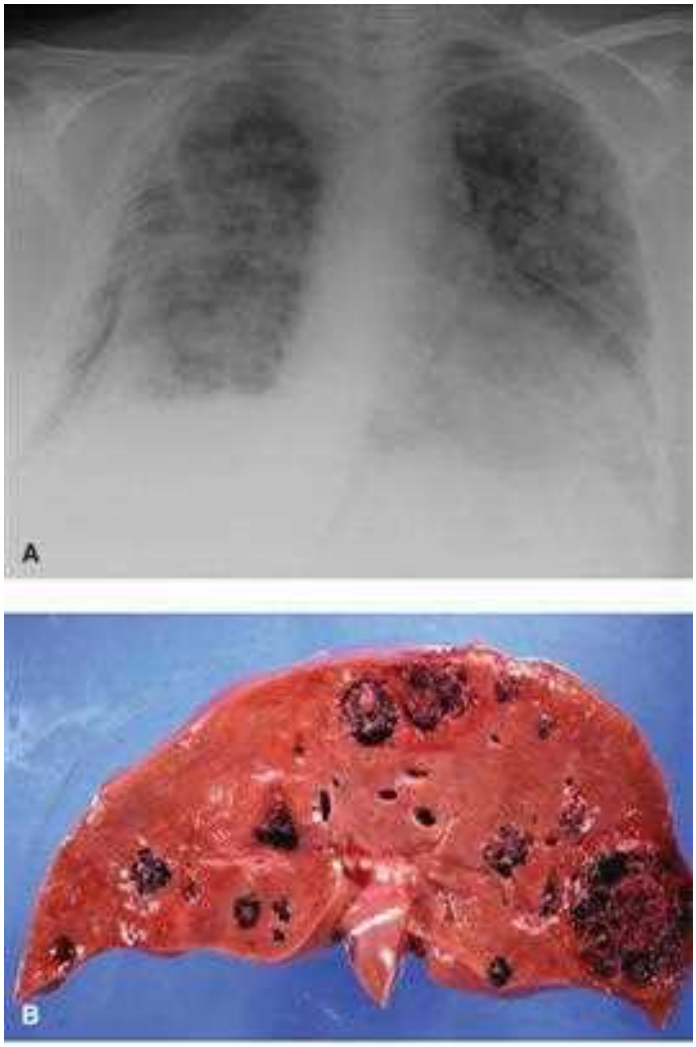
These are the most common trophoblastic neoplasms that follow hydatidiform moles, and almost all invasive moles arise from partial or complete moles. Previously known as *chorioadenoma destruens*, invasive mole is characterized by extensive tissue invasion by trophoblast and whole villi. There is penetration deep into the myometrium, sometimes with involvement of the peritoneum, adjacent parametrium, or vaginal vault. Although locally aggressive, invasive moles are less prone to metastasize.

Gestational Choriocarcinoma

This is the most common type of trophoblastic neoplasm to follow a term pregnancy or a miscarriage, and only a third of cases follow a molar gestation (Soper, 2006). Choriocarcinoma is composed of cells reminiscent of early cytotrophoblast and syncytiotrophoblast, however, it contains no villi. This rapidly growing tumor invades both myometrium and blood vessels to create hemorrhage and necrosis. Myometrial tumor may spread outward and become visible on the uterine surface as dark, irregular nodules. Metastases often develop early and are generally blood-borne (Fig. 20-5). The most common sites are the lungs and vagina, but tumor may travel to the vulva, kidneys, liver, brain, ovaries, and bowel. Bleeding can complicated these metastases (Fatema, 2016; Wei, 2016; Zhang, 2017). Choriocarcinomas are commonly accompanied by ovarian theca-lutein cysts.

FIGURE 20-5

Metastatic choriocarcinoma. **A.** Chest radiograph demonstrates widespread metastatic lesions. **B.** Autopsy specimen with multiple hemorrhagic hepatic metastases. (Used with permission from Dr. Michael Conner.)



Placental Site Trophoblastic Tumor

This rare tumor arises from *intermediate trophoblasts* at the placental site. These tumors have associated serum β-hCG levels that may be only modestly elevated. However, they produce variant forms of hCG, and identification of a high proportion of free β-hCG is considered diagnostic. Treatment of placental site trophoblastic tumor by hysterectomy is preferred because these locally invasive tumors are usually resistant to chemotherapy (Baergen, 2006). For higher-risk stage I and for later stages, adjuvant multidrug chemotherapy is also given (Schmid, 2009).

Epithelioid Trophoblastic Tumor

This rare tumor develops from chorionic-type intermediate trophoblast. The uterus is the main site of involvement, and bleeding and low hCG levels are typical findings (Scott, 2012). Primary treatment is hysterectomy because this tumor is relatively resistant to chemotherapy. Metastatic disease is common, and combination chemotherapy is employed (Davis, 2015).

Treatment

Women with GTN are best managed by oncologists, and some evidence supports treatment in centers specializing in GTN (Kohorn, 2014). The prognosis is excellent with rare exceptions, and patients are routinely cured even in the presence of widespread disease. Chemotherapy alone is usually the primary treatment. Although controversial, some also consider a second uterine evacuation to be an adjuvant therapeutic option in some GTN cases to avoid or minimize chemotherapy (Pezeshki, 2004; van Trommel, 2005). In other cases, suction curettage may infrequently be needed to resolve bleeding or remove a substantial amount of retained molar tissue. In specific cases, hysterectomy may be primary or adjuvant treatment (Clark, 2010).

Single-agent chemotherapy protocols are usually sufficient for nonmetastatic or low-risk metastatic neoplasia (Lawrie, 2016). In their review of 108 women with low-risk disease, Abrão and colleagues (2008) reported that monotherapy protocols with either methotrexate or actinomycin D were equally effective compared with a regimen containing both. In general, methotrexate is less toxic than actinomycin D (Chan, 2006; Seckl, 2010). Regimens are repeated until serum β-hCG levels are undetectable.

Combination chemotherapy is given for high-risk disease, and reported cure rates approximate 90 percent (Lurain, 2010). Several regimens have been used with success. One is EMA-CO, which includes etoposide, methotrexate, actinomycin D, cyclophosphamide, and Oncovin (vincristine). In selected cases, adjuvant surgical and radiotherapy may also be employed (Hanna, 2010). Frequent causes of death include hemorrhage from metastatic sites, respiratory failure, sepsis, and multiorgan failure due to widespread chemoresistant disease (Lybol, 2012; Neubauer, 2015).

With either low- or high-risk disease, once serum β-hCG levels are undetectable, serosurveillance is continued for 1 year. During this time, effective contraception is crucial to avoid any teratogenic effects of chemotherapy to the fetus and to mitigate confusion from rising β-hCG levels caused by superimposed pregnancy (Seckl, 2010; Williams, 2014). For those who conceive despite this within the surveillance year following treatment, pregnancy may continue since most will have a favorable outcome (Tse, 2012; Woolas, 1998). Importantly, this group is advised of the low but important risk of delayed diagnosis if tumor recurs during the pregnancy (Blagden, 2002; Tuncer, 1999b).

A small number of women during surveillance, despite no evidence of metastases, will be found to have very low β-hCG levels that plateau. This phenomenon is called *quiescent hCG* and presumably is caused by dormant trophoblast. Close observation without therapy is recommended, but 20 percent will eventually have recurrent active and progressive trophoblastic neoplasia (Ngu, 2014).

SUBSEQUENT PREGNANCY

Women with prior hydatidiform mole generally do not have impaired fertility, and their pregnancy outcomes are usually normal (Joneborg, 2014; Matsui, 2011; Sebire, 2003). One concern is the 2-percent risk for developing trophoblastic disease in a subsequent pregnancy, which was described earlier. Sonographic evaluation is recommended in early pregnancy, and subsequently if indicated.

Women who have successfully completed GTN chemotherapy are advised to delay pregnancy for 12 months. Fertility and pregnancy outcomes are typically normal, and congenital anomaly rates are not increased (Berkowitz, 2000; Tse, 2012). One exception is an unexplained higher stillbirth rate of 1.5 percent compared with a background rate of 0.8 percent (Vargas, 2014).

After hydatidiform mole or GTN treatment, in subsequent pregnancy, the placenta or products of conception are sent for pathological evaluation at delivery. A serum β-hCG level is measured 6 weeks postpartum (Lurain, 2010).

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CHAPTER 21: Physiology of Labor

From time immemorial inquiring minds have sought an explanation for the fact that labour usually ensues about 280 days after the appearance of the last menstrual period, but thus far no satisfactory universal cause has been discovered.

—J. Whitridge Williams (1903)

INTRODUCTION

The importance of labor physiology was highlighted in the first edition of *Williams Obstetrics*, in which an entire section was devoted to the topic. Given the science at that time, those nine chapters were concerned with the mechanics of labor and delivery. However, the current understanding of labor includes a wide spectrum of preparedness even before the first regular contractions.

Labor is the last few hours of human pregnancy. It is characterized by forceful and painful uterine contractions that effect cervical dilation and cause the fetus to descend through the birth canal. Extensive preparations take place in both the uterus and cervix long before this. During the first 36 to 38 weeks of normal gestation, the myometrium is in a preparatory yet unresponsive state. Concurrently, the cervix begins an early stage of remodeling yet maintains structural integrity. Following this prolonged uterine quiescence, a transitional phase follows during which myometrial unresponsiveness is suspended and the cervix undergoes ripening, effacement, and loss of structural cohesion.

The physiological processes that regulate *parturition*—the bringing forth of young—and the onset of labor continue to be defined. Three general contemporaneous theories describe labor initiation. Viewed simplistically, the first is the *functional loss of pregnancy maintenance factors.* The second focuses on *synthesis of factors that induce parturition*. The third suggests that the mature fetus is the source of the initial *signal for parturition commencement*. Current research supports a model that draws from all three themes. However, labor onset clearly represents the culmination of a series of biochemical changes in the uterus and cervix. These result from endocrine and paracrine signals emanating from both mother and fetus. Their relative contributions vary between species, and it is these differences that complicate elucidation of the exact factors that regulate human parturition. When parturition is abnormal, then preterm labor, dystocia, or postterm pregnancy may result. Of these, preterm labor remains the major contributor to neonatal mortality and morbidity.

MATERNAL AND FETAL COMPARTMENTS

Uterus

The myometrial layer of the uterus is composed of bundles of smooth muscle cells surrounded by connective tissue. In contrast to skeletal or cardiac muscle, the smooth muscle cell is not terminally differentiated and therefore is readily adaptable to environmental changes. Varied stimuli such as mechanical stretch, inflammation, and endocrine and paracrine signals can modulate the transition of the smooth muscle cell among phenotypes that provide cell growth, proliferation, secretion, and contractility.

In addition to this phenotypic plasticity, several smooth muscle qualities confer advantages for uterine contraction efficiency and fetal delivery. First, the degree of smooth muscle cell shortening with contractions may be one order of magnitude greater than that attained in striated muscle cells. Second, forces can be exerted in smooth muscle cells in multiple directions. This differs from the contraction force generated by skeletal muscle, which is always aligned with the axis of the muscle fibers. Third, smooth muscle is not organized in the same manner as skeletal muscle. In myometrium, the thick and thin filaments are found in long, random bundles throughout the cells. This plexiform arrangement aids greater shortening and force-generating capacity. Last, greater multidirectional force generation in the uterine fundus compared with that of the lower uterine segment permits versatility in expulsive force directionality.

Lining the thick muscular uterine walls, the endometrium is transformed by pregnancy hormones and is then termed *decidua*. Composed of stromal cells and maternal immune cells, the decidua serves to maintain the pregnancy via unique immunoregulatory functions that suppress inflammatory signals during gestation. However, at the end of pregnancy, decidual activation ensues. With this, the decidua transitions to induce inflammatory signals and withdraw active immunosuppression, which contribute to parturition initiation.

During pregnancy, the cervix has multiple functions that include: (1) maintenance of barrier function to protect the reproductive tract from infection, (2) maintenance of cervical competence despite greater gravitational forces as the fetus grows, and (3) orchestration of extracellular matrix changes that allow progressively greater tissue compliance.

In nonpregnant women, the cervix is closed and firm, and its consistency is similar to nasal cartilage. By the end of pregnancy, the cervix is easily distensible, and its consistency is similar to the lips of the oral cavity. Observations in three-dimensional sonography and magnetic resonance imaging show increases in

the cross-sectional area of the cervical canal and in the cervical stroma from early to late pregnancy (House, 2009; Lang, 2010). Concurrent with expansion of the stroma, the cervical epithelia proliferate and exert a pregnancy-specific immunoprotection.

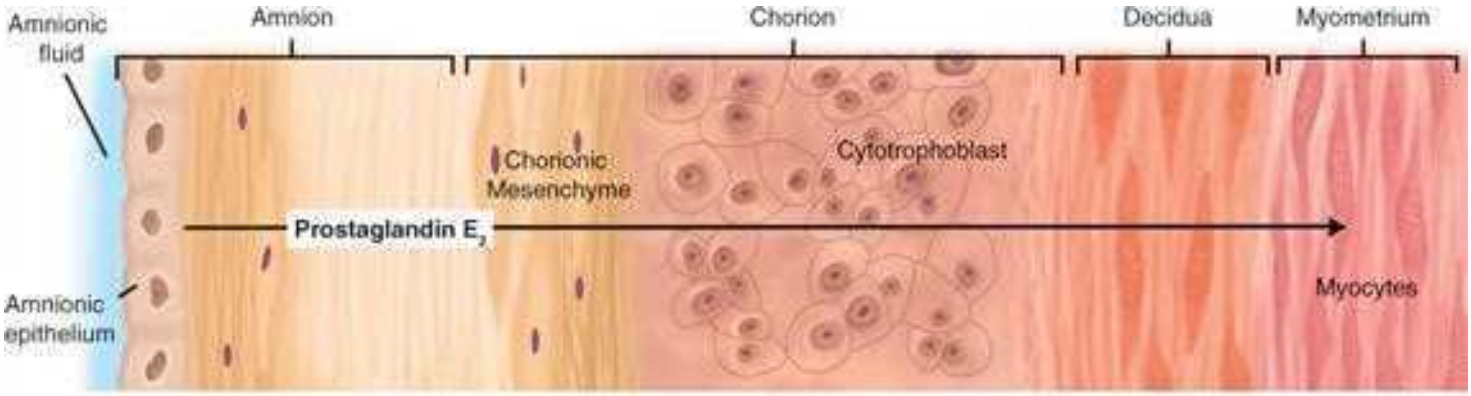
Placenta

In addition to providing the exchange of nutrients and waste between mother and fetus, the placenta is a key source of steroid hormones, growth factors, and other mediators that maintain pregnancy and potentially aid the transition to parturition. The fetal membranes—amnion and chorion and adjacent decidua—make up an important tissue shell around the fetus that serves as a physiological, immunological, and metabolic shield to protect against untimely parturition initiation.

The amnion provides virtually all of the fetal membranes' tensile strength to resist membrane tearing and rupture (Chap. 5, Amnion). This avascular tissue is highly resistant to penetration by leukocytes, microorganisms, and neoplastic cells (Fig. 21-1). It also constitutes a selective filter to prevent fetal particulate-bound lung and skin secretions from reaching the maternal compartment. In this manner, maternal tissues are protected from amnionic fluid constituents that could prematurely accelerate decidual or myometrial activation or could promote adverse events such as amnionic fluid embolism.

FIGURE 21-1

The amnion synthesizes prostaglandins, and late in pregnancy, synthesis is augmented by increased phospholipase A_2 and prostaglandin H synthase, type 2 (PGHS-2) activity. During pregnancy, the transport of prostaglandins from the amnion to maternal tissues is limited by expression of the inactivating enzymes, prostaglandin dehydrogenase (PGDH), in the chorion. During labor, PGDH levels decline, and amnion-derived prostaglandins can influence membrane rupture and uterine contractility. The role of decidual activation in parturition is unclear but may involve local progesterone metabolism and higher prostaglandin receptor concentrations, thus enhancing uterine prostaglandin actions and cytokine production. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)



The chorion is a primarily protective tissue layer and provides immunological acceptance. It is also enriched with enzymes that inactivate *uterotonins,* which are agents that stimulate contractions. Inactivating enzymes include prostaglandin dehydrogenase, oxytocinase, and enkephalinase (Cheung, 1990; Germain, 1994).

SEX STEROID HORMONE ROLE

In many species, the role of sex steroid hormones is clear— estrogen promotes and progesterone inhibits the events leading to parturition. And, the removal of progesterone, that is, *progesterone withdrawal,* directly precedes progression of parturition. In addition, providing progesterone to some species will delay parturition via a decline in myometrial activity and continued cervical competency (Challis, 1994). In humans, however, it seems most likely that both estrogen and progesterone are components of a broader molecular system that maintains uterine quiescence.

Plasma levels of estrogen and progesterone in normal pregnancy are enormous and in great excess of the affinity constants for their receptors. For this reason, it is difficult to comprehend how relatively subtle changes in the ratio of their concentrations could modulate physiological processes during pregnancy. The teleological evidence, however, for an increased progesterone-to-estrogen ratio in the maintenance of pregnancy and a decline in this ratio for parturition is overwhelming. In all species studied, including humans, administration of the progesterone-receptor antagonists *mifepristone (RU-486)* or *onapristone* will promote some or all key features of parturition. These include cervical ripening, greater cervical distensibility, and augmented uterine sensitivity to uterotonins (Bygdeman, 1994; Chwalisz, 1994b; Wolf, 1993).

The exact role of estrogen in regulation of human uterine quiescence and cervical competency is less well understood. That said, estrogen can advance progesterone responsiveness and, in doing so, promote uterine quiescence. At the end of pregnancy, estrogen aids processes that mediate uterine activation and cervical ripening.

Both progesterone and estrogen bind to nuclear receptors that regulate gene transcription in a cell- and context-specific pattern. Two nuclear receptors for estrogen are estrogen receptor α (ERα) and estrogen receptor β (ERβ). Nuclear receptor isoforms of the progesterone receptor (PR-A and PR-B) are encoded

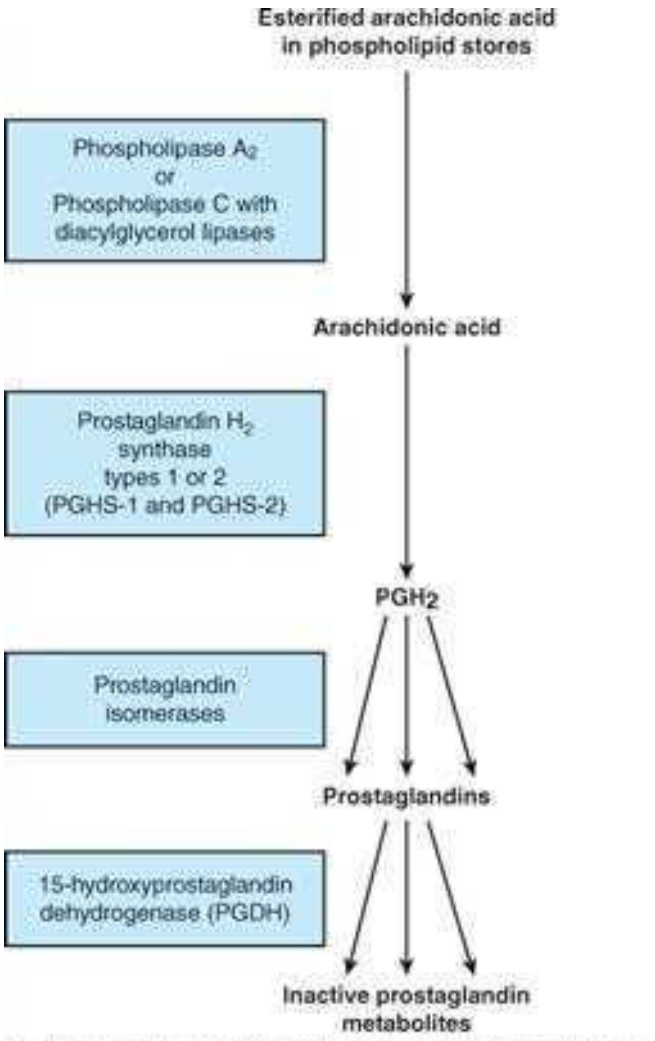
by differing transcripts from a single gene (Patel, 2015).

PROSTAGLANDINS ROLE

Prostaglandins are lipid molecules with varied hormone-like actions. In parturition, they play a prominent role in myometrial contractility, relaxation, and inflammation. Prostaglandins interact with a family of eight different G-protein–coupled receptors (G-Protein–Coupled Receptors), several of which are expressed in myometrium and cervix (Konopka, 2015; Myatt, 2004).

The major synthetic pathways involved in prostaglandin biosynthesis are shown in Figure 21-2. Prostaglandins are produced using plasma membrane-derived arachidonic acid, which usually is released by the action of phospholipase A_2 or C. Arachidonic acid can then act as substrate for both type 1 and 2 prostaglandin H synthase (PGHS-1 and -2), which are also called cyclooxygenase-1 and -2 (COX-1 and -2). Both PGHS isoforms convert arachidonic acid to the unstable prostaglandin G_2 and then to prostaglandin H_2. These enzymes are the target of many nonsteroidal antiinflammatory drugs (NSAIDs). Indeed, the tocolytic actions of specific NSAIDs, as discussed in Chapter 42 (β-Adrenergic Receptor Agonists), were considered promising until they were shown to have adverse fetal effects (Loudon, 2003; Olson, 2003, 2007).

FIGURE 21-2
Overview of the prostaglandin biosynthetic pathway.



Through prostaglandin isomerases, prostaglandin H_2 is converted to active prostaglandins. These include prostaglandins E_2 (PGE_2), $F_{2\alpha}$ ($PGF_{2\alpha}$), and I_2 (PGI_2). Isomerase expression is tissue-specific and thereby controls the relative production of various prostaglandins. Another important control point for prostaglandin activity is its metabolism, which most often is through the action of 15-hydroxyprostaglandin dehydrogenase (PGDH). Expression of this enzyme is upregulated during pregnancy in the uterus and cervix, which provides the important ability to rapidly inactivate prostaglandins (Giannoulias, 2002; Kishore, 2014). Thus, myometrial responses to prostaglandins stem from a balance between prostaglandin synthesis versus metabolism, from the relative expression of various prostaglandin receptors, or from a switch in receptor-signaling pathways (Kandola, 2014; Lyall, 2002; Olson, 2007; Smith, 2001). It is entirely possible that prostanoids contribute to myometrial relaxation at one stage of pregnancy and to myometrial contractions after parturition initiation (Myatt, 2004).

In addition to the myometrium, the amnion synthesizes several bioactive peptides and prostaglandins that cause myometrial relaxation or contraction (see Fig. 21-1). Late in pregnancy, amnionic prostaglandin biosynthesis is increased, and phospholipase A_2 and PGHS-2 show greater activity (Johnson, 2002).

Accordingly, many hypothesize that prostaglandins regulate events leading to parturition. The amnion is likely the major source for amnionic fluid prostaglandins, and their role in the activation of cascades that promote membrane rupture is clear. The influence of amnion-derived prostaglandins on uterine quiescence and activation, however, is less delineated. This is because prostaglandin transport from the amnion through the chorion to access maternal tissues is limited by expression of PGDH.

PHASE 1: UTERINE QUIESCENCE AND CERVICAL SOFTENING

As shown in Figure 21-3, parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy (Casey, 1993, 1997; Challis, 2000; Word, 2007). These phases of parturition include: (1) a prelude to it, (2) the preparation for it, (3) the process itself, and (4) recovery. Importantly, the *phases of parturition* should not be confused with the *clinical stages of labor,* that is, the first, second, and third stages—which make up phase 3 of parturition (Fig. 21-4).

FIGURE 21-3
The phases of parturition.

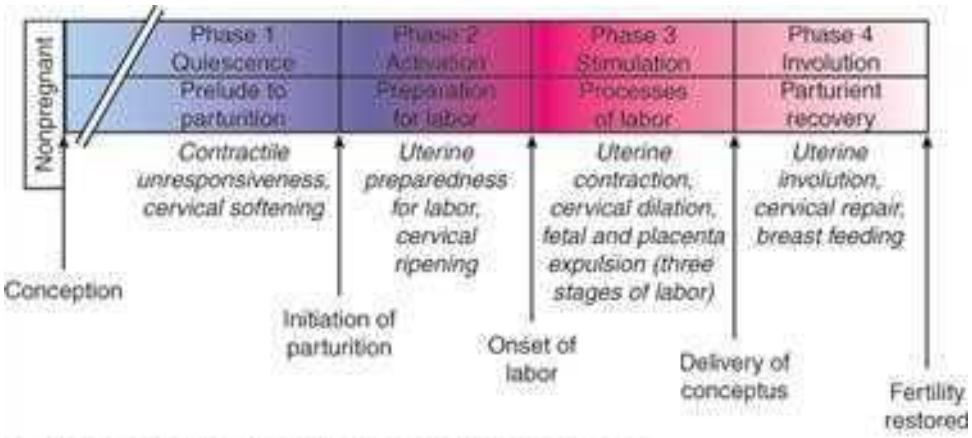
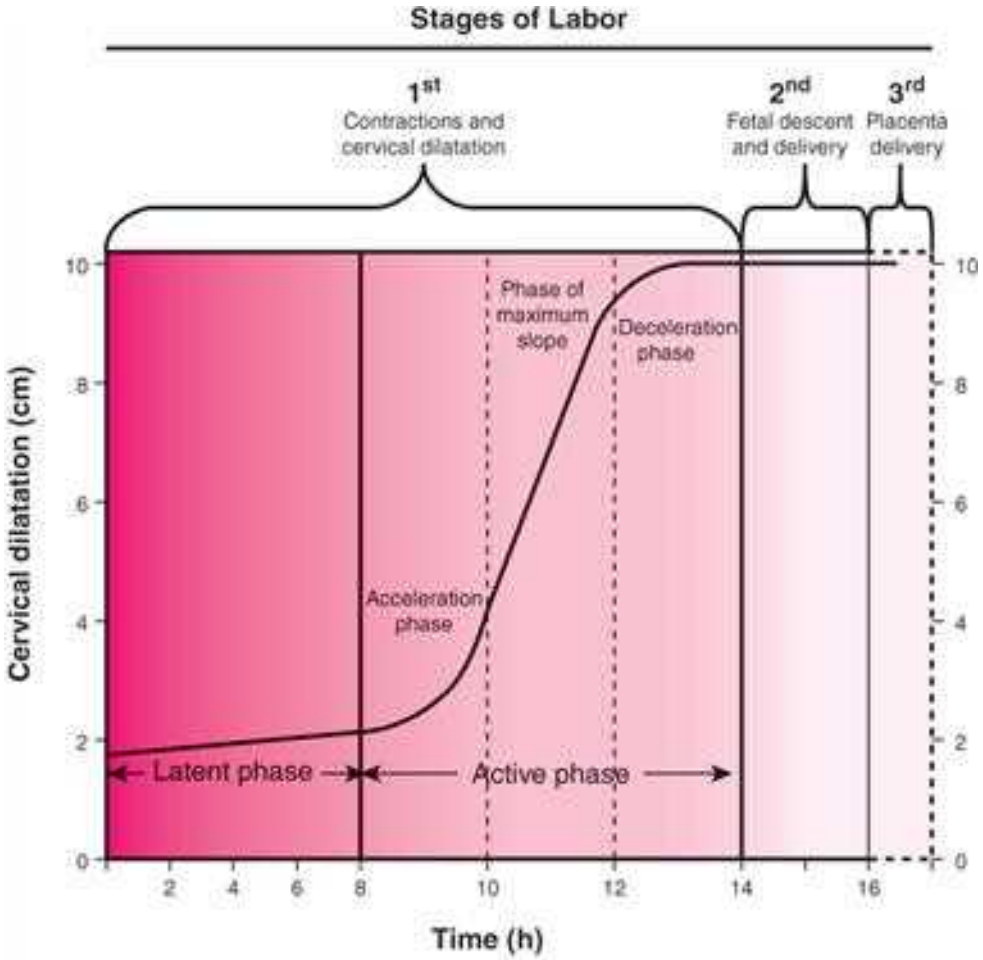


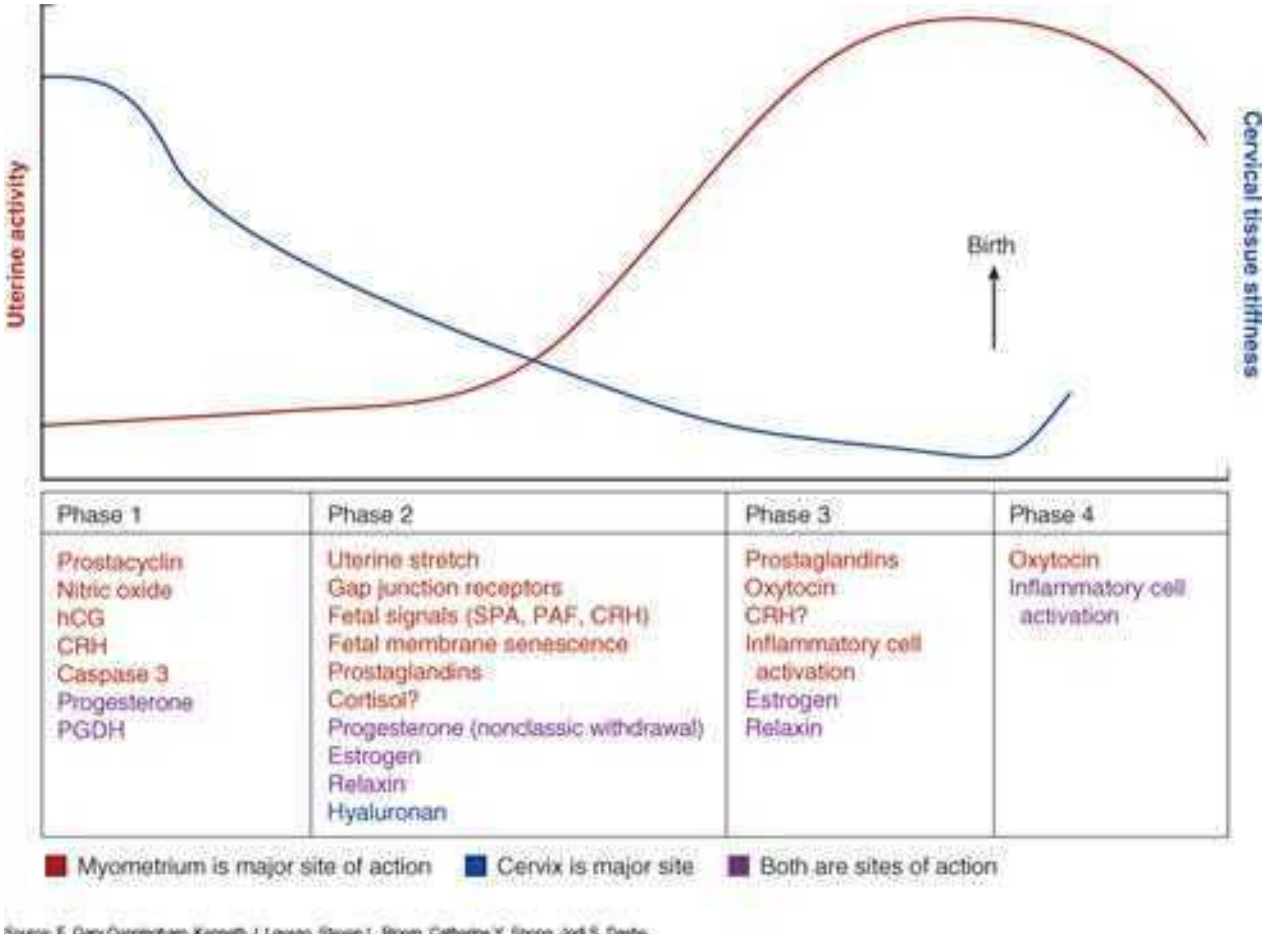
FIGURE 21-4
Composite of the average dilation curve for labor in nulliparous women. The curve is based on analysis of data derived from a large, nearly consecutive series of women. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. In the active phase, there are three identifiable parts: an acceleration phase, a linear phase of maximum slope, and a deceleration phase. (Redrawn from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)



Beginning even before implantation, a remarkably effective period of myometrial quiescence is imposed. This phase 1 normally comprises 95 percent of pregnancy and is characterized by uterine smooth muscle tranquility with maintenance of cervical structural integrity (Fig. 21-5). All manner of molecular systems—neural, endocrine, paracrine, and autocrine—are likely called to implement and coordinate a state of relative uterine unresponsiveness. Moreover, a complementary "fail-safe" system that protects the uterus against agents that could perturb the tranquility of phase 1 also must be in place.

FIGURE 21-5

The key factors thought to regulate the phases of human parturition. CRH = corticotropin-releasing hormone; hCG = human chorionic gonadotropin; PAF = platelet-activating factor; PGDH = prostaglandin dehydrogenase; SPA = surfactant protein A.



During phase 1, the myometrial cells undergo a phenotypic modification to a noncontractile state, and uterine muscle is rendered unresponsive to natural stimuli. Concurrently, the uterus must initiate extensive changes in its size and vascularity to accommodate fetal growth and prepare for uterine contractions. The myometrial unresponsiveness of phase 1 continues until near the end of pregnancy. That said, some low-intensity myometrial contractions are felt during the quiescent phase, but they do not normally cause cervical dilation. These contractions are common toward the end of pregnancy, especially in multiparas, and are referred to as *Braxton Hicks contractions* or *false labor* (Chap. 4, Uterine Contractility).

The quiescence of phase 1 likely stems from: (1) actions of estrogen and progesterone via intracellular receptors, (2) myometrial-cell plasma membrane receptor-mediated increases in cyclic adenosine monophosphate (cAMP), (3) generation of cyclic guanosine monophosphate (cGMP), and (4) other systems, including modification of myometrial-cell ion channels.

Myometrial Relaxation and Contraction

The balance between myometrial relaxation and contraction is controlled by steroid- and peptide-hormone transcriptional regulation of key genes and their protein products. Quiescence is achieved in part by: (1) diminished intracellular crosstalk and reduced intracellular Ca^{2+} ($[Ca^{2+}]_i$) levels; (2) ion- channel regulation of cell membrane potential; (3) activation of the uterine endoplasmic reticulum stress–unfolded protein response; and (4) uterotonin degradation. In contrast, contractility results from: (1) enhanced interactions between the actin and myosin proteins; (2) heightened excitability of individual myometrial cells; and (3) promotion of intracellular crosstalk that allows synchronous contractions to develop.

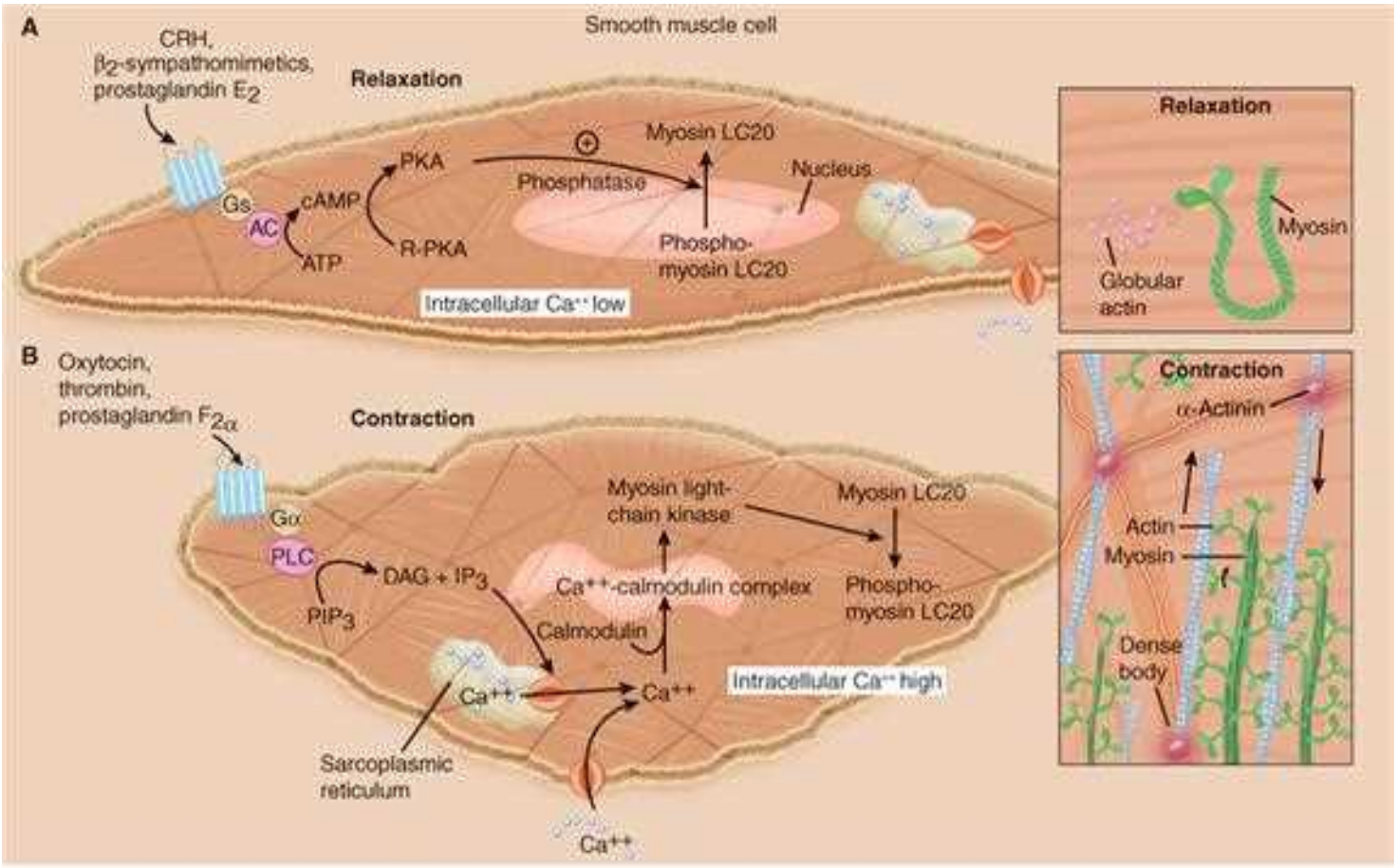
Actin-Myosin Interactions

Actin and myosin proteins are essential to muscle contraction. For this, actin must be converted from a globular to a filamentous form. Indeed, a potential mechanism for maintenance of relaxation is the promotion of actin into a globular form rather than into fibrils, which are required for contraction (Fig. 21-6). Moreover, actin must be attached to the cytoskeleton at focal points in the cell membrane to allow tension to develop.

FIGURE 21-6

Uterine myocyte relaxation and contraction. **A.** Uterine relaxation is maintained by factors that increase myocyte cyclic adenosine monophosphate (cAMP) levels. This activates protein kinase A (PKA) to promote phosphodiesterase activity with dephosphorylation of myosin light-chain kinase (MLCK). Other processes serve to maintain actin in a globular form and thus to prevent the fibril formation necessary for contractions. **B.** Uterine contractions result from reversal of these sequences. Actin now assumes a fibrillar form, and calcium enters the cell to combine with calmodulin to form complexes. These complexes activate MLCK to bring about phosphorylation of the myosin light chains. This generates ATPase activity to cause sliding of myosin over the actin fibrils, which is a uterine contraction. AC = adenylyl cyclase; Ca^{2+} = calcium; DAG = diacylglycerol; Gs and Gα = G-receptor proteins; IP_3 = inositol triphosphate; LC20

= light chain 20; PIP_3 = phosphatidylinositol 3,4,5–triphosphate; PLC = phospholipase C; R-PKA = inactive protein kinase. (Redrawn from Smith R: Parturition. N Engl J Med. 2007 Jan 18;356(3):271–283.)



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Actin must partner with myosin, which is composed of multiple light and heavy chains. The coupling of myosin and actin activates adenosine triphosphatase (ATPase), hydrolyzes adenosine triphosphate, and generates force. This interaction is brought about by enzymatic phosphorylation of the 20-kDa light chain of myosin (Stull, 1998). This is catalyzed by the enzyme *myosin light-chain kinase*, which is activated by calcium. Calcium binds to *calmodulin*, a calcium-binding regulatory protein, which in turn binds to and activates myosin light-chain kinase.

Thus, logically, uterine relaxation ordinarily is promoted by conditions that lower concentrations of $(Ca^{2+})_i$. In contrast, agents that prompt contraction act on myometrial cells to augment $(Ca^{2+})_i$ levels. Or, they allow an influx of extracellular calcium through ligand- or voltage-regulated calcium channels (see Fig. 21-6). Voltage-gated ion channels open, additional calcium ions move into the cell, and cellular depolarization follows. For example, prostaglandin $F_{2\alpha}$ and oxytocin bind their respective receptors during labor to open ligand-activated calcium channels. Activation of these receptors also releases calcium from the sarcoplasmic reticulum to lower electronegativity within the cell. Additionally, greater localization of nonselective cation channels on the cell membrane promotes Ca^{2+} entry (Ying, 2015). The rise in $(Ca^{2+})_i$ levels is often transient. But, contractions can be prolonged by inhibition of myosin phosphatase, an enzyme which dephosphorylates myosin (Woodcock, 2004).

Regulation of Membrane Potentials

As just noted, myocyte excitability is regulated in part by changes in the electrochemical potential gradient across the plasma membrane. Before labor, myocytes maintain a relatively high interior electronegativity. Maintenance of a hyperpolarized membrane potential attenuates smooth muscle cell excitation and is regulated by ion channels.

Consistent with the importance of myometrial quiescence, numerous potassium channels control membrane potential. One key regulator is the large-conductance voltage- and Ca^{2+}-activated K channel (BK_{Ca}) (Pérez, 1993). In normal physiology, the myometrial BK_{Ca} channel plays dual and opposing roles to maintain a balance between uterine quiescence and contractility. The BK_{Ca} channel is abundantly expressed in the myometrium. For most of pregnancy, opening the BK_{Ca} channel allows potassium to leave the cell to maintain interior electronegativity, thus preventing voltage-gated Ca^{2+} influx and contraction. Enhancing BK_{Ca} channel opening results in myometrial relaxation, whereas inhibition of the BK_{Ca} channel augments myometrial contractility.

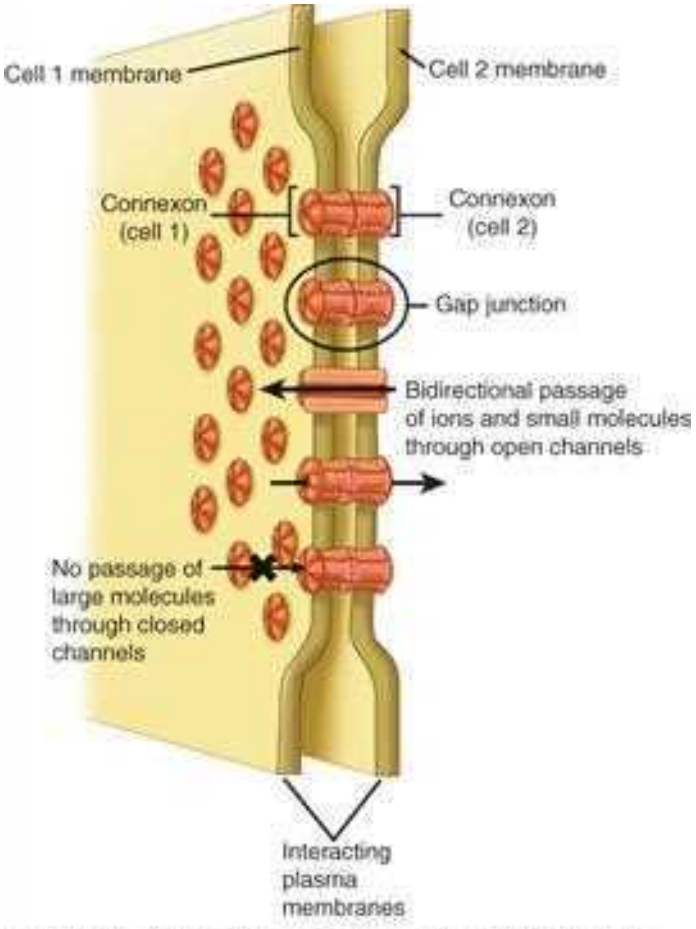
The ability of BK_{Ca} channel to regulate calcium dynamics and ultimately uterine contractility from early to late gestation may result from temporal changes in expression of the BK_{Ca} channel and/or BK_{Ca} interacting partners (Wakle-Prabagaran, 2016).

Myometrial Gap Junctions

Cellular signals that control myometrial contraction and relaxation can be effectively transferred between cells through intercellular junctional channels. Communication is established between myocytes by gap junctions, which aid the passage of electrical or ionic coupling currents as well as metabolite coupling. The transmembrane channels that make up the gap junctions consist of two protein "hemi-channels" (Saez, 2005). These *connexons* are each composed of six *connexin* subunit proteins (Fig. 21-7). Of these, connexin-43 is expressed in myometrium, and concentrations rise near labor onset. Pairs of connexons establish a conduit between coupled cells for the exchange of small molecules that can be nutrients, waste, metabolites, second messengers, or ions. Optimal numbers and types of gap junctions are believed to be important for electrical myometrial synchrony.

FIGURE 21-7

The protein subunits of gap junction channels are called connexins. Six connexins form a hemichannel (connexon), and two connexons (one from each cell) form a gap junction channel. Connexons and gap junction channels can be formed from one or more connexin proteins. The composition of the gap junction channel is important for these channels' selectivity with regard to passage of molecules and communication between cells.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Progesterone maintains uterine quiescence in part by mechanisms that lower expression of various key proteins needed for contractility. These *contraction-associated proteins (CAPs)* include the oxytocin receptor, prostaglandin F receptor, and connexin-43. At the end of pregnancy, increased stretch along with greater estrogen dominance raises CAP levels. Integration of diverse regulatory pathways culminates in released inhibition of connexin-43 and oxytocin receptor levels to promote greater uterine contractility (Nadeem, 2016; Renthal, 2010; Williams, 2012b).

Endoplasmic Reticulum Stress Response

As another potential mechanism, progesterone maintains uterine quiescence through support of myometrial *caspase 3,* which is an anticontractile agent (Jeyasuria, 2009). This protein degrades both actin and the specific gap junction protein, connexin-43 (Kyathanahalli, 2015).

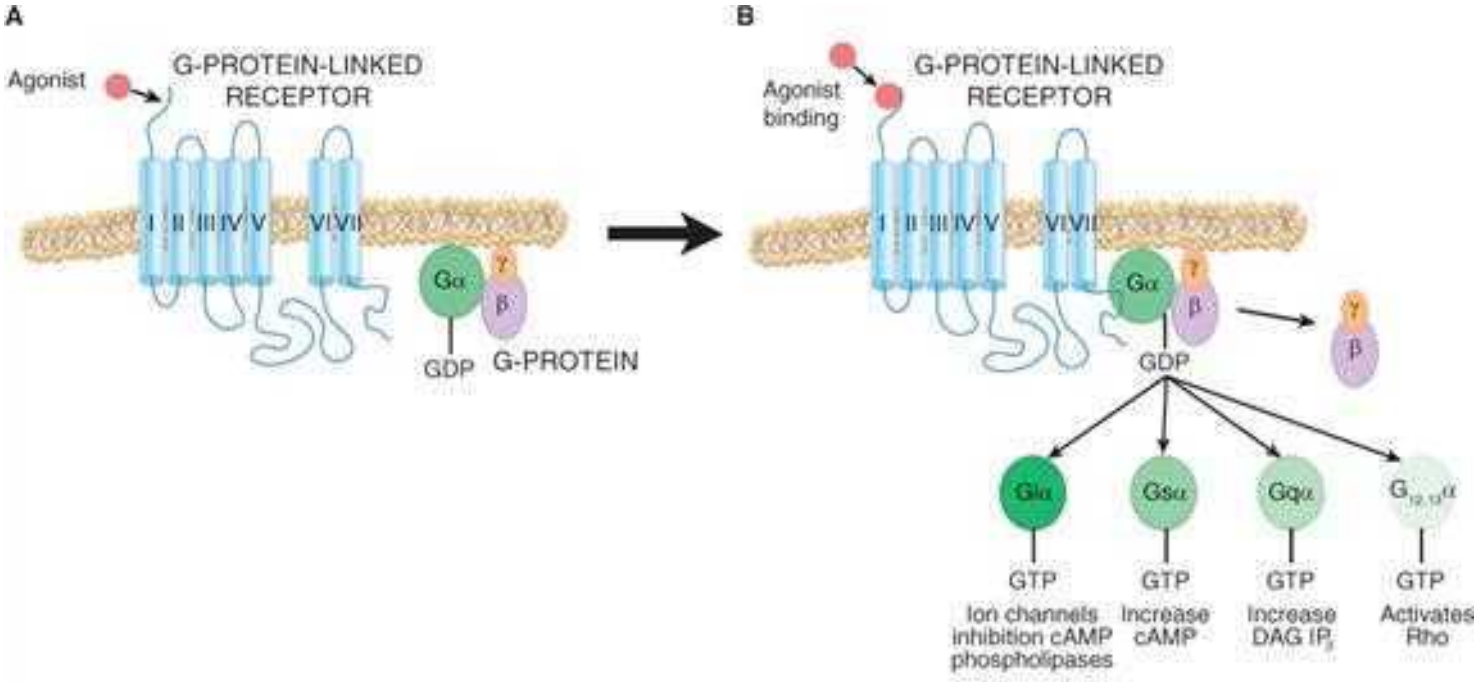
In mice, myometrial caspase 3 activation is regulated by a pregnancy-induced *endoplasmic reticulum stress response (ERSR).* As background, the endoplasmic reticulum aids protein folding and transport. Functional irregularities cause misfolded proteins to accumulate and trigger the ERSR. The ERSR and its *unfolded-protein response (UPR)* are cellular mechanisms that work to maintain homeostasis in the face of stimuli, such as stretch and inflammation. Prolonged ERSR promotes caspase 3 activation to preserve quiescence despite these stimuli.

G-Protein–Coupled Receptors

Various cell surface receptors directly regulate myocyte contractility. Discussions thus far have described ion channel-linked receptors that regulate intracellular Ca^{2+} and membrane potential. In addition, numerous G-protein–coupled receptors appear to be modified during the phases of parturition. Several of these are present in myometrium and associated with $G_{\alpha s}$-mediated activation of adenylyl cyclase to yield higher cAMP levels. These receptors together with appropriate ligands may act with sex steroid hormones to maintain uterine quiescence (Price, 2000; Sanborn, 1998). Examples are the LH receptor and corticotropin-releasing hormone receptor 1 (CRHR1), both described in this section (Fig. 21-8). Other G-protein–coupled myometrial receptors, instead, are associated with G-protein–mediated activation of phospholipase C, which remember releases arachidonic acid. Ligands for the G-protein–coupled receptors include numerous neuropeptides, hormones, and autacoids. Many of these are available to the myometrium during pregnancy in high concentration via *endocrine* or *autocrine* mechanisms.

FIGURE 21-8

G-protein–coupled receptor signal transduction pathways. **A.** Receptors coupled to heterotrimeric guanosine-triphosphate (GTP)-binding proteins (G proteins) are integral transmembrane proteins that transduce extracellular signals to the cell interior. G-protein–coupled receptors exhibit a common structural motif consisting of seven membrane-spanning regions. **B.** Receptor occupation promotes interaction between the receptor and the G protein on the interior surface of the membrane. This induces an exchange of guanosine diphosphate (GDP) for GTP on the G protein α subunit and dissociation of the α subunit from the βγ heterodimer. Depending on its isoform, the GTP-α subunit complex mediates intracellular signaling either indirectly by acting on effector molecules such as adenylyl cyclase (AC) or phospholipase C (PLC), or directly by regulating ion channel or kinase function. cAMP = cyclic adenosine monophosphate; DAG = diacylglycerol; IP_3 = inositol triphosphate.



β-Adrenoreceptors are prototypical examples of cAMP signaling causing myometrium relaxation. β-Adrenergic receptors mediate $G_{\alpha s}$-stimulated increases in adenylyl cyclase, elevated levels of cAMP, and myometrial cell relaxation. The rate-limiting factor is likely the number of receptors expressed and the level of adenylyl cyclase expression. Agents binding to these receptors have been used for tocolysis of preterm labor and include ritodrine and terbutaline (Chap. 42, β-Adrenergic Receptor Agonists).

LH and hCG hormones share the same receptor, and this G-protein–coupled receptor has been found in myometrial smooth muscle and blood vessels (Ziecik, 1992). Levels of myometrial LH-hCG receptors during pregnancy are greater before than during labor. Chorionic gonadotropin acts to activate adenylyl cyclase by way of a plasma membrane receptor $G_{\alpha s}$-linked system. This lessens contraction frequency and force and lowers the number of tissue-specific myometrial cell gap junctions (Ambrus, 1994; Eta, 1994). Thus, high circulating levels of hCG may be one mechanism of uterine quiescence. In the mouse, variations in FSH-receptor density also regulate myometrial contractile activity (Stilley, 2016).

Prostaglandin E_2 mediates its diverse cellular effects through four G-protein–coupled receptors. Specifically, prostaglandin E receptors 1 through 4 (EP_1-EP_4) are expressed in the myometrium during pregnancy and with labor onset (Astle, 2005; Leonhardt, 2003). EP_2 and EP_4 act through $G_{\alpha}s$ to raise cAMP levels and maintain myometrial cell quiescence but switch to a $G_{\alpha}q$/11 calcium-activating pathway during labor (Kandola, 2014). EP_1 and EP_3 receptors act through $G_{\alpha}q$ and $G_{\alpha}i$ to augment intracellular Ca^{2+} and contractility.

The peptide hormone relaxin binds to the G-protein–coupled receptor named *relaxin family peptide receptor 1 (RXFP1). Binding* activates adenylyl cyclase in uterine smooth muscle cells. Adenylyl cyclase in turn prevents increased intracellular Ca^{2+} and thus promotes uterine quiescence (Downing, 1993; Meera, 1995). There are two separate human relaxin genes, designated *H1* and *H2*. Of these, *H1* is primarily expressed in the decidua, trophoblast, and prostate, whereas *H2* is primarily expressed in the corpus luteum. Relaxin in plasma of pregnant women is believed to originate exclusively from corpus luteum secretion. Plasma levels peak at approximately 1 ng/mL between 8 and 12 weeks' gestation. Thereafter, they decline to lower levels that persist until term.

Corticotropin-releasing hormone (CRH) is synthesized in the placenta and hypothalamus. Discussed in Fetal Contributions to Parturition, CRH plasma levels rise dramatically during the final 6 to 8 weeks of normal pregnancy and are implicated in mechanisms that control the timing of human parturition (Smith, 2007; Wadhwa, 1998). CRH appears to promote myometrial quiescence during most of pregnancy but then aids myometrial contractions with parturition onset. Studies suggest that these opposing actions are achieved by differential actions of CRH via its receptor CRHR1. In nonlaboring myometrium at term, the interaction of CRH with its CRHR1 receptor activates the Gs-adenylate cyclase-cAMP signaling pathway. This results in inhibition of inositol triphosphate (IP_3) and stabilization of $(Ca^{2+})_i$ levels (You, 2012). However, in term laboring myometrium, $(Ca^{2+})_i$ concentrations are augmented by CRH activation of G proteins Gq and Gi and prompts stimulation of IP_3 production and greater contractility.

Cyclic Guanosine Monophosphate

As just described, cAMP is an important mediator of myometrial relaxation. However, activation of guanylyl cyclase raises intracellular cyclic guanosine monophosphate (cGMP) levels. This also promotes smooth muscle relaxation (Word, 1993). Intracellular cGMP levels are increased in the pregnant myometrium and can be stimulated by atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) receptors, and nitric oxide (Telfer, 2001). All of these factors and their receptors are expressed in the pregnant uterus.

Accelerated Uterotonin Degradation

In addition to pregnancy-induced compounds that promote myometrial cell refractoriness, the activity of enzymes that degrade or inactivate endogenously produced uterotonins are strikingly increased in phase 1. Some of these degrading enzymes and their respective targets include PGDH and prostaglandins; enkephalinase and endothelins; oxytocinase and oxytocin; diamine oxidase and histamine; catechol *O*-methyltransferase and catecholamines; angiotensinases and angiotensin-II; and platelet-activating factor (PAF) and PAF acetylhydrolase. Levels of several of these enzymes decrease late in gestation (Germain, 1994).

Decidua

To ensure uterine quiescence, the synthesis in the decidua of prostaglandins, in particular $PGF_{2\alpha,}$ is markedly suppressed. Suppression of prostaglandin production here persists throughout most of pregnancy, and suppression withdrawal is a prerequisite for parturition (Norwitz, 2015).

Phase 1 of parturition also promotes an environment of immune tolerance to protect the fetus. Namely, decidual stromal cells proactively ensure that fetal antigens do not elicit a maternal immune response. This stems from a reduced capacity to attract T cells. This limited ability derives in part from epigenetic silencing of T cell–attracting inflammatory chemokine genes (Erlebacher, 2013; Nancy, 2012; PrabhuDas, 2015).

Cervical Softening

The initial stage of cervical remodeling—termed *softening*—begins in phase 1 of parturition. It is characterized by greater tissue compliance, yet the cervix remains firm and unyielding. Hegar (1895) first described palpable softening of the lower uterine segment at 4 to 6 weeks' gestation, and this sign was once used to diagnose pregnancy. Clinically, the maintenance of cervical anatomical and structural integrity is essential for pregnancy to continue to term. Preterm cervical dilation, structural insufficiency, or both may forecast delivery.

Cervical softening results from increased vascularity, cellular hypertrophy and hyperplasia, and slow, progressive compositional and structural changes in the extracellular matrix (Mahendroo, 2012; Myers, 2015; Word, 2007). Key to matrix changes, collagen, which is the main structural protein in the cervix, undergoes conformational changes that alter tissue stiffness and flexibility (Zhang, 2012). Specifically, collagen processing and the number or type of stable covalent cross-links between collagen triple helices is altered. Mature cross-links between newly synthesized collagen monomers are reduced due to diminished expression and activity of the cross-link-forming enzymes beginning in early pregnancy (Akins, 2011; Drewes, 2007; Yoshida, 2014). These enzymes are lysyl hydroxylase and lysyl oxidase. Together, these early pregnancy changes contribute to greater tissue compliance.

Clinical evidence for the importance of matrix changes to cervical softening is supported by in vivo mechanical evaluation of the cervix (Badir, 2013; Parra-Saavedra, 2011). The prevalence of cervical insufficiency is also higher in those with inherited defects in the synthesis or assembly of collagen or elastic fibers (Anum, 2009; Hermanns-Le, 2005; Rahman, 2003; Wang, 2006). Examples are Ehlers-Danlos and Marfan syndromes, discussed in Chapter 59 (Hereditary Connective Tissue Disorders). Concurrent with matrix remodeling in the softening period, genes involved in cervical dilation and parturition are actively repressed (Hari Kishore, 2012).

PHASE 2: PREPARATION FOR LABOR

To prepare for labor, the myometrial tranquility of phase 1 of parturition must be suspended—so-called *uterine awakening* or *activation.* This phase 2 of parturition is a progression of uterine changes during the last few weeks of pregnancy. Importantly, shifting events associated with phase 2 can cause either

preterm or delayed labor.

Progesterone Withdrawal

Key factors in uterine activation are depicted in Figure 21-5. In species that exhibit progesterone withdrawal, parturition progression to labor can be blocked by administering progesterone to the mother. Whether progesterone administration in the absence of classic progesterone withdrawal in pregnant women can delay the timely onset of parturition or prevent preterm labor continues to be investigated. The possibility that progesterone-containing injections or vaginal suppositories may prevent preterm labor has been studied in several randomized trials conducted during the past 15 years. These are discussed in Chapter 42 (Prophylaxis with Progestogen Compounds), and their use in preventing recurrent preterm birth continues to be debated (Norman, 2016).

Classic progesterone withdrawal resulting from decreased secretion does not occur in human parturition. However, a mechanism for progesterone inactivation, whereby the myometrium and cervix become refractory to progesterone's inhibitory actions, is supported by studies using progesterone-receptor antagonists. Mifepristone is a classic steroid antagonist, acting at the level of the progesterone receptor. Although less effective in inducing abortion or labor in women later in pregnancy, mifepristone appears to have some effect on cervical ripening and on increasing myometrial sensitivity to uterotonins (Berkane, 2005; Chwalisz, 1994a).

The diverse mechanisms by which functional progesterone withdrawal or antagonism is achieved is an active area of research. These include: (1) changes in the relative expression of the nuclear progesterone-receptor isoforms, PR-A, PR-B, and PR-C; (2) differential interaction of PR-A and PB-B with enhancers and inhibitors of gene expression; (3) alterations in PR activity through changes in the expression of coactivators or corepressors that directly influence receptor function; (4) local inactivation of progesterone by steroid-metabolizing enzymes or synthesis of a natural antagonist; and (5) microRNA regulation of progesterone-metabolizing enzymes and transcription factors that modulate uterine quiescence (Condon, 2003; Mahendroo, 1999; Mesiano, 2002; Nadeem, 2016; Renthal, 2010; Williams, 2012a). Taken together, these observations support the concept that multiple pathways exist for a functional progesterone withdrawal.

Myometrial Changes

Phase 2 myometrial changes prepare it for labor contractions. This results from a shift in the expression of key proteins that control uterine quiescence to an expression of contraction-associated proteins, described earlier (Myometrial Gap Junctions) (Renthal, 2015). Of these CAPs, myometrial oxytocin receptors and gap junction proteins, such as connexin-43, markedly rise in number. These CAPs increase uterine irritability and responsiveness to *uterotonins.*

Another critical change in phase 2 is formation of the lower uterine segment from the isthmus. With this development, the fetal head often descends to or even through the pelvic inlet—so-called *lightening.* The abdomen commonly undergoes a shape change, sometimes described by women as "the baby dropped." It is also likely that the lower segment myometrium is unique from that in the upper uterine segment, resulting in distinct roles for each near term and during labor. This is supported by human studies that demonstrate differential expression of prostaglandin receptors and CAPs within the upper- and lower-segment myometrial regions (Astle, 2005; Blanks, 2003; Sparey, 1999). Near term, elevated expression of the *HoxA13* gene in the lower myometrial segment compared with the upper segment also induces CAP expression and regionalized contractility of the lower segment (Li, 2016).

Oxytocin Receptors

Because of its long-standing application for labor induction, it seemed logical that oxytocin must play a central role in spontaneous human labor. Myometrial oxytocin receptor levels do rise during phase 2 of parturition, and the level of oxytocin receptor mRNA in human myometrium at term is greater than that found in preterm myometrium (Wathes, 1999). However, it is unclear whether oxytocin plays a role in the early phases of uterine activation or whether its sole function is in the expulsive phase of labor. Most studies of regulation of myometrial oxytocin receptor synthesis have been performed in rodents. Disruption of the oxytocin receptor gene in the mouse does not affect parturition. This suggests that, at least in this species, multiple systems likely ensure that parturition occurs.

Progesterone and estradiol appear to be the primary regulators of oxytocin receptor expression. Estradiol treatment in vivo or in myometrial explants raises myometrial oxytocin receptor concentrations. This action, however, is prevented by simultaneous treatment with progesterone (Fuchs, 1983). Progesterone also may act within the myometrial cell to enhance oxytocin receptor degradation and inhibit oxytocin activation of its receptor at the cell surface (Bogacki, 2002). These data indicate that one of the mechanisms whereby progesterone maintains uterine quiescence is through inhibition of a myometrial oxytocin response.

Cervical Ripening

Before contractions begin, the cervix must undergo extensive remodeling. This eventually leads to the cervix yielding and dilating from forceful uterine contractions. Cervical modifications during phase 2 principally involve connective tissue changes—termed *cervical ripening.* The transition from the softening to the ripening phase begins weeks or days before labor. During this transformation, the cervical matrix changes its total amounts of *glycosaminoglycans*, which are large linear polysaccharides, and *proteoglycans,* which are proteins bound to these glycosaminoglycans.

Many of the processes that aid cervical remodeling are controlled by the same hormones regulating uterine function. That said, the molecular events of each are varied because of differences in cellular composition and physiological requirements. For example, the hormone relaxin regulates myometrial quiescence. It also regulates cervical ripening, but through cell proliferation and modulation of extracellular matrix components (Park, 2005; Soh, 2012). The uterine corpus is predominantly smooth muscle. In contrast, the cervix has a high ratio of fibroblasts to smooth muscle cells, and extracellular matrix

contributes significantly to overall tissue mass. Recent studies in the nonpregnant human cervix report a spatial gradient of smooth muscle cells. Specifically, smooth muscle cells make up approximately 50 percent of stromal cells at the internal os but only 10 percent at the external os (Vink, 2016).

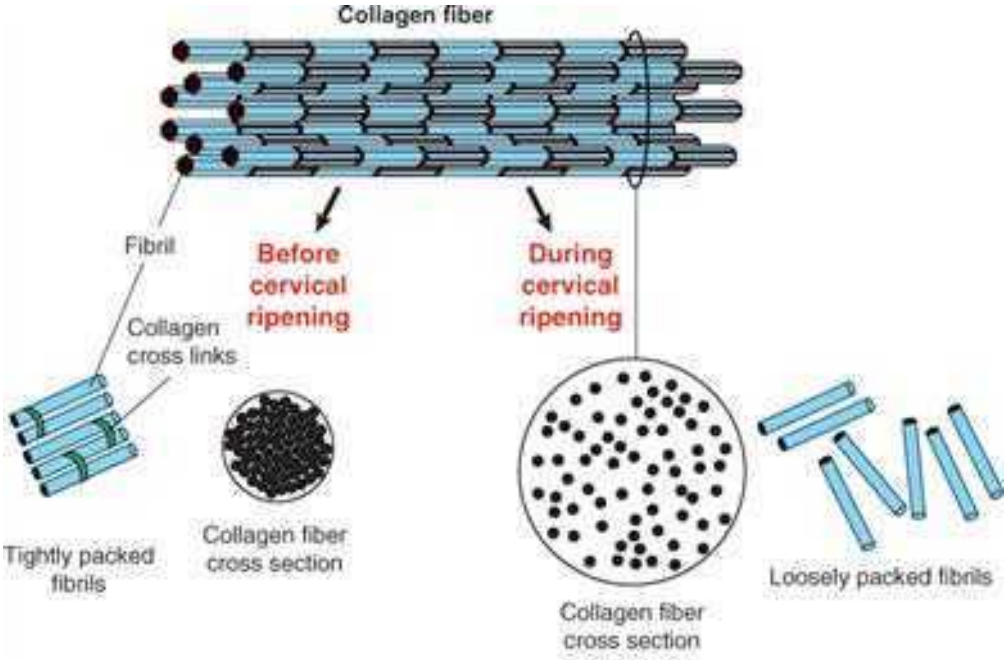
Cervical Connective Tissue

Collagen

The cervix is an extracellular-matrix-rich tissue. Constituents of the matrix include type I, III, and IV collagen, matricellular proteins, glycosaminoglycans, proteoglycans, and elastic fibers. Of these, collagen is largely responsible for the structural disposition of the cervix. During collagen assembly, multiple collagen triple-helical molecules are cross-linked to one another by the actions of lysyl oxidase to form fibrils. In addition, fibril size, packing, and organization determine the strength and mechanical properties of the cervix. These properties are regulated in part by collagen-binding proteoglycans such as decorin or biglycan, as well as matricellular proteins such as thrombospondin 2 (Fig. 21-9).

FIGURE 21-9

The collagen fiber architecture is reorganized in phases 1 and 2 of parturition to allow a gradual increase in mechanical compliance of the cervix. A collagen fiber is made up of many fibrils. Fibril size and packing are regulated in part by small proteoglycans such as decorin and by the density of collagen cross-links. In phase 1, fibril size is uniform and fibrils are well organized, although a decline in cross-link density aids softening. During cervical ripening in phase 2, fibril size is less uniform, and spacing between collagen fibrils and fibers is greater and disorganized.



Higher turnover of collagen during pregnancy likely allows the gradual replacement of mature cross-linked collagen fibrils with poorly cross-linked fibrils, which yield greater collagen disorganization. This increased turnover, rather than loss of collagen to achieve cervical remodeling, is supported by mouse and human studies that document no changes in collagen content between nonpregnant states and term pregnancy (Akins, 2011; Myers, 2008; Read, 2007; Yoshida, 2014). In further support, polymorphisms or mutations in genes required for collagen assembly are associated with an elevated incidence of cervical insufficiency (Anum, 2009; Rahman, 2003; Warren, 2007).

Glycosaminoglycans and Proteoglycans

Hyaluronan is a high-molecular-weight polysaccharide that functions alone, whereas most other glycosaminoglycans (GAGs) complex with proteins to form proteoglycans. Hyaluronan is a hydrophilic, space-filling molecule, and thus greater hyaluronan production during cervical ripening is thought to increase viscoelasticity, hydration, and matrix disorganization. Hyaluronan synthesis is carried out by hyaluronan synthase isoenzymes, and expression of these enzymes is elevated in the cervix during ripening (Akgul, 2012; Straach, 2005).

Although not well defined, changes in proteoglycan composition are also suggested to accompany cervical ripening. At least three small leucine-rich proteoglycans are expressed in the cervix—decorin, biglycan, and fibromodulin (Westergren-Thorsson, 1998). In other connective tissues, decorin interacts with collagen to regulate the packing, order, and strength of collagen fibrils (see Fig. 21-9) (Ameye, 2002). In addition to the cervix, these proteoglycans are expressed in the fetal membranes and uterus.

Inflammatory Changes

In phase 2, resident immune cells are localized to the cervical stroma, although a functional role for these cells in this phase of remodeling has been challenged. Microarray studies comparing gene expression patterns at term both before and after cervical ripening show little rise in proinflammatory gene expression. In contrast, proinflammatory and immunosuppressive gene expression in the cervix after delivery increases markedly compared with that during cervical ripening (Bollapragada, 2009; Hassan, 2006, 2009). Further, detailed studies in mice provide evidence that leukocyte migration but not activation

takes place before labor. Once labor is underway, activation of neutrophils, proinflammatory M1 macrophages, and tissue repair M2 macrophages in the cervix is augmented. This suggests a role for inflammatory cells in postpartum cervical remodeling and repair (Mahendroo, 2012).

Induction of Cervical Ripening

No therapies prevent premature cervical ripening. In contrast, treatment to promote cervical ripening for labor induction includes direct application of prostaglandins PGE_2 and $PGF_{2\alpha}$. Prostaglandins likely modify extracellular matrix structure to aid ripening. Although the role of prostaglandins in the normal physiology of cervical ripening remains unclear, this property is useful clinically to assist labor induction (Chap. 26, Preinduction Cervical Ripening).

In some nonhuman species, the cascades of events that allow cervical ripening are induced by dropping serum progesterone concentrations. And in humans, administration of progesterone antagonists causes cervical ripening.

Endocervical Epithelia

In addition to matrix changes, during pregnancy, endocervical epithelial cells proliferate such that endocervical glands account for a significant percentage of cervical mass. The endocervical canal is lined with mucus-secreting columnar and stratified squamous epithelia. These cells form both a mucosal barrier and a tight junctional barrier that protect against microbial invasion (Akgul, 2014; Blaskewicz, 2011; Timmons, 2007). The mucosal epithelium recognizes and deters pathogen invasion via expression of toll-like receptors that identify pathogens and via antimicrobial peptides and protease inhibitors. In addition, these epithelia express signals to underlying immune cells when a pathogenic challenge exceeds their protective capacity (Wira, 2005).

Fetal Contributions to Parturition

It is intriguing to envision that the mature human fetus provides the signal to initiate parturition, and evidence for fetal signaling is mounting (Mendelson, 2017). The fetus may give signals through blood-borne agents that act on the placenta or through secretion into the amnionic fluid.

Uterine Stretch

Fetal growth is an important component in uterine activation in phase 2 of parturition. With uterine activation, stretch is required for induction of specific CAPs. Namely, stretch increases expression of connexin-43 and oxytocin receptors. Levels of gastrin-releasing peptide, a stimulatory agonist for smooth muscle, are also augmented by stretch in the myometrium (Tattersall, 2012).

Clinical clues for a role of stretch come from the observation that multifetal pregnancies carry a much greater risk for preterm labor than singleton ones. And, preterm labor is also significantly more common in pregnancies complicated by hydramnios. Although the mechanisms causing preterm birth in these two examples are debated, a role for uterine stretch must be considered.

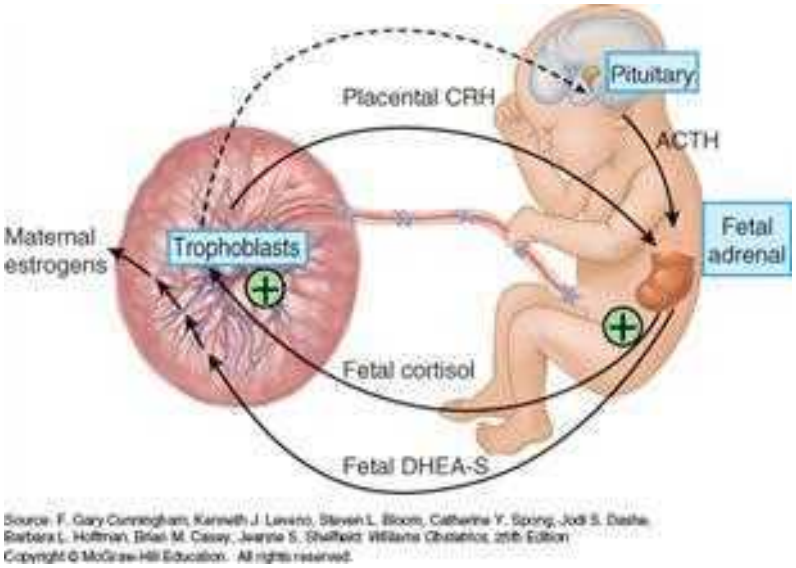
Cell signaling systems that are influenced by stretch to regulate the myometrial cell continue to be defined. This process—*mechanotransduction*—may include activation of cell-surface receptors or ion channels, transmission of signals through extracellular matrix, or release of autocrine molecules that act directly on myometrium (Shynlova, 2007; Young, 2011).

Fetal Endocrine Cascades

The ability of the fetus to provide endocrine signals that initiate parturition has been demonstrated in several species. However, evidence suggests that it is not regulated in the same manner in humans. That said, the human fetal hypothalamic-pituitary-adrenal-placental axis is considered a critical component of normal parturition. Moreover, premature activation of this axis is considered to prompt many cases of preterm labor (Challis, 2000, 2001). As in the sheep, steroid products of the human fetal adrenal gland are believed to have effects on the placenta and membranes that eventually transform the myometrium from a quiescent to a contractile state. A key component in the human may be the unique ability of the placenta to produce large amounts of CRH (Fig. 21-10).

FIGURE 21-10

The placental–fetal adrenal endocrine cascade. In late gestation, placental corticotropin-releasing hormone (CRH) stimulates fetal adrenal production of dehydroepiandrosterone sulfate (DHEA-S) and cortisol. The latter stimulates production of placental CRH, which leads to a feed-forward cascade that enhances adrenal steroid hormone production. ACTH = adrenocorticotropic hormone.



A CRH hormone that is identical to maternal and fetal hypothalamic CRH is synthesized by the placenta in relatively large amounts (Grino, 1987; Saijonmaa, 1988). However, unlike hypothalamic CRH, which is under glucocorticoid negative feedback, cortisol instead *stimulates* placental CRH production. This ability makes it possible to create a feed-forward endocrine cascade that does not end until delivery.

Maternal plasma CRH levels are low in the first trimester and rise from midgestation to term. In the last 12 weeks, CRH plasma levels rise exponentially, peak during labor, and then fall precipitously after delivery (Frim, 1988; Sasaki, 1987). Amnionic fluid CRH concentrations similarly increase in late gestation. CRH is the only trophic hormone-releasing factor to have a specific serum binding protein. During most of pregnancy, CRH-binding protein (CRH-BP) binds most maternal circulating CRH, and this inactivates it (Lowry, 1993). During later pregnancy, however, CRH-BP levels in both maternal plasma and amnionic fluid decline, leading to markedly greater levels of bioavailable CRH (Perkins, 1995; Petraglia, 1997).

In pregnancies in which the fetus can be considered "stressed" from various complications, concentrations of CRH in fetal plasma, amnionic fluid, and maternal plasma are greater than those seen in normal gestation (Berkowitz, 1996; McGrath, 2002). The placenta is the likely source of this elevated CRH concentration. For example, placental CRH content is fourfold higher in placentas from women with preeclampsia than in those from normal pregnancies (Perkins, 1995).

Placental CRH is thought to play several roles in parturition regulation. It may enhance fetal cortisol production to provide positive feedback so that the placenta produces more CRH. Late in pregnancy—phase 2 or 3 of parturition—modification in the CRH receptor favors a switch from cAMP formation to increased myometrial cell calcium levels via protein kinase C activation (You, 2012). Oxytocin acts to attenuate CRH-stimulated accumulation of cAMP in myometrial tissue. CRH acts to augment myometrial contractile force in response to $PGF_{2\alpha}$ (Benedetto, 1994). Finally, CRH stimulates fetal adrenal C_{19}-steroid synthesis, thereby increasing substrate for placental aromatization.

Some have proposed that the rising CRH level at the end of gestation reflects a *fetal-placental clock* (McLean, 1995). CRH concentrations vary greatly among women, and the rate of rise in maternal CRH levels is a more accurate predictor of pregnancy outcome than is a single measurement (Leung, 2001; McGrath, 2002). In this regard, the placenta and fetus, through endocrinological events, influence the timing of parturition at the end of normal gestation.

Fetal Lung Surfactant and Platelet-Activating Factor

Surfactant protein A (SP-A) produced by the fetal lung is required for lung maturation. SP-A is expressed by the human amnion and decidua, is present in the amnionic fluid, and prompts signaling pathways in human myometrial cells (Garcia-Verdugo, 2008; Lee, 2010; Snegovskikh, 2011). The exact mechanisms by which SP-A activates myometrial contractility in women, however, remain to be clarified. One mode may be its effects on prostaglandins. Namely, SP-A selectively inhibits prostaglandin $F_{2\alpha}$ in the term decidua, but SP-A levels drop in the amnionic fluid at term (Chaiworapongsa, 2008). In addition to SP-A, the fetal lung makes the uterotonic agent platelet-activating factor (Frenkel, 1996; Toyoshima, 1995). This factor and SP-A play a role in fetal–maternal signaling for parturition (Gao, 2015).

Fetal-Membrane Senescence

Toward the end of pregnancy, fetal membranes undergo physiological aging termed cellular senescence (Menon, 2016). In human fetal membranes and animal models, stretch and oxidative stress induce senescent fetal membrane to manifest a form of sterile inflammation termed senescent-associated secretory phenotype (SASP). This in turn propagates inflammatory signals that further weaken the fetal membrane and activate signals in the decidua and myometrium to initiate parturition. Thus, as the functional necessity of fetal membranes declines at term, they are able to promote signals that contribute to parturition initiation.

Fetal Anomalies and Delayed Parturition

Some evidence shows that pregnancies with markedly diminished estrogen production may be associated with prolonged gestation. These "natural experiments" include women with inherited placental sulfatase deficiency and fetal anencephaly with adrenal hypoplasia. The broad range of gestational length seen with these disorders, however, calls into question the exact role of estrogen in human parturition initiation.

Other fetal abnormalities that prevent or severely reduce the entry of fetal urine or lung secretions into amnionic fluid do not prolong human pregnancy. Examples are renal agenesis and pulmonary hypoplasia, respectively. Thus, a fetal signal through the paracrine arm of the fetal–maternal communication system does not appear to be mandated for parturition initiation.

Some brain anomalies of the fetal calf, fetal lamb, and sometimes the human fetus delay the normal timing of parturition. More than a century ago, Rea (1898) observed an association between fetal anencephaly and prolonged human gestation. Malpas (1933) extended these observations and described a pregnancy with an anencephalic fetus that was prolonged to 374 days—53 weeks. He concluded that the association between anencephaly and prolonged gestation was attributable to anomalous fetal brain-pituitary-adrenal function. Indeed, the adrenal glands of the anencephalic fetus are very small and, at term, may be only 5 to 10 percent as large as those of a normal fetus. This is caused by developmental failure of the fetal zone that normally accounts for most of fetal adrenal mass and production of C_{19}-steroid hormones (Chap. 5, Fetal Adrenal Gland–Placental Interactions). Such pregnancies are associated with delayed labor and suggest that the fetal adrenal glands are important for the timely onset of parturition.

PHASE 3: LABOR

This phase is synonymous with active labor, which is customarily divided into three stages. These compose the commonly used labor graph shown in Figure 21-4. The first stage begins when spaced uterine contractions of sufficient frequency, intensity, and duration are attained to bring about cervical thinning, termed *effacement*. Several uterotonins may be important to the success of this stage of active labor (see Fig. 21-5). These have been shown to stimulate smooth muscle contraction through G-protein coupling. This labor stage ends when the cervix is fully dilated—about 10 cm—to allow passage of the term-sized fetus. The first stage of labor, therefore, is the *stage of cervical effacement and dilation.* The second stage begins when cervical dilation is complete and ends with delivery. Thus, the second stage of labor is the *stage of fetal expulsion.* Last, the third stage begins immediately after delivery of the fetus and ends with the delivery of the placenta. Thus, the third stage of labor is the *stage of placental separation and expulsion*.

First Stage: Clinical Onset of Labor

Uterine Labor Contractions

In some women, forceful uterine contractions that effect delivery begin suddenly. In others, labor initiation is heralded by spontaneous release of a small amount of blood-tinged mucus from the vagina. This extrusion of the mucus plug that had previously filled the cervical canal during pregnancy is referred to as “show” or “bloody show.” Its passage indicates that labor is already in progress or likely will ensue in hours to days.

Unique among physiological muscular contractions, those of uterine smooth muscle during labor are painful. Several possible causes have been suggested: (1) hypoxia of the contracted myometrium—such as that with angina pectoris; (2) compression of nerve ganglia in the cervix and lower uterus by contracted interlocking muscle bundles; (3) cervical stretching during dilation; and (4) stretching of the peritoneum overlying the fundus.

Of these, compression of nerve ganglia in the cervix and lower uterine segment by the contracting myometrium is an especially attractive hypothesis. Paracervical infiltration with local anesthetic usually produces appreciable pain relief with contractions (Chap. 25, Neuraxial Analgesia). Uterine contractions are involuntary and, for the most part, independent of extrauterine control. Neural blockade from epidural analgesia does not diminish their frequency or intensity. In other examples, myometrial contractions in paraplegic women and in women after bilateral lumbar sympathectomy are normal but painless.

Mechanical stretching of the cervix enhances uterine activity in several species, including humans. This phenomenon is the *Ferguson reflex* (Ferguson, 1941). Its exact mechanism is unclear, and release of oxytocin has been suggested but not proven. Manipulation of the cervix and “stripping” the fetal membranes is associated with a rise in blood levels of prostaglandin $F_{2\alpha}$ metabolites.

The interval between contractions narrows gradually from approximately 10 minutes at the onset of first-stage labor to as little as 1 minute or less in the second stage. Periods of relaxation between contractions, however, are essential for fetal welfare. Unremitting contractions compromise uteroplacental blood flow sufficiently to cause fetal hypoxemia. In active-phase labor, the duration of each contraction ranges from 30 to 90 seconds and averages 1 minute. Contraction intensity varies appreciably during normal labor. Specifically, amnionic fluid pressures generated by contractions during spontaneous labor average 40 mm Hg, but vary from 20 to 60 mm Hg (Chap. 24, Patterns of Uterine Activity).

Distinct Lower and Upper Uterine Segments

During active labor, the anatomical uterine divisions that were initiated in phase 2 of parturition become increasingly evident (Figs. 21-11 and 21-12). By abdominal palpation, even before membrane rupture, the two segments can sometimes be differentiated. The upper segment is firm during contractions, whereas the lower segment is softer, distended, and more passive. This mechanism is imperative because if the entire myometrium, including the lower uterine segment and cervix, were to contract simultaneously and with equal intensity, the net expulsive force would markedly decline. Thus, the upper segment contracts, retracts, and expels the fetus. In response to these contractions, the softened lower uterine segment and cervix dilate and thereby form a greatly expanded, thinned-out tube through which the fetus can pass.

FIGURE 21-11

Sequence of development of the segments and rings in the uterus at term and in labor. Note comparison between the uterus of a nonpregnant woman, the uterus at term, and the uterus during labor. The passive lower uterine segment is derived from the isthmus, and the physiological retraction ring develops at the junction of the upper and lower uterine segments. The pathological retraction ring develops from the physiological ring. Anat. I.O. = anatomical internal os; E.O. = external os; Hist. I.O. = histological internal os; Ph.R.R. = physiological retraction ring.

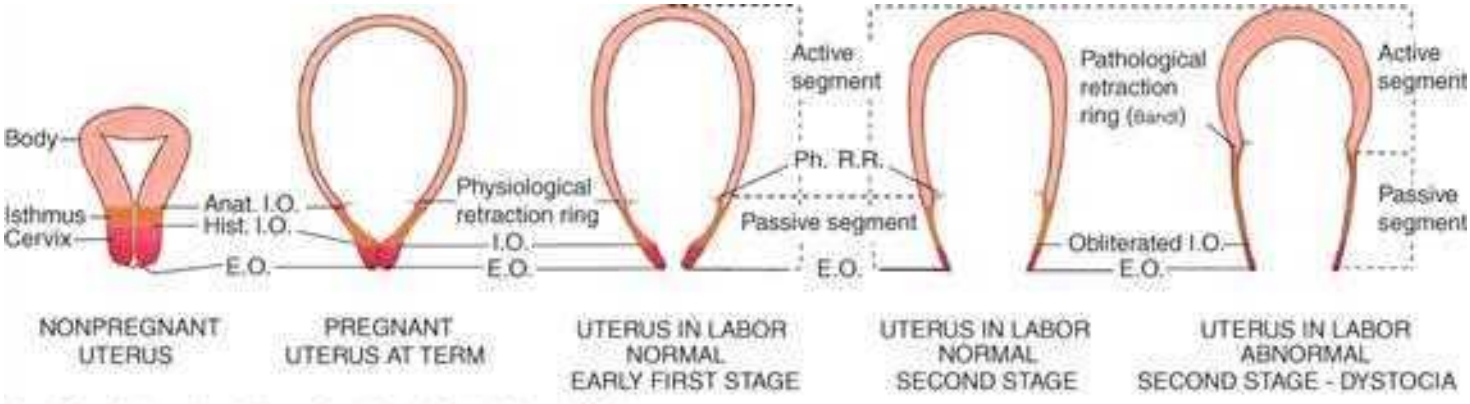


FIGURE 21-12

The uterus at the time of vaginal delivery. The active upper segment retracts around the presenting part as the fetus descends through the birth canal. In the passive lower segment, there is considerably less myometrial tone.

The myometrium of the upper segment does not relax to its original length after contractions. Instead, it becomes relatively fixed at a shorter length. The upper active uterine segment contracts down on its diminishing contents, but myometrial tension remains constant. The net effect is to take up slack, thus maintaining the advantage gained in expulsion of the fetus. Concurrently, the uterine musculature is kept in firm contact with the uterine contents. As the consequence of retraction, each successive contraction commences where its predecessor left off. Thus, the upper part of the uterine cavity becomes slightly smaller with each successive contraction. Because of the successive shortening of the muscular fibers, the upper active segment becomes progressively thickened throughout first- and second-stage labor (see Fig. 21-11). This process continues and results in a tremendously thickened upper uterine segment immediately after delivery.

Clinically, it is important to understand that the phenomenon of upper segment retraction is contingent on a decrease in the volume of its contents. For this to happen, particularly early in labor when the entire uterus is virtually a closed sac with only minimal cervical dilation, the musculature of the lower segment must stretch. This permits a greater portion of the uterine contents to occupy the lower segment. The upper segment retracts only to the extent that the lower segment distends and the cervix dilates.

Relaxation of the lower uterine segment mirrors the same gradual progression of retraction. Recall that after each contraction of the upper segment, the muscles do not return to their previous length, but tension remains essentially the same. By comparison, in the lower segment, successive lengthening of the fibers with labor is accompanied by thinning, normally to only a few millimeters in the thinnest part. As a result of the lower segment thinning and concomitant upper segment thickening, a boundary between the two is marked by a ridge on the inner uterine surface—the *physiological retraction ring.* When the thinning of the lower uterine segment is extreme, as in obstructed labor, the ring is prominent and forms a *pathological retraction ring*. This abnormal condition is also known as the *Bandl ring,* which is discussed further in Chapter 23 (Perinatal Complications).

Changes in Uterine Shape

Each contraction gradually elongates the ovoid uterine shape and thereby narrows the horizontal diameter. This change in shape has important effects on the labor process. First, there is greater *fetal axis pressure,* that is, the smaller horizontal diameter serves to straighten the fetal vertebral column. This presses the upper pole of the fetus firmly against the fundus, whereas the lower pole is thrust farther downward. The lengthening of the ovoid shape has been estimated at 5 to 10 cm. Second, with lengthening of the uterus, the longitudinal muscle fibers are drawn taut. As a result, the lower segment and cervix are the only parts of the uterus that are flexible, and these are pulled upward and around the lower pole of the fetus.

Ancillary Forces

After the cervix is dilated fully, the most important force in fetal expulsion is produced by maternal intraabdominal pressure. Contraction of the abdominal muscles simultaneously with forced respiratory efforts with the glottis closed is referred to as *pushing*. The force is similar to that with defecation, but the intensity usually is much greater. The importance of intraabdominal pressure is shown by the prolonged descent during labor in paraplegic women and in those with a dense epidural block. And, although increased intraabdominal pressure is necessary to complete second-stage labor, pushing accomplishes little in the first stage. It exhausts the mother, and its associated elevated intrauterine pressures may be harmful to the fetus.

Cervical Changes

As the result of contraction forces, two fundamental changes—effacement and dilation—occur in the ripened cervix. For an average-sized fetal head to pass through the cervix, its canal must dilate to a diameter of approximately 10 cm. At this time, the cervix is said to be completely or fully dilated. Although there may be no fetal descent during cervical effacement, most commonly the presenting fetal part descends somewhat as the cervix dilates.

Cervical effacement is “obliteration” or “taking up” of the cervix. It is manifest clinically by shortening of the cervical canal from a length of approximately 3 cm to a mere circular orifice with almost paper-thin edges. The muscular fibers at the level of the internal cervical os are pulled upward, or “taken up,” into the lower uterine segment. The condition of the external os remains temporarily unchanged (Fig. 21-13).

FIGURE 21-13

Schematic showing effacement and dilation. **A.** Before labor, the primigravid cervix is long and undilated in contrast to that of the multipara, which has dilation of the internal and external os. **B.** As effacement begins, the multiparous cervix shows dilation and funneling of the internal os. This is less apparent in the primigravid cervix. **C.** As complete effacement is achieved in the primigravid cervix, dilation is minimal. The reverse is true in the multipara.

Effacement may be compared to a funneling process in which the whole length of a narrow cylinder is converted into a very obtuse, flaring funnel with a small distal circular opening. Because of growing myometrial activity during uterine preparedness for labor, appreciable effacement of a softened cervix sometimes is accomplished before active labor begins. Effacement causes expulsion of the mucous plug as the cervical canal is shortened.

Because the lower segment and cervix have less resistance during a contraction, a centrifugal pull is exerted on the cervix and creates *cervical dilation* (Fig. 21-14). As uterine contractions cause pressure on the membranes, the hydrostatic action of the amnionic sac in turn dilates the cervical canal like a wedge. The process of cervical effacement and dilation causes formation of the *forebag* of amnionic fluid. This is the leading portion of fluid and amnionic sac located in front of the presenting part. In the absence of intact membranes, the pressure of the presenting fetal part against the cervix and lower uterine segment is similarly effective. Early rupture of the membranes does not retard cervical dilation so long as the presenting fetal part is positioned to exert pressure against the cervix and lower segment.

FIGURE 21-14
Hydrostatic action of membranes in effecting cervical effacement and dilation. With labor progression, note the changing relations of the internal and external os in **(A)**, **(B)**, and **(C)**. Although not shown in this diagram, with membrane rupture, the presenting part, applied to the cervix and the forming lower uterine segment, acts similarly.

Referring back to Figure 21-4, recall that cervical dilation is divided into latent and active phases. The active phase is subdivided further into the acceleration phase, the phase of maximum slope, and the deceleration phase (Friedman, 1978). The duration of the latent phase is more variable and sensitive to extraneous factors. For example, sedation may prolong the latent phase, and myometrial stimulation shortens it. The latent phase duration has little bearing on the subsequent course of labor, whereas the characteristics of the accelerated phase are usually predictive of labor outcome. The first stage ends when cervical dilation is complete.

Second Stage: Fetal Descent

In many nulliparas, engagement of the head is accomplished before labor begins. That said, the head may not descend further until late in labor. In the descent pattern of normal labor, a typical hyperbolic curve is formed when the station of the fetal head is plotted as a function of labor duration. *Station* describes descent of the fetal biparietal diameter in relation to a line drawn between maternal ischial spines (Chap. 22, Management of First-Stage Labor). Active descent usually takes place after dilation has progressed for some time (Fig. 21-15). During second-stage labor, the speed of descent is maximal and is maintained until the presenting part reaches the perineal floor (Friedman, 1978). In nulliparas, the presenting part typically descends slowly and steadily. In multiparas, however, particularly those of high parity, descent may be rapid.

FIGURE 21-15
Labor course divided on the basis of expected evolution of the dilatation and descent curves into three functional divisions. The preparatory division includes the latent and acceleration phases. The dilatational division is the phase of maximum slope of dilatation. The pelvic division encompasses both the deceleration phase and the second stage, which is concurrent with the phase of maximum slope of fetal descent. (Redrawm from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)

Pelvic Floor Changes

The birth canal is supported and functionally closed by the pelvic floor (Chap. 2, Pelvic Diaphragm). The most important component of the floor is the levator ani muscle and the fibromuscular connective tissue that covers its upper and lower surfaces. The biomechanical properties of these structures and of the vaginal wall change markedly during parturition. These result from altered extracellular matrix structure or composition (Alperin, 2015; Rahn, 2008; Lowder, 2007).

The levator ani muscle closes the lower end of the pelvic cavity as a diaphragm. Thereby, a concave upper and a convex lower surface are presented. The posterior and lateral portions of the pelvic floor, which are not spanned by the levator ani muscle, are occupied bilaterally by the piriformis and coccygeus muscles.

The levator ani muscle varies in thickness from 3 to 5 mm, although its margins encircling the rectum and vagina are somewhat thicker. During pregnancy, the levator ani usually undergoes hypertrophy, forming a thick band that extends backward from the pubis and encircles the vagina about 2 cm above the plane of the hymen. On contraction, the levator ani draws both the rectum and the vagina forward and upward in the direction of the symphysis pubis and thereby acts to close the vagina.

In the first stage of labor, the membranes, when intact, and the fetal presenting part serve to dilate the upper vagina. The most marked change consists of stretching levator ani muscle fibers. This is accompanied by thinning of the central portion of the perineum, which becomes transformed from a wedge-shaped, 5-cm-thick tissue mass to a thin, almost transparent membranous structure less than 1 cm thick. When the perineum is distended maximally, the anus becomes markedly dilated and presents an opening that varies from 2 to 3 cm in diameter and through which the anterior wall of the rectum bulges.

Third Stage: Delivery of Placenta and Membranes

This stage begins immediately after fetal delivery and involves separation and expulsion of the placenta and membranes. As the neonate is born, the uterus spontaneously contracts around its diminishing contents. Normally, by the time the newborn is completely delivered, the uterine cavity is nearly obliterated. The organ consists of an almost solid mass of muscle, several centimeters thick, above the thinner lower segment. The uterine fundus now lies just below the level of the umbilicus.

This sudden diminution in uterine size is inevitably accompanied by a decrease in the area of the placental implantation site (Fig. 21-16). For the placenta to accommodate itself to this reduced area, it thickens, but because of limited placental elasticity, it is forced to buckle. The resulting tension pulls the weakest layer—decidua spongiosa—from that site. Thus, placental separation follows the disproportion created between the relatively unchanged placental size and the reduced implantation site size.

FIGURE 21-16
Diminution in size of the placental site after birth of the newborn. **A.** Spatial relations before birth. **B.** Placental spatial relations after birth.

Cleavage of the placenta is aided greatly by the loose structure of the spongy decidua. As detachment proceeds, a hematoma forms between the separating placenta and the adjacent decidua, which remains attached to the myometrium. The hematoma is usually the result rather than the cause of the separation, because in some cases bleeding is negligible.

The great decline in uterine cavity surface area simultaneously throws the fetal membranes—the amniochorion and the parietal decidua—into innumerable folds (Fig. 21-17). Membranes usually remain in situ until placental separation is nearly completed. These are then peeled off the uterine wall, partly by further contraction of the myometrium and partly by traction that is exerted by the separated placenta as it descends during expulsion.

FIGURE 21-17
Postpartum, membranes are thrown up into folds as the uterine cavity decreases in size. (Used with permission from Dr. Kelley S. Carrick.)

After the placenta has detached, it can be expelled by increased abdominal pressure. Completion of the third stage is also accomplished by alternately compressing and elevating the fundus, while exerting minimal traction on the umbilical cord. The retroplacental hematoma either follows the placenta or is found within the inverted sac formed by the membranes. In this process, known as the *Schultze mechanism* of placental expulsion, blood from the placental site pours into the membrane sac and does not escape externally until after extrusion of the placenta. In the other form of placental extrusion, known as the *Duncan mechanism,* the placenta separates first at the periphery and blood collects between the membranes and the uterine wall and escapes from the vagina. In this circumstance, the placenta descends sideways, and its maternal surface appears first.

UTEROTONINS IN PARTURITION PHASE 3

Oxytocin

Late in pregnancy, during phase 2 of parturition, the number of myometrial oxytocin receptors grows appreciably (Fuchs, 1982; Kimura, 1996). This increase coincides with a greater uterine contractile responsiveness to oxytocin. Prolonged gestation is associated with a delay in the rise of these receptor levels (Fuchs, 1984).

Oxytocin—literally, *quick birth*—was the first uterotonin to be implicated in parturition initiation. This nanopeptide is synthesized in the magnocellular neurons of the supraoptic and paraventricular neurons. The prohormone is transported with its carrier protein, *neurophysin*, along the axons to the neural lobe of the posterior pituitary gland in membrane-bound vesicles for storage and later release. The prohormone is converted enzymatically to oxytocin during transport (Gainer, 1988; Leake, 1990).

In addition to its effectiveness in pharmacologically inducing labor at term, oxytocin is a potent uterotonin and occurs naturally in humans. Subsequent observations provide additional support for this theory: (1) the number of oxytocin receptors strikingly rises in myometrial and decidual tissues near the end of gestation; (2) oxytocin acts on decidual tissue to promote prostaglandin release; and (3) oxytocin is synthesized directly in decidual and extraembryonic fetal tissues and in the placenta (Chibbar, 1993; Zingg, 1995).

Although little evidence suggests a role for oxytocin in phase 2 of parturition, abundant data support its important role during second-stage labor and in the puerperium—phase 4 of parturition. Specifically, maternal serum oxytocin levels are elevated: (1) during second-stage labor, which is the end of phase 3 of parturition; (2) in the early puerperium; and (3) during breastfeeding (Nissen, 1995). Immediately after delivery of the fetus, placenta, and membranes, which completes parturition phase 3, firm and persistent uterine contractions are essential to prevent postpartum hemorrhage. Oxytocin likely causes persistent contractions.

Prostaglandins

Although their role in phase 2 of parturition in uncomplicated pregnancies is less well defined, a critical role for prostaglandins in phase 3 of parturition is clear (MacDonald, 1993). First, levels of prostaglandins—or their metabolites—in amnionic fluid, maternal plasma, and maternal urine are increased during labor. Second, receptors for PGE_2 and $PGF_{2\alpha}$ are expressed in the uterus and cervix. Thus, if these tissues are exposed to prostaglandins, they will respond.

Third, treatment of pregnant women with prostaglandins, by any of several administration routes, causes abortion or labor at all gestational ages. Moreover,

administration of prostaglandin H synthase type 2 (PGHS-2) inhibitors to pregnant women will delay spontaneous labor onset and sometimes arrest preterm labor (Loudon, 2003). Last, prostaglandin treatment of myometrial tissue in vitro sometimes causes contraction, dependent on the prostanoid tested and the physiological status of the tissue treated.

During labor, prostaglandin production within the myometrium and decidua is an efficient mechanism of activating contractions. For example, prostaglandin synthesis is high and unchanging in the decidua during phase 2 and 3 of parturition. Moreover, the receptor level for $PGF_{2\alpha}$ is augmented in the decidua at term, and this increase most likely is the regulatory step in prostaglandin action in the uterus.

The fetal membranes and placenta also produce prostaglandins. Primarily $PGE_{2,}$ but also $PGF_{2\alpha}$, are detected in amnionic fluid at all gestational ages. As the fetus grows, prostaglandin levels in the amnionic fluid rise gradually. Their greatest elevation in concentration within amnionic fluid, however, is demonstrable after labor begins. These higher levels likely result as the cervix dilates and exposes decidual tissue (Fig. 21-18). These higher levels in the forebag, compared with those in the upper compartment, are believed to follow an inflammatory response that signals the events leading to active labor. Together, the rise in cytokine and prostaglandin concentrations further degrade the extracellular matrix, thus weakening fetal membranes.

FIGURE 21-18
Sagittal view of the exposed forebag and attached decidual fragments after cervical dilation during labor. (Redrawn from MacDonald PC, Casey ML: Preterm birth. Sci Am 3:42, 1996.)

Endothelin-1

The endothelins are a family of 21-amino-acid peptides that powerfully induce myometrial contraction (Word, 1990). The endothelin A receptor is preferentially expressed in smooth muscle, and when activated, it effects a rise in intracellular calcium. Endothelin-1 is produced in myometrium of term gestations and is able to induce synthesis of other contractile mediators such as prostaglandins and inflammatory mediators (Momohara, 2004; Sutcliffe, 2009). The requirement of endothelin-1 in normal parturition physiology remains to be established.

Angiotensin II

Two G-protein-linked angiotensin II receptors are expressed in the uterus—AT1 and AT2. In nonpregnant women, the AT2 receptor predominates, but the AT1 receptor is preferentially expressed in gravidas (Cox, 1993). Angiotensin II binding to the plasma-membrane receptor evokes contraction. During pregnancy, the vascular smooth muscle that expresses the AT2 receptor is refractory to the pressor effects of infused angiotensin II (Chap. 4, Renin, Angiotensin II, and Plasma Volume).

PHASE 4: THE PUERPERIUM

Immediately and for about an hour after delivery, the myometrium remains persistently contracted. This directly compresses large uterine vessels and allows thrombosis of their lumens to prevent hemorrhage. This is typically augmented by endogenous and pharmacological uterotonic agents (Chap. 27, Management of the Third Stage).

Uterine involution and cervical repair are prompt remodeling processes that restore these organs to the nonpregnant state. These protect the reproductive tract from invasion by commensal microorganisms and restore endometrial responsiveness to normal hormonal cyclicity.

During the early puerperium, lactogenesis and milk let-down begin in mammary glands (Chap. 36, Lactation and Breastfeeding). Reinstitution of ovulation signals preparation for the next pregnancy. Ovulation generally occurs within 4 to 6 weeks after birth. However, it is dependent on the duration of breastfeeding and lactation-induced, prolactin-mediated anovulation and amenorrhea.

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CHAPTER 22: Normal Labor

It follows that some process of adaptation or accommodation of suitable portions for the head to the various pelvic planes is necessary to insure the completion of childbirth. This is brought about by certain movement of the presenting part, which belong to what is termed the mechanism of labour.

—J. Whitridge Williams (1903)

INTRODUCTION

Labor is the process that leads to childbirth. It begins with the onset of regular uterine contractions and ends with delivery of the newborn and expulsion of the placenta. Pregnancy and birth are physiological processes, and thus, labor and delivery should be considered normal for most women.

MECHANISMS OF LABOR

Pelvic Floor Changes

Many adaptive changes are required for pregnancy and for labor and delivery. According to Nygaard (2015), vaginal delivery is a traumatic event. To assess this in part, Staer-Jensen and colleagues (2015) obtained transperineal sonographic measurements of the pelvic floor muscles at 21 weeks' and 37 weeks' gestation, and again at 6 weeks, 6 months, and 12 months postpartum. In 300 nulliparas, they measured bladder neck mobility and the area within the urogenital hiatus during Valsalva. This hiatus is the U-shaped opening in the pelvic floor muscles through which the urethra, vagina, and rectum pass (Chap. 2, Perineum). In this study, the levator hiatus area was significantly larger at 37 weeks' gestation and at 6 weeks postpartum compared with earlier pregnancy. Then, by 6 months postpartum, the hiatus had improved and narrowed to return to an area comparable to that at 21 weeks' gestation. However, no further improvement was noted by 12 months postpartum. Of note, hiatal area enlargement was only seen in those who delivered vaginally.

These findings demonstrate antepartum changes in pelvic floor structure that may reflect adaptations needed to permit vaginal delivery (Nygaard, 2015). Additional pelvic floor changes are discussed in Chapter 4 (Fallopian Tubes), and the contributions of pregnancy and delivery to later pelvic organ prolapse and incontinence are described in Chapter 30 (Cesarean Delivery Risks).

Fetal Lie

At the onset of labor, the position of the fetus with respect to the birth canal is critical to the route of delivery and thus should be determined in early labor. Important relationships include fetal lie, presentation, attitude, and position.

Fetal lie describes the relationship of the fetal long axis to that of the mother. In more than 99 percent of labors at term, the fetal lie is *longitudinal*. A *transverse lie* is less frequent, and predisposing factors include multiparity, placenta previa, hydramnios, and uterine anomalies (Chap. 23, Brow Presentation). Occasionally, the fetal and maternal axes may cross at a 45-degree angle, forming an *oblique lie.* This is unstable and becomes longitudinal or transverse during labor.

Fetal Presentation

The presenting part is the portion of the fetal body that is either foremost within the birth canal or in closest proximity to it. It typically can be felt through the cervix during vaginal examination. Accordingly, in longitudinal lies, the presenting part is either the fetal head or the breech, creating *cephalic* and *breech presentations*, respectively. When the fetus lies with the long axis transversely, the *shoulder* is the presenting part. Table 22-1 describes the incidences of these various presentations.

TABLE 22-1

Fetal Presentation in 68,097 Singleton Pregnancies at Parkland Hospital

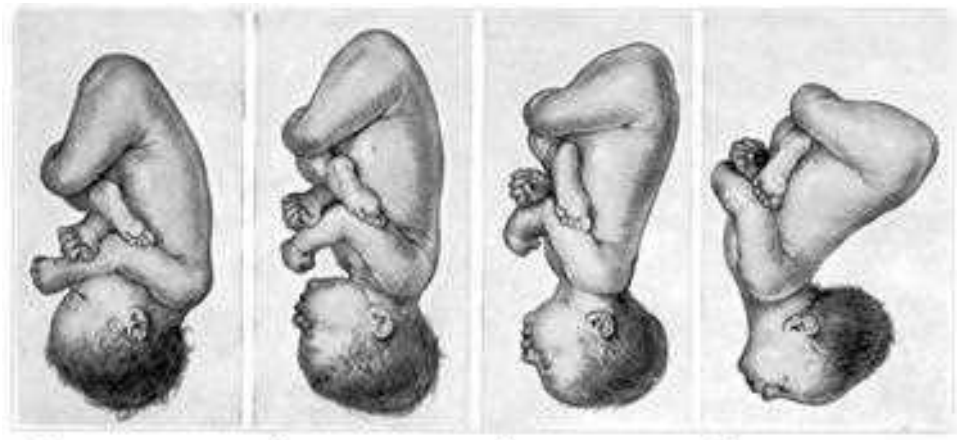
Presentation	Percent	Incidence
Cephalic	96.8	—
Breech	2.7	1:36
Transverse lie	0.3	1:335
Compound	0.1	1:1000
Face	0.05	1:2000
Brow	0.01	1:10,000

Cephalic Presentation

These presentations are classified according to the relationship between the head and body of the fetus (Fig. 22-1). Ordinarily, the head is flexed sharply so that the chin contacts the thorax. The occipital fontanel is the presenting part, and this presentation is referred to as a *vertex* or *occiput presentation.* Much less often, the fetal neck may be sharply extended so that the occiput and back come into contact, and the face is foremost in the birth canal—*face presentation.* The fetal head may assume a position between these extremes. When the neck is only partly flexed, the anterior (large) fontanel may present—*sinciput presentation.* When the neck is only partially extended, the brow may emerge—*brow presentation.* These latter two are usually transient. As labor progresses, sinciput and brow presentations almost always convert into vertex or face presentations by neck flexion or extension, respectively. Failure to do so can lead to dystocia, discussed in Chapter 23 (Brow Presentation).

FIGURE 22-1

Longitudinal lie. Cephalic presentation. Differences in attitude of the fetal body in **(A)** vertex, **(B)** sinciput, **(C)** brow, and **(D)** face presentations. Note changes in fetal attitude in relation to fetal vertex as the fetal head becomes less flexed.



The term fetus usually presents with the vertex, most logically because the uterus is piriform or pear shaped. Although the fetal head at term is slightly larger than the breech, the entire *podalic pole* of the fetus—that is, the breech and extremities—is bulkier and more mobile than the cephalic pole. The *cephalic pole* is composed of the fetal head only. Until approximately 32 weeks, the amnionic cavity is large compared with the fetal mass, and the fetus is not crowded by the uterine walls. Subsequently, however, the ratio of amnionic fluid volume declines relative to the growing fetal mass. As a result, the uterine walls are apposed more closely to the fetal parts. The fetus orients its polarity to make use of the roomier fundus for its bulkier and more mobile podalic pole. The high incidence of breech presentation in hydrocephalic fetuses is in accord with this theory, as the larger fetal cephalic pole requires more room than its podalic pole.

Breech Presentation

The incidence of breech presentation drops with gestational age and approximates 3 percent at term.

When the fetus presents breech, the three general configurations are *frank, complete,* and *footling presentations,* described in Chapter 28 (Classification of Breech Presentations). Breech presentation may result from circumstances that prevent normal version from taking place. One example is a septum that protrudes into the uterine cavity (Chap. 3, Diethylstilbestrol Reproductive Tract Abnormalities (Class VII)). Variances of fetal attitude, particularly extension of the vertebral column as

seen in frank breeches, also may prevent the fetus from turning. If the placenta is implanted in the lower uterine segment, it may distort normal intrauterine anatomy and result in a breech presentation.

Fetal Attitude

In the later months of pregnancy, the fetus assumes a characteristic posture described as attitude or habitus (see Fig. 22-1). As a rule, the fetus forms an ovoid mass that corresponds roughly to the shape of the uterine cavity. The fetus becomes folded upon itself to create a convex back. The head is sharply flexed; the chin is almost in contact with the chest; the thighs are flexed over the abdomen; and the legs are bent at the knees. In all cephalic presentations, the arms usually lie across the thorax or parallel to the sides. The umbilical cord fills the space between the extremities. This characteristic posture results from the mode of fetal growth and its accommodation to the uterine cavity.

Abnormal exceptions to this attitude occur as the fetal head becomes progressively more extended from the vertex to the face presentation. This results in a progressive change in fetal attitude from a convex (flexed) to a concave (extended) contour of the vertebral column.

Fetal Position

Position refers to the relationship of an arbitrarily chosen portion of the fetal presenting part to the right or left side of the birth canal. Accordingly, with each presentation, there may be two positions—right or left. The fetal occiput, chin (mentum), and sacrum are the determining points in vertex, face, and breech presentations, respectively (Figs. 22-2 to 22-6). Because the presenting part may be in either the left or right position, there are left and right occipital (LO and RO), left and right mental (LM and RM), and left and right sacral (LS and RS) designations.

FIGURE 22-2
Longitudinal lie. Vertex presentation. **A.** Left occiput anterior (LOA). **B.** Left occiput posterior (LOP).

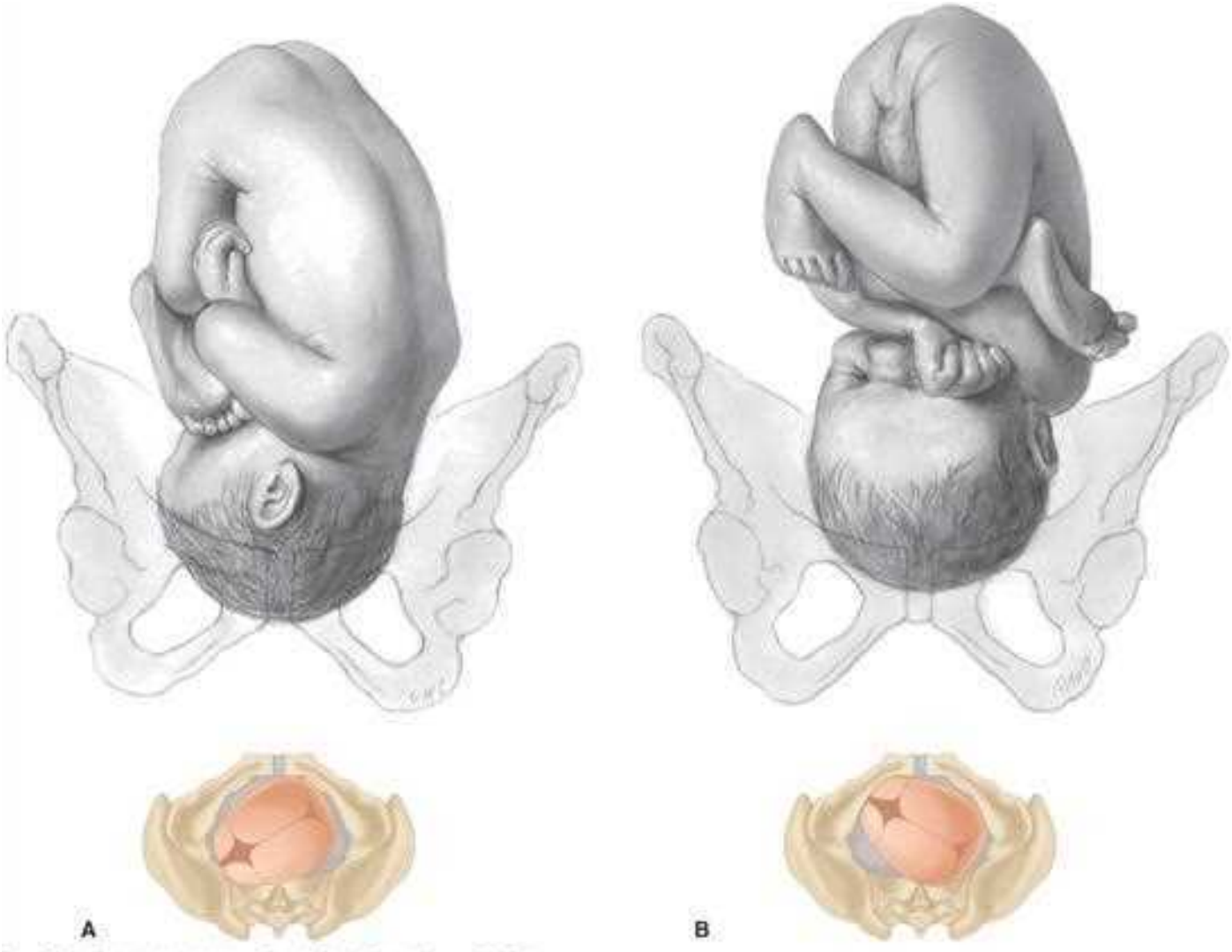


FIGURE 22-3
Longitudinal lie. Vertex presentation. **A.** Right occiput posterior (ROP). **B.** Right occiput transverse (ROT).

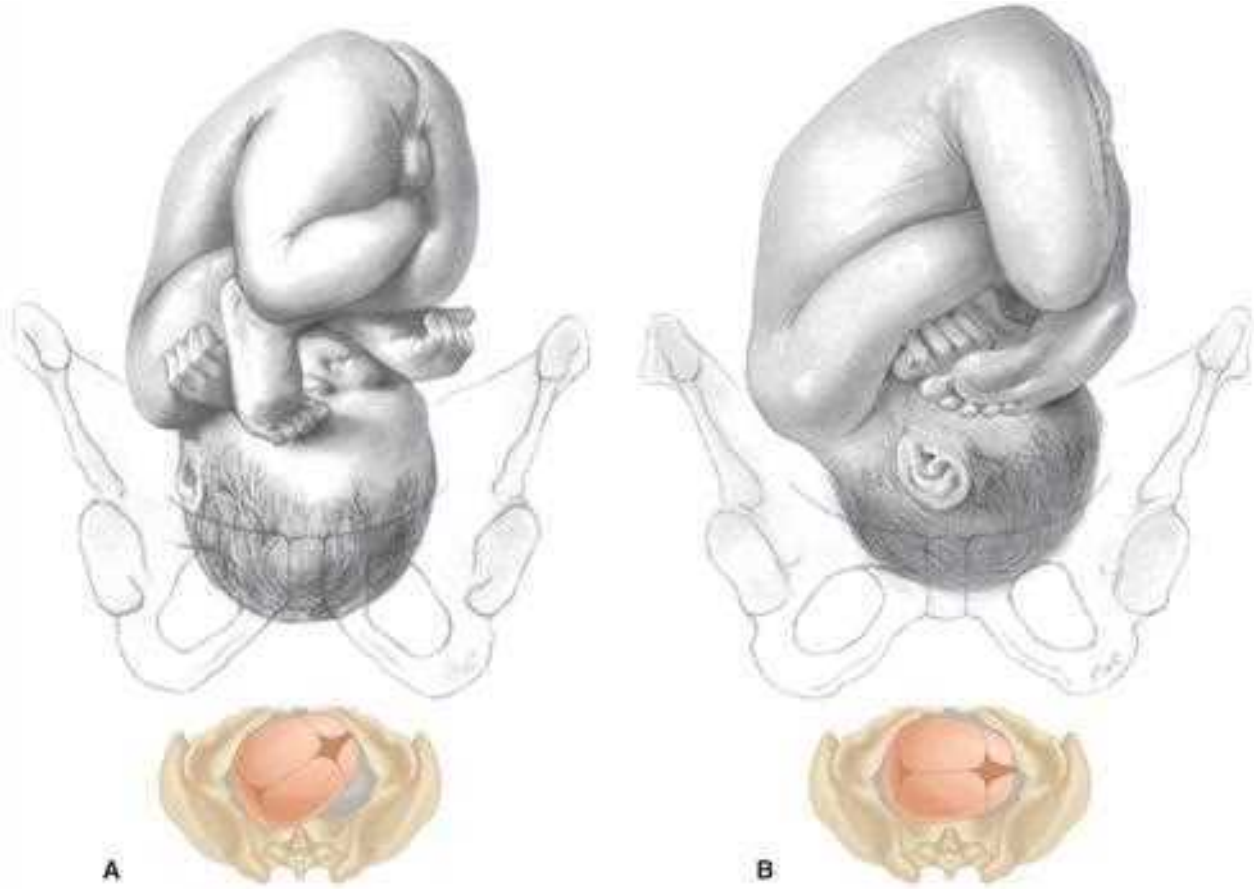


FIGURE 22-4

Longitudinal lie. Vertex presentation. Right occiput anterior (ROA).

FIGURE 22-5

Longitudinal lie. Face presentation. Left and right mentum anterior and right mentum posterior positions.

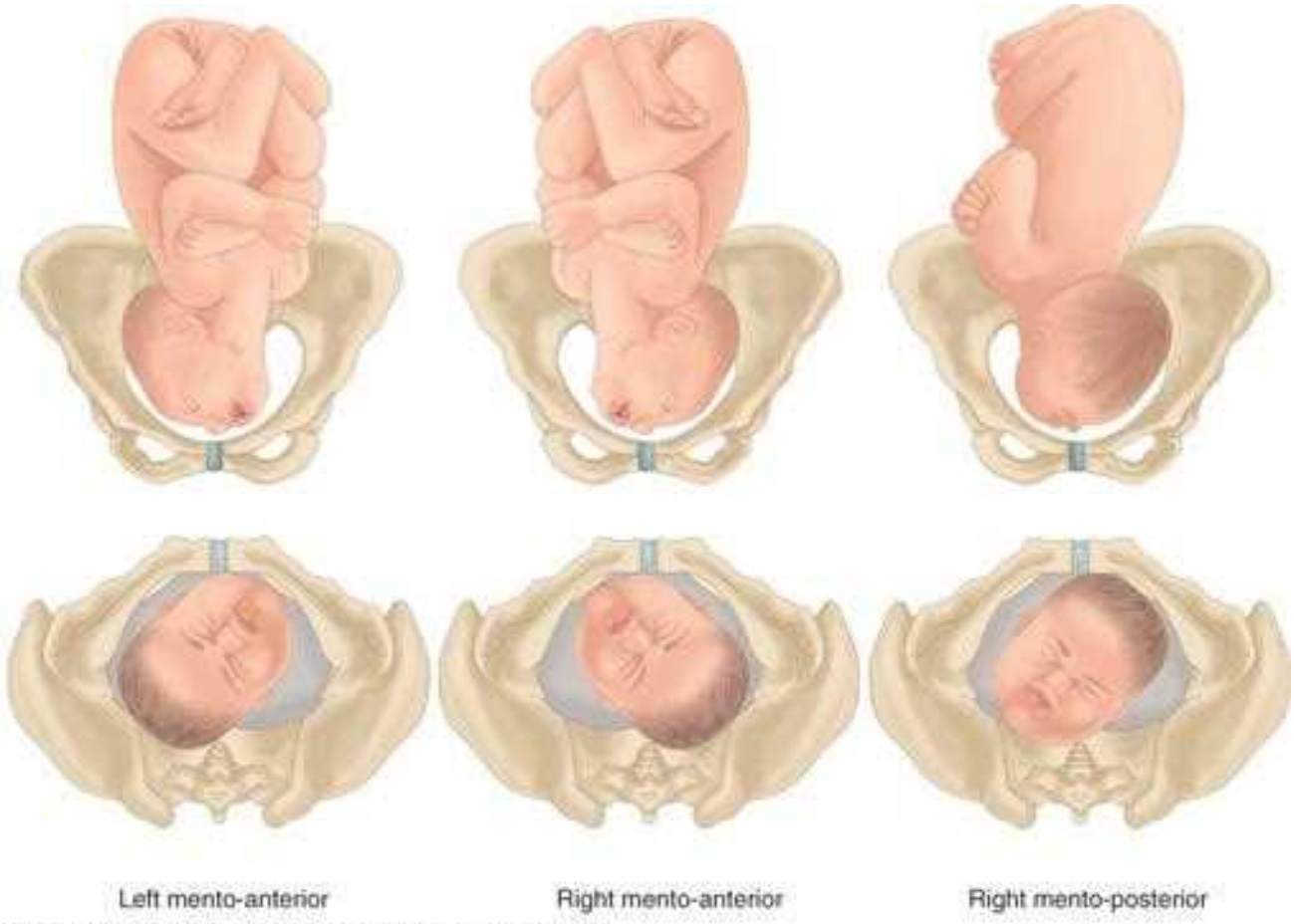
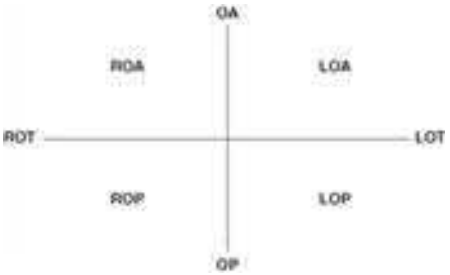


FIGURE 22-6

Longitudinal lie. Breech presentation. Left sacrum posterior (LSP).

Further, the relationship of a given portion of the presenting part to the anterior (A), transverse (T), or posterior (P) portion of the maternal pelvis is considered. As shown in Figures 22-2 to 22-6, there are six varieties of each of the three presentations. Thus, in an occiput presentation, the presentation, position, and variety may

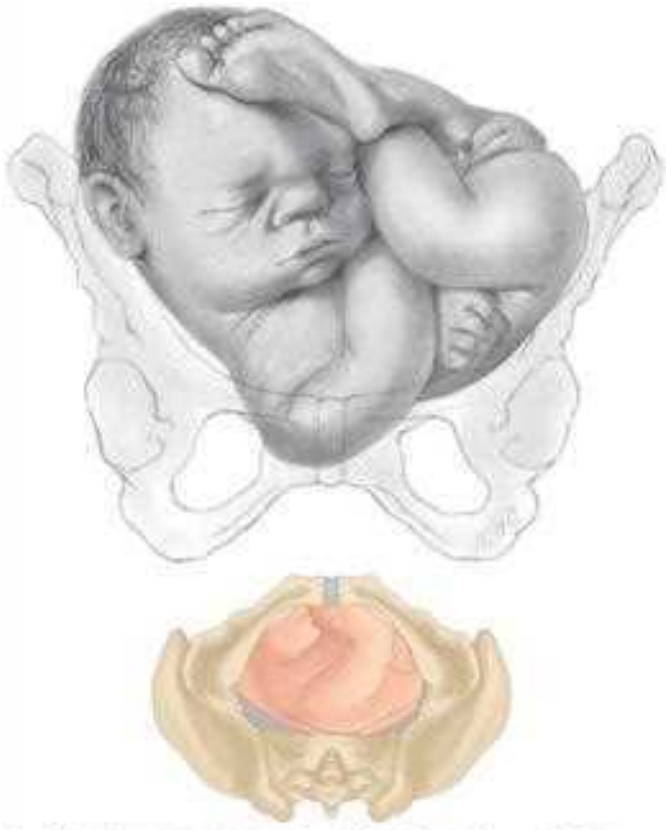
be abbreviated in clockwise fashion as:



Approximately two thirds of all vertex presentations are in the left occiput position, and one third in the right.

In shoulder presentations, the acromion (scapula) is the portion of the fetus arbitrarily chosen for orientation with the maternal pelvis. One example of the terminology sometimes employed for this purpose is illustrated in Figure 22-7. The acromion or back of the fetus may be directed either posteriorly or anteriorly and superiorly or inferiorly. Because it is impossible to differentiate exactly the several varieties of shoulder presentation by clinical examination and because such specific differentiation serves no practical purpose, it is customary to refer to all transverse lies simply as *shoulder presentations.* Another term used is *transverse lie,* with *back up* or *back down*, which is clinically important when deciding incision type for cesarean delivery (Chap. 23, Etiology).

FIGURE 22-7
Transverse lie. Right acromiodorsoposterior (RADP). The shoulder of the fetus is to the mother's right, and the back is posterior.

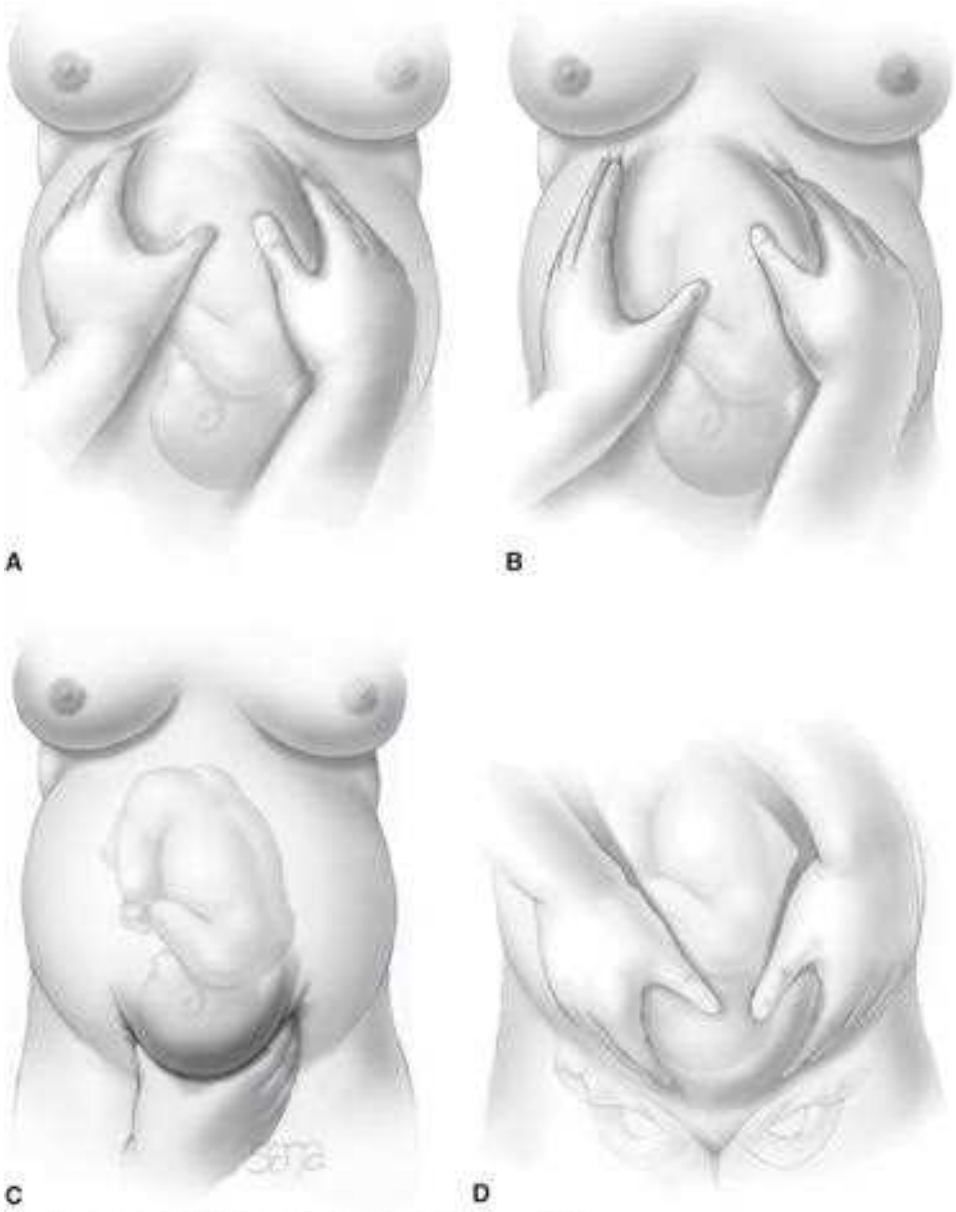


Diagnosis

Leopold Maneuvers

Several methods can be used to diagnose fetal presentation and position. Abdominal examination can be conducted systematically employing the four maneuvers described by Leopold in 1894 and shown in Figure 22-8. The mother lies supine and comfortably positioned with her abdomen bared. These maneuvers may be difficult if not impossible to perform and interpret if the patient is obese, if amnionic fluid volume is excessive, or if the placenta is anteriorly implanted.

FIGURE 22-8
Leopold maneuvers **(A–D)** performed in fetus with a longitudinal lie in the left occiput anterior position (LOA).



The first maneuver assesses the uterine fundus. It permits identification of fetal lie and determination of which fetal pole—that is, cephalic or podalic—occupies the fundus. The breech gives the sensation of a large, nodular mass, whereas the head feels hard and round and is more mobile.

The second maneuver is accomplished as the palms are placed on either side of the maternal abdomen, and gentle but deep pressure is exerted. On one side, a hard, resistant structure is felt—the back. On the other, numerous small, irregular, mobile parts are felt—the fetal extremities. By noting whether the back is directed anteriorly, transversely, or posteriorly, fetal orientation can be determined.

The third maneuver aids confirmation of fetal presentation. The thumb and fingers of one hand grasp the lower portion of the maternal abdomen just above the symphysis pubis. If the presenting part is not engaged, a movable mass will be felt, usually the head. The differentiation between head and breech is made as in the first maneuver.

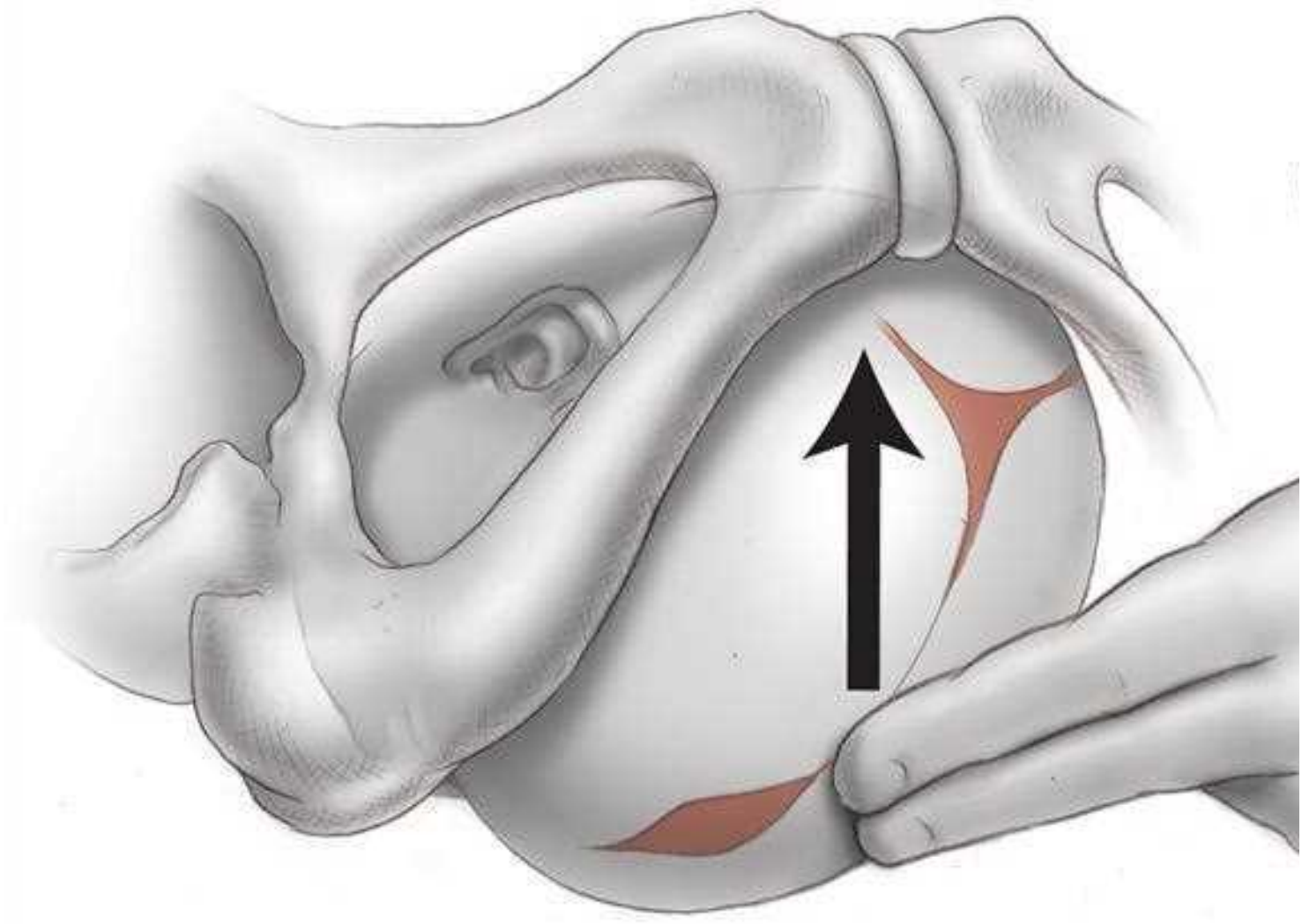
The fourth maneuver helps determine the degree of descent. The examiner faces the mother's feet, and the fingertips of both hands are positioned on either side of the presenting part. They exert inward pressure and then slide caudad along the axis of the pelvic inlet. In many instances, when the head has descended into the pelvis, the anterior shoulder or the space created by the neck may be differentiated readily from the hard head.

Abdominal palpation can be performed throughout the latter months of pregnancy and during and between the contractions of labor. At least in the past, according to Lydon-Rochelle and colleagues (1993), experienced clinicians have accurately identified fetal malpresentation using Leopold maneuvers with a high sensitivity—88 percent, specificity—94 percent, positive-predictive value—74 percent, and negative-predictive value—97 percent. With experience, it is possible to estimate the size of the fetus with these maneuvers (Field, 1995). However, and especially with an obese woman, estimates by palpation and actual birth weights often correlate poorly (Fox, 2009; Goetzinger, 2014; Noumi, 2005).

Vaginal Examination

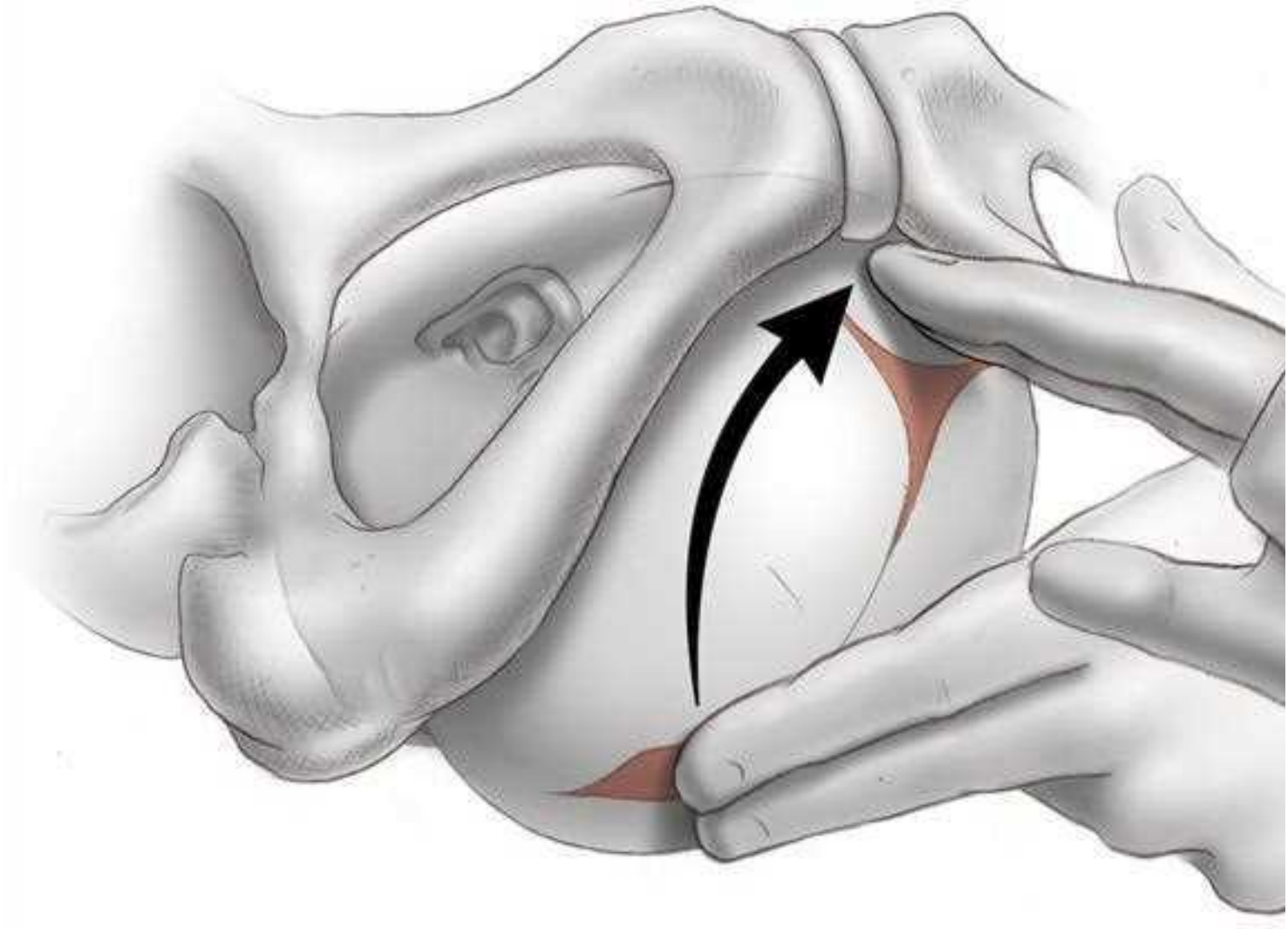
Before labor, the diagnosis of fetal presentation and position by vaginal examination is often inconclusive because the presenting part must be palpated through a closed cervix and lower uterine segment. With the onset of labor and after cervical dilation, vertex presentations and their positions are recognized by palpation of the various fetal sutures and fontanels. Face and breech presentations are identified by palpation of facial features or the fetal sacrum and perineum, respectively. During this vaginal examination, it is advisable to pursue a definite routine, comprising four movements. First, the examiner inserts two fingers into the vagina and the presenting part is found. Differentiation of vertex, face, and breech is then accomplished readily. Second, if the vertex is presenting, the fingers are directed posteriorly and then swept forward over the fetal head toward the maternal symphysis (Fig. 22-9). During this movement, the fingers necessarily cross the sagittal suture, and its linear course is delineated. Next, the positions of the two fontanels, found at either end of the sagittal suture, are ascertained. For this, fingers are passed to the most anterior extension of the sagittal suture, and the fontanel encountered there is examined and identified. Then, the fingers pass along the suture to the other end of the head until the other fontanel is felt and differentiated (Fig. 22-10). Last, the station, or extent to which the presenting part has descended into the pelvis, can also be established at this time (Management of First-Stage Labor). Using these maneuvers, the various sutures and fontanels are determined (Fig. 29-1).

FIGURE 22-9
Locating the sagittal suture by vaginal examination.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

FIGURE 22-10
Differentiating the fontanels by vaginal examination.



Sonography and Radiography

Sonographic techniques can aid fetal position identification, especially in obese women or in women with muscular abdominal walls. Compared with digital examinations, sonography for fetal head position determination during second-stage labor is more accurate (Ramphul, 2014; Wiafe, 2016).

Occiput Anterior Presentation

In most cases, the vertex enters the pelvis with the sagittal suture lying in the transverse pelvic diameter. The fetus enters the pelvis in the *left occiput transverse (LOT)* position more commonly than *right occiput transverse (ROT)* position (Caldwell, 1934). In *occiput anterior positions—LOA* or *ROA*—either the head enters the pelvis with the occiput rotated 45 degrees anteriorly from the transverse position, or this rotation occurs subsequently. The mechanism of labor in all these presentations is usually similar.

The positional changes of the presenting part required to navigate the pelvic canal constitute the *mechanisms of labor.* The *cardinal movements of labor* are engagement, descent, flexion, internal rotation, extension, external rotation, and expulsion (Fig. 22-11). During labor, these movements not only are sequential but also show great temporal overlap. For example, as part of engagement, there is both flexion and descent of the head. It is impossible for the movements to be completed unless the presenting part descends simultaneously. Concomitantly, uterine contractions effect important modifications in fetal attitude, or habitus, especially after the head has descended into the pelvis. These changes consist principally of fetal straightening, with loss of dorsal convexity and closer application of the extremities to the body. As a result, the fetal ovoid is transformed into a cylinder, with the smallest possible cross section typically passing through the birth canal.

FIGURE 22-11
Cardinal movements of labor and delivery from a left occiput anterior position.

Engagement

The mechanism by which the biparietal diameter—the greatest transverse diameter in an occiput presentation—passes through the pelvic inlet is designated *engagement.* The fetal head may engage during the last few weeks of pregnancy or not until after labor commencement. In many multiparas and some nulliparas, the fetal head is freely movable above the pelvic inlet at labor onset. In this circumstance, the head is sometimes referred to as "floating." A normal-sized head usually does not engage with its sagittal suture directed anteroposteriorly. Instead, as discussed, the fetal head usually enters the pelvic inlet either transversely or obliquely. Segel and coworkers (2012) analyzed labor in 5341 nulliparous women and found that fetal head engagement before labor onset did not affect vaginal delivery rates in either spontaneous or induced labor.

The fetal head tends to accommodate to the transverse axis of the pelvic inlet, whereas the sagittal suture, while remaining parallel to that axis, may not lie exactly midway between the symphysis and the sacral promontory. The sagittal suture frequently is deflected either posteriorly toward the promontory or anteriorly toward the symphysis (Fig. 22-12). Such lateral deflection to a more anterior or posterior position in the pelvis is called *asynclitism.* If the sagittal suture approaches the sacral promontory, more of the anterior parietal bone presents itself to the examining fingers, and the condition is called *anterior asynclitism.* If, however, the sagittal suture lies close to the symphysis, more of the posterior parietal bone will present, and the condition is called *posterior asynclitism.* With extreme posterior asynclitism, the posterior ear may be easily palpated.

FIGURE 22-12
Synclitism and asynclitism.

Moderate degrees of asynclitism are the rule in normal labor. However, if severe, the condition is a common reason for cephalopelvic disproportion even with an otherwise normal-sized pelvis. Successive fetal head shifting from posterior to anterior asynclitism aids descent.

Descent

This movement is the first requisite for birth of the newborn. In nulliparas, engagement may take place before the onset of labor, and further descent may not follow until the onset of the second stage. In multiparas, descent usually begins with engagement. Descent is brought about by one or more of four forces: (1) pressure of the amnionic fluid, (2) direct pressure of the fundus upon the breech with contractions, (3) bearing-down efforts of maternal abdominal muscles, and (4) extension and straightening of the fetal body.

Flexion

As soon as the descending head meets resistance, whether from the cervix, pelvic walls, or pelvic floor, it normally flexes. With this movement, the chin is brought into more intimate contact with the fetal thorax, and the appreciably shorter suboccipitobregmatic diameter is substituted for the longer occipitofrontal diameter (Fig. 22-13).

FIGURE 22-13
Lever action produces flexion of the head. Conversion from occipitofrontal (*left*) to suboccipitobregmatic (*right*) diameter typically reduces the anteroposterior diameter from nearly 12 to 9.5 cm.

Internal Rotation

This movement turns the occiput gradually away from the transverse axis. Usually the occiput rotates anteriorly toward the symphysis pubis, but less commonly, it may rotate posteriorly toward the hollow of the sacrum (Figs. 22-14 and 22-15). Internal rotation is essential for completion of labor, except when the fetus is unusually small.

FIGURE 22-14
Mechanism of labor for the left occiput transverse position, lateral view. **A.** Engagement with posterior asynclitism at the pelvic brim. During descent, the sagittal suture is then deflected toward the sacrum. **B.** This leads to anterior asynclitism. **C.** Internal rotation and descent. **D.** Further internal rotation and descent with extension of the neck.

FIGURE 22-15
Mechanism of labor for right occiput posterior position showing anterior rotation.

Calkins (1939) studied more than 5000 women in labor to ascertain the time of internal rotation. He concluded that in approximately two thirds, internal rotation is completed by the time the head reaches the pelvic floor; in about another fourth, internal rotation is completed shortly after the head reaches the pelvic floor; and in the remaining 5 percent, rotation does not take place. When the head fails to turn until reaching the pelvic floor, it typically rotates during the next one or two contractions in multiparas. In nulliparas, rotation usually occurs during the next three to five contractions.

Extension

After internal rotation, the sharply flexed head reaches the vulva and undergoes extension. If the sharply flexed head, on reaching the pelvic floor, did not extend but was driven farther downward, it would impinge on the posterior portion of the perineum and would eventually be forced through the perineal tissues. When the head presses on the pelvic floor, however, two forces come into play. The first force, exerted by the uterus, acts more posteriorly, and the second, supplied by the resistant pelvic floor and the symphysis, acts more anteriorly. The resultant vector is in the direction of the vulvar opening, thereby causing head extension. This brings the base of the occiput into direct contact with the inferior margin of the symphysis pubis (see Fig. 22-14).

With progressive distention of the perineum and vaginal opening, an increasingly large portion of the occiput gradually appears. The head is born as the occiput, bregma, forehead, nose, mouth, and finally the chin pass successively over the anterior margin of the perineum. Immediately after its delivery, the head drops

downward so that the chin lies over the maternal anus.

External Rotation

The delivered head next undergoes *restitution* (see Fig. 22-11). If the occiput was originally directed toward the left, it rotates toward the left ischial tuberosity. If it was originally directed toward the right, the occiput rotates to the right. Restitution of the head to the oblique position is followed by external rotation completion to again reach a transverse position. This movement corresponds to rotation of the fetal body and serves to bring its bisacromial diameter into relation with the anteroposterior diameter of the pelvic outlet. Thus, one shoulder is anterior behind the symphysis and the other is posterior. This movement apparently is brought about by the same pelvic factors that produced internal rotation of the head.

Expulsion

Almost immediately after external rotation, the anterior shoulder appears under the symphysis pubis, and the perineum soon becomes distended by the posterior shoulder. After delivery of the shoulders, the rest of the body quickly passes. When the anterior shoulder is tightly wedged beneath the symphysis, then *shoulder dystocia* is diagnosed, which is described in Chapter 27 (Shoulder Dystocia).

Occiput Posterior Presentation

In approximately 20 percent of labors, the fetus enters the pelvis in an *occiput posterior (OP)* position (Caldwell, 1934). The right occiput posterior (ROP) is slightly more common than the left (LOP). It appears likely from radiographic evidence that posterior positions are more often associated with a narrow forepelvis. They also are more commonly seen in association with anterior placentation (Gardberg, 1994a).

In most occiput posterior presentations, the mechanism of labor is identical to that observed in the transverse and anterior varieties, except that the occiput has to internally rotate to the symphysis pubis through 135 degrees, instead of 90 and 45 degrees, respectively (see Fig. 22-15).

Effective contractions, adequate head flexion, and average fetal size together permit most posteriorly positioned occiputs to rotate promptly as soon as they reach the pelvic floor, and labor is not lengthened appreciably. In perhaps 5 to 10 percent of cases, however, rotation may be incomplete or may not take place at all, especially if the fetus is large (Gardberg, 1994b). Poor contractions, faulty head flexion, or epidural analgesia, which diminishes abdominal muscular pushing and relaxes pelvic floor muscles, may predispose to incomplete rotation. If rotation is incomplete, *transverse arrest* may result. If no rotation toward the symphysis takes place, the occiput may remain in the direct occiput posterior position, a condition known as *persistent occiput posterior.* Both can lead to dystocia and cesarean delivery. Techniques to manually rotate from OP to OA positions are illustrated in Chapter 29 (Occiput Posterior Positions).

Fetal Head Shape Changes

In vertex presentations, labor forces alter fetal head shape. In prolonged labors before complete cervical dilation, the portion of the fetal scalp immediately over the cervical os becomes edematous. This swelling is known as the *caput succedaneum* (Fig. 22-16). It usually attains a thickness of only a few millimeters, but in prolonged labors it may be sufficiently extensive to prevent differentiation of the various sutures and fontanels. More commonly, the caput is formed when the head is in the lower portion of the birth canal and frequently only after the resistance of a rigid vaginal outlet is encountered. Because it develops over the most dependent area of the head, one may deduce the original fetal head position by noting the location of the caput succedaneum.

FIGURE 22-16
Considerable molding of the head and caput succedaneum formation in a recently delivered newborn.

Molding refers to changes in the bony fetal head shape as a result of external compressive forces (see Fig. 22-16). Possibly related to Braxton Hicks contractions, some molding develops before labor. Most studies indicate that there is seldom overlapping of the parietal bones. A “locking” mechanism at the coronal and lambdoidal sutures actually prevents such overlapping (Carlan, 1991). Molding results in a shortened suboccipitobregmatic diameter and a lengthened mentovertical diameter. These changes are of greatest importance in women with contracted pelves or asynclitic presentations. In these circumstances, the degree to which the head is capable of molding may make the difference between spontaneous vaginal delivery and an operative delivery. Some older literature cited severe head molding as a cause for possible cerebral trauma. Because of the multitude of associated factors, for example, prolonged labor with fetal sepsis and acidosis, it is impossible to link molding to any alleged fetal or neonatal neurological sequelae. Most cases of molding resolve within the week following delivery, although persistent cases have been described (Graham, 2006). Differentiation of molding, caput succedaneum, and *cephalohematoma* is discussed in Chapter 33 (Intracranial Hemorrhage).

NORMAL LABOR CHARACTERISTICS

The greatest impediment to understanding normal labor is recognizing its start. The strict definition of labor is: *uterine contractions that bring about demonstrable effacement and dilation of the cervix.* This does not easily aid the clinician in determining when labor has actually begun, because this diagnosis is confirmed only retrospectively. Several methods may be used to mark its start. One defines onset as the clock time when painful contractions become regular. Unfortunately, uterine activity that causes discomfort, but that does not represent true labor, may develop at any time during pregnancy. False labor often stops spontaneously, or it may proceed rapidly into effective contractions.

A second method defines the onset of labor as beginning at the time of admission to the labor unit. In the United States, admission for labor is frequently based on the extent of cervical dilation accompanied by painful contractions. If a woman has intact membranes, then a cervical dilation of 3 to 4 cm or greater is presumed to be a reasonably reliable threshold for the diagnosis of labor. In this case, labor onset commences with the time of admission. This presumptive method obviates many of the uncertainties in diagnosing labor during earlier stages of cervical dilation. Laughon and associates (2012) compared the duration of spontaneous labor

at term in nulliparas delivered in the United States between 1959 and 1966 to that of those delivered from 2002 to 2008. As shown in Figure 22-17, during those 50 years, the length of labor increased by approximately 2 hours.

FIGURE 22-17
Average labor curves for women with singleton term pregnancies presenting in spontaneous labor with vaginal delivery for nulliparas from 1959–1966 compared with those from 2002–2008. (Redrawn from Laughon SK, Branch W, Beaver J, et al: Changes in labor patterns over 50 years. Am J Obstet Gynecol 206:419.e1.9, 2012.)

First Stage of Labor

For labor, Friedman (1954) described a characteristic sigmoid pattern by graphing cervical dilation against time. This graphical approach, which was based on statistical observations, changed labor management. Friedman developed the concept of three functional labor divisions to describe the physiological objectives of each division (Fig. 22-18). First, during the *preparatory division,* although the cervix dilates little, its connective tissue components change considerably (Chap. 21, Ancillary Forces). Sedation and conduction analgesia are capable of arresting this labor division. The *dilational division,* during which dilation proceeds at its most rapid rate, is unaffected by sedation. Last, the *pelvic division* commences with the deceleration phase of cervical dilation. The classic labor mechanisms that involve the cardinal fetal movements of the cephalic presentation take place principally during this pelvic division. In actual practice, however, the onset of the pelvic division is seldom clearly identifiable.

FIGURE 22-18
Labor course divided functionally on the basis of dilatation and descent curves into: (1) a preparatory division, including latent and acceleration phases; (2) a dilatational division, occupying the phase of maximum slope; and (3) a pelvic division, encompassing both deceleration phase and second stage concurrent with the phase of maximum slope of descent. (Redrawn from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)

As shown in Figure 22-18, the pattern of cervical dilation during the preparatory and dilational divisions of normal labor is a sigmoid curve. Two phases of cervical dilation are defined. The *latent phase* corresponds to the preparatory division, and the *active phase* to the dilational division. Friedman further subdivided the active phase into the *acceleration phase,* the *phase of maximum slope,* and the *deceleration phase* (Fig. 22-19).

FIGURE 22-19
Composite of the average dilatation curve for nulliparous labor. The first stage is divided into a relatively flat latent phase and a rapidly progressive active phase. In the active phase, there are three identifiable component parts that include an acceleration phase, a phase of maximum slope, and a deceleration phase. (Redrawn from Friedman EA: Labor: Clinical Evaluation and Management, 2nd ed. New York, Appleton-Century-Crofts, 1978.)

Latent Phase

The onset of latent labor, as defined by Friedman (1972), is the point at which the mother perceives regular contractions. The latent phase for most women ends once dilation of 3 to 5 cm is achieved. This threshold may be clinically useful, for it defines dilation limits beyond which active labor can be expected. More recently, a Consensus Committee of the American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine (2016c) has redefined active labor to begin at 6 cm. A fuller discussion of these labor changes is found in Chapter 23 (Background for the 6-cm Rule).

This concept of a latent phase has great significance in understanding normal human labor, because labor is considerably longer when a latent phase is included. To better illustrate this, Figure 22-20 shows eight labor curves from nulliparas in whom labor was diagnosed beginning with their admission, rather than with the onset of regular contractions. When labor is defined similarly, individual labor curves are remarkably comparable.

FIGURE 22-20
Progress of labor in primigravid women from the time of admission. When the starting point on the abscissa begins with admission to the hospital, a latent phase is not observed.

A *prolonged latent phase* was defined by Friedman and Sachtleben (1963) as one exceeding 20 hours in the nullipara and 14 hours in the multipara. These times corresponded to the 95th percentiles. Factors that affected latent phase duration include excessive sedation or epidural analgesia; unfavorable cervical condition, that is, thick, uneffaced, or undilated; and false labor. Of women who had been administered heavy sedation, 85 percent eventually entered active labor. In another 10 percent, uterine contractions ceased, suggesting that they had false labor. The remaining 5 percent experienced persistence of an abnormal latent phase and required oxytocin stimulation. Amniotomy was discouraged because of the 10-percent incidence of false labor. Sokol and associates (1977) reported a 3- to 4-percent incidence of prolonged latent phase, regardless of parity. Friedman (1972) reported that latent phase prolongation did not adversely influence fetal or maternal morbidity or mortality rates. However, Chelmow and coworkers (1993) disputed the long-held belief that prolongation of the latent phase is benign.

Active Phase

The progress of labor in nulliparas has particular significance because these curves all reveal a rapid change in the slope of cervical dilation rates between 3 and 5 cm (see Fig. 22-20). *Thus, cervical dilation of 3 to 6 cm or more, in the presence of uterine contractions, can be taken to reliably represent the threshold for active labor.* Similarly, these curves provide useful guideposts for labor management.

Turning again to Friedman (1955), the mean duration of active-phase labor in nulliparas was 4.9 hours. But, the standard deviation of 3.4 hours is large, hence, the active phase was reported to have a statistical maximum of 11.7 hours. Indeed, rates of cervical dilation ranged from a minimum of 1.2 up to 6.8 cm/hr. Friedman (1972) also found that multiparas progress somewhat faster in active-phase labor, with a *minimum* normal rate of 1.5 cm/hr. His analysis of active-phase labor concomitantly describes rates of fetal descent and cervical dilation (see Fig. 22-18). Descent begins in the later stage of active dilation, commencing at 7 to 8 cm in nulliparas and becoming most rapid after 8 cm.

Hendricks and coworkers (1970) challenged Friedman's conclusions about the course of normal human labor. Their principal differences included: (1) absence of a latent phase, (2) no deceleration phase, (3) brevity of labor, and (4) dilation at similar rates for nulliparas and multiparas after 4 cm. They disputed the concept of a latent phase because they observed that the cervix dilated and effaced slowly during the 4 weeks preceding labor. They contended that the *latent phase* actually progressed over several weeks. They also reported that labor was relatively rapid. Specifically, the average time from admission to complete dilation was 4.8 hours for nulliparas and 3.2 hours for multiparas.

Others have reassessed the Friedman labor curves. Zhang and associates (2010) studied electronic labor records from 62,415 parturients with spontaneous labor at term and vaginal birth. For nulliparas, the median time to progress from 4 to 5 cm was 1.3 hours, from 5 to 6 cm 0.8 hours, and thereafter, additional centimeters were gained approximately each 0.5 hours. They found that normal labor may take more than 6 hours to progress from 4 to 5 cm and more than 3 hours to progress from 5 to 6 cm dilation. Rates for multiparas were similar from 4 to 6 cm. Then, labor accelerated much faster in multiparas. Data from this study form the foundation for new guidelines regarding cesarean delivery indications for labor arrest put forth in the Obstetric Care Consensus document by the American College of Obstetrics and Gynecology and Society for Maternal-Fetal Medicine (2016c) and described in Chapter 23 (Obstetric Care Consensus Committee).

In a study performed at Parkland Hospital, epidural analgesia was found to lengthen the active phase of the Friedman labor curve by 1 hour (Alexander, 2002). This increase was the result of a slight but significant decline in the rate of cervical dilation—1.4 cm/hr in women given epidural analgesia compared with 1.6 cm/hr in those without such analgesia. Several other reports also note that maternal obesity lengthens the first stages of labor by 30 to 60 minutes (Chin, 2012; Kominiarek, 2011). Finally, Adams and coworkers (2012) found that maternal fear prolonged labor by approximately 45 minutes.

Active-phase abnormalities have been reported to occur in 25 percent of nulliparous and 15 percent of multiparous labors (Sokol, 1977). Friedman (1972) subdivided active-phase problems into *protraction* and *arrest disorders*. Abnormal labor patterns, diagnostic criteria, and treatment methods are summarized in Chapter 23 (Abnormalities of the Expulsive Forces).

Second Stage of Labor

This stage begins with complete cervical dilation and ends with fetal delivery. The median duration is approximately 50 minutes for nulliparas and about 20 minutes for multiparas, but it is highly variable (Kilpatrick, 1989). In a woman of higher parity with a previously dilated vagina and perineum, two or three expulsive efforts after full cervical dilation may suffice to complete delivery. Conversely, in a woman with a contracted pelvis, with a large fetus, or with impaired expulsive efforts from conduction analgesia or sedation, the second stage may be longer. Higher maternal body mass index does not interfere with second-stage labor length (Carlhäll, 2013; Robinson, 2011). Abnormalities of this labor stage are described in Chapter 23 (Second-Stage Descent Disorders).

Labor Duration

The normal duration of labor may be clouded by the many clinical variables that affect the conduct of labor in modern obstetrical units. Kilpatrick and Laros (1989) reported that the mean length of first- and second-stage labor was approximately 9 hours in nulliparas without regional analgesia, and that the 95th percentile upper limit was 18.5 hours. Corresponding times for multiparas were a mean of 6 hours and a 95th percentile maximum of 13.5 hours. These authors defined labor onset as the time when a woman recalled regular, painful contractions every 3 to 5 minutes that led to cervical change.

Spontaneous labor was analyzed in nearly 25,000 women delivered at term at Parkland Hospital in the early 1990s. Almost 80 percent of women were admitted with a cervical dilation of 5 cm or less. Parity—nulliparous versus multiparous—and cervical dilation at admission were significant determinants of the length of spontaneous labor. The median time from admission to spontaneous delivery for all parturients was 3.5 hours, and 95 percent of all women delivered within 10.1 hours. These results suggest that normal human labor is relatively short.

Summary of Normal Labor

Labor is characterized by brevity and considerable biological variation. Active labor can be reliably diagnosed when cervical dilation is ≥3 cm in the presence of uterine contractions. Once this cervical dilation threshold is reached, normal progression to delivery can be expected, depending on parity, in the ensuing 4 to 6 hours. Anticipated progress during a 1- to 3-hour second stage is monitored to ensure fetal safety. Finally, most women in spontaneous labor, regardless of parity, if left unaided, will deliver within approximately 10 hours after admission for spontaneous labor. Insufficient uterine activity is a common and correctable cause of abnormal labor progress. *Therefore, when the length of otherwise normal labor exceeds the expected norm, interventions other than cesarean delivery—for example, oxytocin administration—must be first considered.*

MANAGEMENT OF NORMAL LABOR

The ideal management of labor and delivery requires two potentially opposing viewpoints on the part of clinicians. First, birthing should be recognized as a normal physiological process that most women experience without complications. Second, intrapartum complications, often arising quickly and unexpectedly, should be anticipated. Thus, clinicians must simultaneously make every woman and her supporters feel comfortable, yet ensure safety for the mother and newborn if complications suddenly develop. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have collaborated in the development of *Guidelines for Perinatal Care*. These provide detailed information on the appropriate content of intrapartum care, including both personnel and facility requirements (Table 22-2).

TABLE 22-2

Recommended Nurse/Patient Ratios for Labor and Delivery

Ratio	Clinical Setting
2:1	Birth
1:2	Patients in labor without complications
1:1	Patients in second-stage labor
1:1	Patients with medical/obstetrical complications
1:1	Oxytocin induction/augmentation
1:1	During epidural analgesia initiation
1:1	Circulation for cesarean delivery

Labor and delivery outside the hospital is elected by some parturients. This option and its risks and benefits are discussed in Chapter 27 (Special Populations).

Emergency Medical Treatment and Labor Act—EMTALA

Congress enacted EMTALA in 1986 to ensure public access to emergency services regardless of the ability to pay. All Medicare-participating hospitals with emergency services must provide an appropriate screening examination for any pregnant woman experiencing contractions and presenting to the emergency department for evaluation.

The definition of an emergency condition makes specific reference to a pregnant woman who is having contractions. Labor is defined as "the process of childbirth beginning with the latent phase of labor continuing through delivery of the placenta. A woman experiencing contractions is in true labor unless a physician certifies that after a reasonable time of observation the woman is in false labor." A woman in true labor is considered "unstable" for interhospital transfer purposes until the newborn and placenta are delivered. A stable woman may, however, be transferred at the direction of the patient or by a physician who certifies that the benefits of treatment at another facility outweigh the transfer risks. Physicians and hospitals violating these federal requirements are subject to civil penalties and termination from participation in the Medicare program.

Identification of Labor

Pregnant women are urged to report early in labor rather than to procrastinate until delivery is imminent for fear that they might be experiencing false labor. Early admittance is especially important if during antepartum care the woman, her fetus, or both are found to have risk factors for intrapartum complications.

Although the differentiation between false and true labor is difficult at times, the diagnosis usually can be clarified by contraction frequency and intensity and by cervical dilation. Pates and associates (2007) studied one commonly used recommendation given to pregnant women. Namely, in the absence of ruptured membranes or bleeding, uterine contractions 5 minutes apart for 1 hour—that is, ≥12 contractions in 1 hour—may signify labor onset. Among 768 women in this study at Parkland Hospital, active labor defined as cervical dilation ≥4 cm was diagnosed within 24 hours in three fourths of women with ≥12 contractions per hour. Bailit and coworkers (2005) compared labor outcomes of 6121 women who presented in active labor defined as uterine contractions plus cervical dilation ≥4 cm with those of 2697 women who presented in the latent phase. Women admitted during latent-phase labor had more active-phase arrest, more frequent need for oxytocin labor stimulation, and higher rates of chorioamnionitis. It was concluded that physician interventions in women presenting in the latent phase may have been the cause of subsequent labor abnormalities.

In those instances when a diagnosis of labor cannot be established with certainty, observation for a longer period is often wise. Women who present to Parkland Hospital for labor symptoms at $24^{0/7}$ weeks' gestation or greater are routinely evaluated in a labor triage unit contiguous to our labor and delivery unit. All women in the triage area are evaluated by nurse practitioners and certified nurse midwives using written protocols. Women with uncomplicated pregnancies with intact membranes and cervical dilation <4 cm receive continuous external fetal monitoring for up to 2 hours. Women diagnosed with labor by either cervical change or persistent uterine contractions are admitted. After review by a physician, women without cervical change or with abatement of contractions return home with a diagnosis of false labor. In a recent study, a total of 3949 women with uncomplicated pregnancies between $37^{0/7}$ and $41^{6/7}$ weeks' gestation were diagnosed with false labor. The mean interval from hospital discharge to when they again presented was 4.9 days (Nelson, 2017). Within this protocol, hospital discharge with false labor at term was not associated with higher rates of adverse neonatal outcomes or cesarean delivery. The American College of Obstetricians and Gynecologists (2016a) has endorsed hospital-based obstetrical triage units.

Initial Evaluation

Maternal blood pressure, temperature, pulse, and respiratory rate are recorded. Fetal heart rate is evaluated using a portable Doppler device, sonography, or fetoscope. The pregnancy record is promptly reviewed to identify complications. Problems identified or anticipated during prenatal care should be displayed

prominently in the pregnancy record. Most often, *unless there has been bleeding in excess of bloody show,* a cervical examination is performed. The gloved index and second fingers are introduced into the vagina while avoiding the anal region.

Ruptured Membranes

During prenatal care, the woman is instructed to be aware of fluid leakage from the vagina and to report such an event promptly. Rupture of the membranes is significant for three reasons. First, if the presenting part is not fixed in the pelvis, the umbilical cord can prolapse and be compressed. Second, labor is likely to begin soon if the pregnancy is at or near term. Third, if delivery is delayed after membrane rupture, intrauterine and neonatal infection is more likely as the time interval increases (Herbst, 2007).

During sterile speculum examination, ruptured membranes are diagnosed if amnionic fluid pools in the posterior fornix or clear fluid flows from the cervical canal. Although several diagnostic tests for the detection of ruptured membranes have been recommended, none is completely reliable. If the diagnosis remains uncertain, another method involves pH determination of vaginal fluid. The pH of vaginal secretions normally ranges from 4.5 to 5.5, whereas that of amnionic fluid is usually >7.0. The use of the indicator *nitrazine* to identify ruptured membranes is a simple and fairly reliable method. Test papers are impregnated with the dye, and the color of the reaction between these paper strips and vaginal fluids is interpreted by comparison with a standard color chart. A pH above 6.5 is consistent with ruptured membranes. False-positive test results may occur with coexistent blood, semen, or bacterial vaginosis, whereas false-negative tests may result with scant fluid.

Other tests to identify amnionic fluid include arborization or ferning of vaginal fluid, which suggests amnionic rather than cervical fluid. Amnionic fluid crystallizes to form a fernlike pattern due to its relative concentrations of sodium chloride, proteins, and carbohydrates. Detection of alpha-fetoprotein in the vaginal vault has been used to identify amnionic fluid (Yamada, 1998). Although rarely required, identification may also follow injection of indigo carmine into the amnionic sac via abdominal amniocentesis. Last, specific amnionic fluid proteins can be sought using point-of-care assays. These include AmniSure, which binds placental alpha microglobulin-1, and ROM Plus, which detects insulin growth factor binding protein-1 plus alpha-fetoprotein (Doret, 2013; Igbinosa, 2017).

Cervical Assessment

The degree of *cervical effacement* reflects the length of the cervical canal compared with that of an uneffaced cervix. When the length of the cervix is reduced by one half, it is 50-percent effaced. When the cervix becomes as thin as the adjacent lower uterine segment, it is completely, or 100-percent, effaced.

Cervical dilation is determined by estimating the average diameter of the cervical opening by sweeping the examining finger from the margin of the cervical opening on one side to that on the opposite side. The diameter traversed is estimated in centimeters. The cervix is said to be fully dilated when the diameter measures 10 cm, because the presenting part of a term-size newborn usually can pass through a cervix this widely dilated.

The *position* of the cervix is determined by the relationship of the cervical os to the fetal head and is categorized as posterior, midposition, or anterior. Along with position, the *consistency* of the cervix is determined to be soft, firm, or intermediate between these two.

The *fetal station*, that is, the level of the presenting fetal part in the birth canal, is described in relationship to the ischial spines. These spines lie halfway between the pelvic inlet and the pelvic outlet. When the lowermost portion of the presenting fetal part is at the level of the spines, it is designated as being at zero (0) station.

In the past, the long axis of the birth canal above and below the ischial spines was arbitrarily divided into thirds by some and into fifths (approximately 1 cm) by other groups. In 1989, the American College of Obstetricians and Gynecologists adopted the classification of station that divides the pelvis above and below the spines into fifths. Each fifth represents 1 cm above or below the spines. Thus, as the presenting fetal part descends from the inlet *toward* the ischial spines, the designation is –5, –4, –3, –2, –1, then 0 station. Below the spines, as the presenting fetal part descends, it passes +1, +2, +3, +4, and +5 stations to delivery. Station +5 cm corresponds to the fetal head being visible at the introitus.

If the leading part of the fetal head is at 0 station or below, most often the fetal head has engaged—thus, the biparietal plane has passed through the pelvic inlet. *If the head is unusually molded or if caput succedaneum formation is extensive, or both, engagement might not have taken place although the head appears to be at 0 station.*

In a study done at five teaching centers in Denver, residents, nurses, and faculty were surveyed to determine what definitions were being used to describe fetal station (Carollo, 2004). Four different definitions were in use. Disturbingly, these investigators found that few caregivers were aware that others were using different definitions of station! Dupuis and associates (2005) tested the reliability of clinical estimations of station using the position of the leading part in centimeters above or below the spines. A birth simulator was used in which station could be precisely measured and compared with the vaginal examination done by clinicians. They reported that the clinical examiners were incorrect a third of the time.

These five characteristics—cervical dilation, effacement, consistency, position, and fetal station—are assessed when tabulating the Bishop score. This score is commonly used to predict labor induction outcome and is discussed in Chapter 26 (Preinduction Cervical Ripening). Taken together, these factors suggest the subjective “favorability” of the cervix for induction success.

Laboratory Studies

When a woman is admitted in labor, most often the hematocrit or hemoglobin concentration is checked. The hematocrit can be measured easily and quickly. At Parkland Hospital, blood is collected in a standard collection tube with anticoagulant. From this, a heparinized capillary tube is filled to spin in a microhematocrit centrifuge in the labor and delivery unit. This provides a hematocrit value within 3 minutes. The initial collection tube is also sent to the hematology laboratory for evaluation if the point-of-care hematocrit is <30 volume percent. Another labeled tube of blood is allowed to clot and sent to the blood bank for blood type and

antibody screen, if needed. A final sample is collected for syphilis and human immunodeficiency virus (HIV) serology. In some labor units, a clean-catch voided specimen is examined in all women for protein and glucose. At Parkland Hospital, however, we obtain a urine specimen for protein determination in hypertensive women only (Table 40-1).

Women with no prenatal care are considered to be at risk for syphilis, hepatitis B, and HIV, and laboratory screening studies for these, as well as a blood type and antibody screen, are performed (American Academy of Pediatrics and American College of Obstetricians and Gynecologists, 2017). Some states, for example, Texas, require routine testing for syphilis, hepatitis B, and HIV in all women admitted to labor and delivery units, even if these were done during prenatal care.

Management of First-Stage Labor

As soon as possible after admittance, the remainder of a general examination is completed. Whether a pregnancy is normal can best be determined when all examinations, including record and laboratory review, are completed. A rational plan for monitoring labor can then be established based on the needs of the fetus and the mother. Because labor lengths vary markedly among individuals, precise statements regarding anticipated labor duration are unwise.

In general, pain relief should depend on the needs and desires of the woman. The American College of Obstetricians and Gynecologists (2017) has specified optimal goals for anesthesia care in obstetrics. This is discussed in detail in Chapter 25. In some units, women can choose to spend part of first-stage labor in a large water tub. Risks and benefits are described in Chapter 27 (Special Populations).

Intrapartum Fetal Monitoring

This is discussed in detail in Chapter 24. Briefly, the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017) recommend that during first-stage labor, in the absence of any abnormalities, the fetal heart rate should be checked immediately after a contraction at least every 30 minutes and then every 15 minutes during the second stage. If continuous electronic monitoring is used, the tracing is evaluated at least every 30 minutes during the first stage and at least every 15 minutes during second-stage labor. For women with pregnancies at risk, fetal heart auscultation is performed at least every 15 minutes during first-stage labor and every 5 minutes during the second stage. Continuous electronic monitoring may be used with evaluation of the tracing every 15 minutes during the first stage of labor, and every 5 minutes during the second stage.

Maternal Monitoring

Temperature, pulse, and blood pressure are evaluated at least every 4 hours. If membranes have been ruptured for many hours before labor onset or if there is a borderline temperature elevation, the temperature is checked hourly.

Although uterine contractions are usually assessed with electronic monitoring, they can be quantitatively and qualitatively evaluated manually (Chap. 24, Intrapartum Surveillance of Uterine Activity). With the palm of the hand resting lightly on the uterus, the time of contraction onset is determined. Its intensity is gauged from the degree of firmness the uterus achieves. At the acme of effective contractions, the finger or thumb cannot readily indent the uterus during a “firm” contraction. The time at which the contraction disappears is noted next. This sequence is repeated to evaluate the frequency, duration, and intensity of contractions.

During the first stage of labor, the need for subsequent vaginal examinations to monitor cervical change and presenting part position will vary considerably. When the membranes rupture, an examination to exclude cord prolapse is performed expeditiously if the fetal head was not definitely engaged at the previous examination. The fetal heart rate is also checked immediately and during the next uterine contraction to help detect occult umbilical cord compression. At Parkland Hospital, periodic pelvic examinations are typically performed at 2- to 3-hour intervals to evaluate labor progress. Evidence implicating the number of vaginal examinations in infection-related morbidity is conflicting (Cahill, 2012; Soper, 1989).

Oral Intake

Food and liquids with particulate matter should be withheld during active labor and delivery. Gastric emptying time is remarkably prolonged once labor is established and analgesics are administered. As a consequence, ingested food and most medications remain in the stomach and are not absorbed. Instead, they may be vomited and aspirated (Chap. 25, Inhalational Anesthetics). According to the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), oral intake of moderate amounts of clear liquids is reasonable for women with uncomplicated labor. Modest amounts of clear liquids such as water, clear tea, black coffee, carbonated beverages, Popsicles, and pulp-free fruit juices are allowed in uncomplicated laboring women. In those with appreciable risks for aspiration or those with significant risks for cesarean delivery, further restriction may be instituted. For example, for those with planned cesarean delivery, liquids are halted 2 hours before and solids are stopped 6 to 8 hours prior to surgery (American College of Obstetricians and Gynecologists, 2016b).

Intravenous Fluids

Although an intravenous (IV) infusion system is often routinely established early in labor, real need for this in the normal pregnant woman is limited, at least until analgesia is administered. However, venous access is advantageous during the immediate puerperium to administer oxytocin prophylactically and at times therapeutically when uterine atony persists. Moreover, with longer labors, the administration of glucose, sodium, and water to the otherwise fasting woman at the rate of 60 to 120 mL/hr prevents dehydration and acidosis. Shrivastava and associates (2009) noted shorter labors in nulliparas delivering vaginally who were provided an intravenous normal saline with dextrose solution compared with those given saline solution only. In another study, 195 women in labor received lactated Ringer or isotonic sodium chloride solution at a rate of either 125 or 250 mL/hr. The mean volume of total IV fluid was 2008 mL in the 125 mL/hr group and 2487 mL in the 250 mL/hr group (Garite, 2000). Labor lasted more than 12 hours in significantly more of the women given a 125 mL/hr infusion compared with those given 250 mL/hr—26 versus 13 percent, respectively. In yet another study, 311 nulliparas with uncomplicated pregnancies in spontaneous labor at term received one of three IV infusions (Edwards, 2014). Group 1 was given 125 mL/hr of lactated Ringer solution with 5 percent dextrose (D5LR), Group 2 received 250 mL/hour of the

same solution (D5LR), and Group 3 was administered 25 mL/hr of D5LR. Groups 1 and 2 were allowed ice chips, Popsicles, and hard candy, and Group 3 also received Gatorade. Oral intake was limited in Groups 1 and 2 but was ad libitum in Group 3. The authors concluded that any of the regimens studied was safe but none was superior for labor performance.

Maternal Position

In bed, the laboring woman may assume the position she finds most comfortable, and often this will be lateral recumbency. Lying supine is typically avoided to avert aortocaval compression and its potential to lower uterine perfusion (Chap. 4, Hemodynamic Function in Late Pregnancy). However, the normal laboring woman need not be confined to bed early in labor. A comfortable chair may be beneficial psychologically and perhaps physiologically. Others encourage ambulation.

Proponents of walking report that it shortens labor, lowers rates of oxytocin augmentation, diminishes the need for analgesia, and decreases the frequency of operative vaginal delivery (Flynn, 1978; Read, 1981). In their Cochrane review, Lawrence and associates (2013) found that labor in ambulant or upright positions shortened first-stage labor by about 1 hour and lowered cesarean delivery and epidural analgesia rates. Lupe and Gross (1986) concluded, however, that no conclusive evidence supports assertions that upright maternal posture or ambulation improves labor. They reported that women preferred to lie on their side or sit in bed. Few chose to walk, fewer to squat, and none wanted the knee-chest position. Parturients tended to assume fetal positions in later labor. Most women enthusiastic about ambulation returned to bed when active labor began (Carlson, 1986; Williams, 1980).

Bloom and colleagues (1998) conducted a randomized trial to study the effects of walking during first-stage labor. In 1067 women with uncomplicated term pregnancies delivered at Parkland Hospital, these investigators reported that ambulation did not affect labor duration. Ambulation did not reduce the need for analgesia, nor was it harmful to the newborn. Because of these observations, we give women without complications the option to select either recumbency or supervised ambulation during labor.

Rupture of Membranes

If the membranes are intact, temptation is great, even during normal labor, to perform amniotomy. The presumed benefits are more rapid labor, earlier detection of meconium-stained amnionic fluid, and the opportunity to apply an electrode to the fetus or insert a pressure catheter into the uterine cavity for monitoring. The advantages and disadvantages of amniotomy are discussed in Chapter 26 (Amniotomy for Induction and Augmentation). Importantly, the fetal head must be well applied to the cervix and not be dislodged from the pelvis during the procedure to avoid umbilical cord prolapse.

In cases with prolonged membrane rupture, defined as greater than 18 hours, antimicrobial administration for prevention of group B streptococcal infections is recommended. This is discussed in Chapter 64 (GBS Vaccine). This practice similarly lowers rates of chorioamnionitis and endometritis (Saccone, 2015).

Urinary Bladder Function

Distention of the bladder can hinder descent of the fetal presenting part and lead to subsequent bladder hypotonia and infection. Periodically during labor, the suprapubic region is inspected and palpated to detect distention. If the bladder is readily seen or palpated above the symphysis, the woman should be encouraged to void. At times, those who may be unable to void on a bedpan may be able to ambulate with assistance to a toilet and successfully void. If the bladder is distended and voiding is not possible, catheterization is indicated. Carley and coworkers (2002) found that 51 of 11,332 vaginal deliveries (1 in 200) were complicated by postpartum urinary retention. Most women resumed normal voiding before discharge from the hospital. Musselwhite and associates (2007) reported retention in 4.7 percent of women who had labor epidural analgesia. Risk factors for retention were primiparity, oxytocin-induced or augmented labor, perineal lacerations, operative vaginal delivery, catheterization during labor, and labor duration >10 hours.

Management of Second-Stage Labor

With full cervical dilation, which signifies the onset of the second stage, a woman typically begins to bear down. With descent of the presenting part, she develops the urge to defecate. Uterine contractions and the accompanying expulsive forces may now last 1 minute and recur at an interval no longer than 90 seconds. As discussed earlier, the median duration of the second stage is 50 minutes in nulliparas and 20 minutes in multiparas, although the interval can vary. Monitoring intervals of the fetal heart rate were discussed in Management of First-Stage Labor, and interpretation of second-stage electronic fetal heart rate patterns is discussed in Chapter 24 (Fetal Heart Rate Patterns During Second-Stage Labor).

In most cases, bearing down is reflexive and spontaneous during second-stage labor. Occasionally, a woman may not employ her expulsive forces to good advantage and coaching is desirable. Her legs should be half-flexed so that she can push with them against the mattress. When the next uterine contraction begins, she is instructed to exert downward pressure as though she were straining at stool. A woman is not encouraged to push beyond the completion of each contraction. Instead, she and her fetus are allowed to rest and recover. During this period of actively bearing down, the fetal heart rate auscultated during the contraction is likely to be slow but should recover to normal range before the next expulsive effort. Fetal and obstetrical outcomes appear to be unaffected whether pushing is coached or uncoached during second-stage labor (Bloom, 2006; Tuuli, 2012). Bloom and colleagues (2006) studied effects of actively coaching expulsive efforts in women without epidural analgesia. They reported that although the second stage was slightly shorter in coached women, no other maternal advantages were gained.

Several positions during the second stage have been recommended to augment pushing efforts. Eason and colleagues (2000) reviewed various positions and their effect on the incidence of perineal trauma. They found that the supported upright position had no advantages over the recumbent one. Upright positions include sitting, kneeling, squatting, or resting with the back at a 30-degree elevation. In women with regional analgesia, one recent randomized trial found higher vaginal delivery rates in those in a recumbent position compared with an upright one—41 versus 35 percent (The Epidural and Position Trial Collaborative Group, 2017). In women without epidural analgesia, Gupta (2017) in their review compared upright positions with supine or lithotomy positions and their effect on labor. Upright positions offered a slightly shorter interval to delivery as well as fewer episiotomies and operative vaginal deliveries. However, rates of blood loss >500 mL and

perhaps of second-degree lacerations were increased. Berghella and coworkers (2008) hypothesized that parity, less intense aortocaval compression, improved fetal alignment, and larger pelvic outlet diameters might explain these findings. In an earlier study, a 20- to 30-percent increase in the area of the pelvic outlet was noted with squatting compared with the supine position (Russell, 1969). Finally, Babayer and associates (1998) cautioned that prolonged sitting or squatting during the second stage may cause neuropathy of the common fibular (formerly common peroneal) nerve.

As the head descends through the pelvis, the perineum begins to bulge and the overlying skin becomes stretched. Now the scalp of the fetus may be visible through the vulvar opening. At this time, the woman and her fetus are prepared for delivery, which is described in Chapter 27 (Preparation for Delivery).

LABOR MANAGEMENT PROTOCOLS

An orderly and systematic approach to labor management results in reproducible beneficial maternal and perinatal outcomes (Althabe, 2008). Several labor management protocols are subsequently presented. These include those from the National Maternity Hospital in Dublin, from the World Health Organization, and from Parkland Hospital.

In Dublin more than 30 years ago, O'Driscoll and associates (1984) pioneered the concept that a disciplined, standardized labor management protocol reduced the number of cesarean deliveries for dystocia. Their overall cesarean delivery rate was 5 percent in the 1970s and 1980s with such management. The approach is now referred to as *active management of labor.* Two of its components—amniotomy and oxytocin—have been widely used, especially in English-speaking countries outside the United States. With this protocol, labor is diagnosed when painful contractions are accompanied by complete cervical effacement, bloody "show," or ruptured membranes. Women with such findings are committed to delivery within 12 hours. Pelvic examination is performed each hour for the next 3 hours, and thereafter at 2-hour intervals. When dilation has not increased by at least 1 cm/hr, amniotomy is performed. Progress is again assessed at 2 hours, and high-dose oxytocin infusion, described in Chapter 26 (Oxytocin), is started unless dilation of at least 1 cm/hr is attained. Women are constantly attended by midwives. If membranes rupture before admission, oxytocin is begun for no progress at the 1-hour mark.

López-Zeno and colleagues (1992) prospectively compared such active management with their "traditional" approach to labor management at Northwestern Memorial Hospital in Chicago. They randomly assigned 705 nulliparas with uncomplicated pregnancies in spontaneous labor at term. The cesarean delivery rate was significantly lower with active versus traditional management—10.5 versus 14.1 percent, respectively. Subsequent studies did not show this. Wei and associates (2013) in a Cochrane database review found a modest reduction in cesarean delivery rates when active management of labor was compared with standard care. Frigoletto and coworkers (1995) reported another randomized trial with 1934 nulliparous women at Brigham and Women's Hospital in Boston. Although they found that such management somewhat shortened labor, it did not affect the cesarean delivery rate. These observations have since been reported by others (Brown, 2013).

A *partograph* was designed by the World Health Organization (WHO) for use in developing countries (Dujardin, 1992). According to Orji (2008), the partograph is similar for nulliparas and multiparas. Labor is divided into a latent phase, which should last no longer than 8 hours, and an active phase. The active phase starts at 3 cm dilation, and progress should be no slower than 1 cm/hr. A 4-hour wait is recommended before intervention when the active phase is slow. Labor is graphed, and analysis includes use of alert and action lines. Lavender and colleagues (2006) randomized 3000 nulliparous women to labor interventions at 2 hours versus 4 hours as recommended by WHO. Their cesarean delivery rate was unaffected, and they concluded that interventions such as amniotomy and oxytocin were needlessly increased using the 2-hour time interval. From their Cochrane Database review, Lavender and associates (2013) do not recommend use of the partograph for standard labor management.

At Parkland Hospital, women are admitted if active labor is diagnosed or if ruptured membranes are confirmed. Labor is defined as cervical dilation of 3 to 4 cm or more in the presence of uterine contractions. Management guidelines direct that a pelvic examination be performed approximately every 2 hours. Ineffective labor is suspected when the cervix does not dilate within approximately 2 hours of admission. Amniotomy is then performed, and labor progress determined at the next 2-hour evaluation. In women whose labors do not progress, an intrauterine pressure catheter is placed to assess uterine function. Hypotonic contractions and no cervical dilation after an additional 2 to 3 hours result in stimulation of labor using the high-dose oxytocin regimen described in Chapter 26 (Oxytocin). The goal is uterine activity of 200 to 250 Montevideo units for 2 to 4 hours before dystocia can be diagnosed. If hypotonic contractions are strongly suspected, internal monitors may be placed with amniotomy and again cervical change and contraction pattern are assessed in 2 hours. Confirmation of deficient Montevideo units at that time may prompt oxytocin augmentation for maternal or fetal indications.

Dilation rates of 1 to 2 cm/hr are accepted as evidence of progress after satisfactory uterine activity has been established with oxytocin. This can require up to 8 hours or more before cesarean delivery is performed for dystocia. The cumulative time required to effect this stepwise management approach permits many women to establish effective labor. This management protocol has been evaluated in more than 20,000 women with uncomplicated pregnancies. Importantly, these labor interventions and the relatively infrequent use of cesarean delivery did not jeopardize the fetus–newborn.

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CHAPTER 23: Abnormal Labor

… pains become less frequent and less intense, although giving rise to quite as much or even more suffering than previously. At the same time, the cervix, which was becoming obliterated and dilated in a satisfactory manner, ceases to make further progress and labour apparently comes to a standstill.

—J. Whitridge Williams (1903)

INTRODUCTION

The term *dystocia* as described by Williams in the first edition of this text still applies today. It literally means *difficult labor* and is characterized by abnormally slow labor progress. Similar to the factors described by Williams, dystocia arises from three distinct abnormality categories. First, uterine contractions may be insufficiently strong or inappropriately coordinated to efface and dilate the cervix—*uterine dysfunction*. Also, voluntary maternal muscle effort during second-stage labor may be inadequate. Second, fetal abnormalities of presentation, position, or anatomy may slow progress. Last, structural changes can contract the maternal bony pelvis. Or, soft tissue abnormalities of the reproductive tract may form an obstacle to fetal descent. More simply, these alterations can be mechanistically simplified into three categories that include abnormalities of the *powers*—uterine contractility and maternal expulsive effort; of the *passenger*—the fetus; and of the *passage*—the pelvis and lower reproductive tract.

DYSTOCIA

Descriptors

Abnormalities shown in Table 23-1 often interact singly or in combination to produce dysfunctional labor. Commonly used expressions today such as *cephalopelvic disproportion* and *failure to progress* are used to describe ineffective labors. Of these, *cephalopelvic disproportion* is a term that came into use before the 20th century to describe obstructed labor resulting from disparity between the fetal head size and maternal pelvis. But, the term originated at a time when the main indication for cesarean delivery was overt pelvic contracture due to rickets (Olah, 1994). Such absolute disproportion is now rare, and most cases result from malposition of the fetal head within the pelvis (asynclitism) or from ineffective uterine contractions. True disproportion is a tenuous diagnosis because many women who undergo cesarean delivery for this reason subsequently deliver even larger newborns vaginally in subsequent pregnancies. A second phrase, *failure to progress* in either spontaneous or stimulated labor, has become an increasingly popular description of ineffectual labor. This term reflects lack of progressive cervical dilation or lack of fetal descent. Neither of these two terms is specific.

TABLE 23-1

Common Clinical Findings in Women with Ineffective Labor

Inadequate cervical dilation or fetal descent:
Protracted labor—slow progress
Arrested labor—no progress
Inadequate expulsive effort—ineffective pushing
Fetopelvic disproportion:
Excessive fetal size
Inadequate pelvic capacity
Malpresentation or position of the fetus
Abnormal fetal anatomy
Ruptured membranes without labor

Mechanisms of Dystocia

At the end of pregnancy, the fetal head encounters a relatively thick lower uterine segment and undilated cervix. With the onset of labor, the factors influencing progress are uterine contractions, cervical resistance, and the forward pressure exerted by the leading fetal part.

After complete cervical dilation, the mechanical relationship between the fetal head size and position and the pelvic capacity, namely *fetopelvic proportion*, becomes clearer as the fetus attempts to descend. Because of this, abnormalities in fetopelvic proportions become more apparent once the second stage is reached.

Uterine muscle malfunction can result from uterine overdistention, obstructed labor, or both. *Thus, ineffective labor is generally accepted as a possible warning sign of fetopelvic disproportion.* Although artificial separation of labor abnormalities into pure *uterine dysfunction* and *fetopelvic disproportion* simplifies classification, it is an incomplete characterization because these two abnormalities are closely interlinked. Indeed, the bony pelvis rarely limits vaginal delivery. In the absence of objective means of precisely distinguishing these two causes of labor failure, clinicians must rely on a *trial of labor* to determine if labor can be successful in effecting vaginal delivery.

ABNORMALITIES OF THE EXPULSIVE FORCES

Cervical dilation as well as propulsion and expulsion of the fetus are brought about by uterine contractions. During second-stage labor, these contractions are then reinforced by voluntary or involuntary muscular action of the abdominal wall—"pushing." The diagnosis of uterine dysfunction in the latent phase is difficult and sometimes can be made only in retrospect. Women who are not yet in active labor commonly are erroneously treated for this dysfunction.

Beginning in the 1960s, at least three significant advances have aided treatment of uterine dysfunction. First is the realization that undue labor prolongation may contribute to maternal and perinatal morbidity and mortality rates. Second, dilute intravenous infusion of oxytocin is administered to treat certain types of uterine dysfunction. Last, cesarean delivery is selected rather than difficult midforceps delivery when oxytocin fails or its use is inappropriate.

Types of Uterine Dysfunction

Reynolds and coworkers (1948) emphasized that uterine contractions of normal labor are characterized by a gradient of myometrial activity. These forces are greatest and last longest at the fundus—considered *fundal dominance*—and they diminish toward the cervix. Caldeyro-Barcia and colleagues (1950) from Montevideo, Uruguay, inserted small balloons into the myometrium at various levels (Chap. 24, Intrapartum Surveillance of Uterine Activity). They reported that in addition to a gradient of activity, the onset of the contractions differed in the fundus, midzone, and lower uterine segments. Larks (1960) described the stimulus as starting in one cornu and then several milliseconds later in the other. The excitation waves then join and sweep over the fundus and down the uterus. Normal spontaneous contractions often exert pressures approximating 60 mm Hg (Hendricks, 1959). Even so, the Montevideo group ascertained that the lower limit of contraction pressure required to dilate the cervix is 15 mm Hg.

From these observations, two physiological types of uterine dysfunction are defined. In the more common *hypotonic uterine dysfunction,* there is no basal hypertonus, and uterine contractions have a normal gradient pattern (synchronous). However, pressure during a contraction is insufficient to dilate the cervix.

In the second type, *hypertonic uterine dysfunction* or *incoordinate uterine dysfunction,* either basal tone is elevated appreciably or the pressure gradient is distorted. Gradient distortion may result from more forceful contraction of the uterine midsegment than the fundus, from complete asynchrony of the impulses originating in each cornu, or from a combination of these two.

Labor Disorders

Latent-Phase Prolongation

These just-described types of uterine dysfunction can in turn lead to labor abnormalities (Table 23-2). First, the latent phase may be prolonged, which is defined as exceeding 20 hours in the nullipara and 14 hours in the multipara. In some, uterine contractions cease, suggesting false labor. In the remainder, an abnormally long latent phase persists and is often treated with oxytocin stimulation.

TABLE 23-2

Abnormal Labor Patterns, Diagnostic Criteria, and Methods of Treatment

	Diagnostic Criteria			
Labor Pattern	**Nulliparas**	**Multiparas**	**Preferred Treatment**	**Exceptional Treatment**
Prolongation Disorder				
Prolonged latent phase	>20 hr	>14 hr	Bed rest	Oxytocin or cesarean delivery for urgent problems
Protraction Disorders				
Protracted active-phase dilation Protracted descent	<1.2 cm/hr <1 cm/hr	1.5 cm/hr <2 cm/hr	Expectant and support	Cesarean delivery for CPD
Arrest Disorders				
Prolonged deceleration phase Secondary arrest of dilation Arrest of descent Failure of descent	>3 hr >2 hr >1 hr	>1 hr >2 hr >1 hr	Evaluate for CPD: CPD: cesarean No CPD: oxytocin	Rest if exhausted Cesarean delivery
	No descent in deceleration phase or second stage			

CPD = cephalopelvic disproportion.

Modified from Cohen, 1983.

Active-Phase Disorders

In active labor, disorders are divided into slower-than-normal progress—a *protraction disorder*—or complete cessation of progress—an *arrest disorder*. Terms presented in Table 23-2 and their diagnostic criteria more precisely describe abnormal labor. To be diagnosed with either of these, a woman must be in the active phase of labor, which is defined by cervical change.

These criteria and management of abnormal labor have recently undergone a sea change. In 2014, the American College of Obstetricians and Gynecologists and the Society for Maternal–Fetal Medicine issued their first Obstetric Care Consensus titled *Safe Prevention of the Primary Cesarean Delivery*. It was reaffirmed in 2016. This consensus statement was a response to concerns that cesarean delivery was overused in the United States. Namely, approximately one in three women who give birth each year undergoes this surgery (Fig. 31-1). New recommendations from the Consensus Committee are based on "more recent data used to revise the definition of contemporary normal labor progress" and reflect a significant revision of the preexisting understanding of abnormal labor.

Active-Phase Protraction

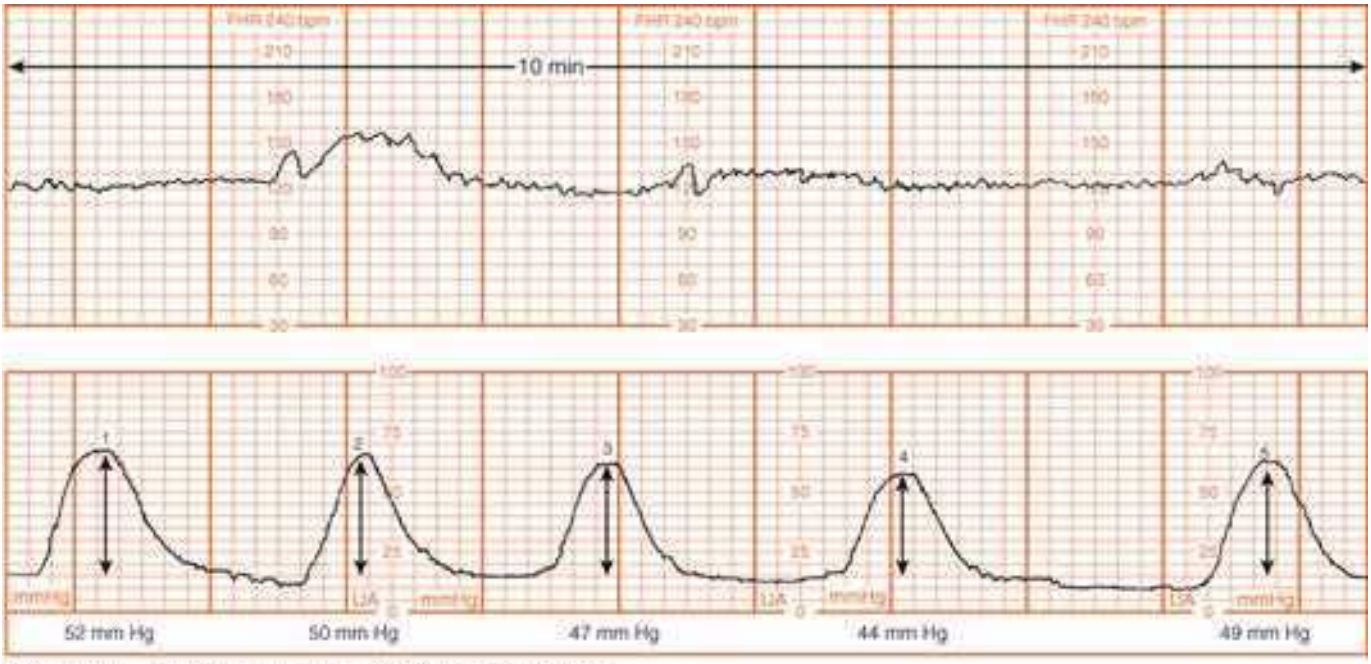
Of active-phase disorders, protraction disorders are less well described, and the time necessary before diagnosing slow progress is undefined. The World Health Organization (1994) has proposed a labor management *partograph* in which protraction is defined as <1 cm/hr cervical dilation for a minimum of 4 hours. These criteria were adapted from those of Cohen and Friedman (1983) and shown in Table 23-2. For this disorder, observation for further progress is appropriate treatment. If insufficient Montevideo units are noted, oxytocin augmentation is initiated. According to the Consensus Committee (2016), slow but progressive first-stage labor should not be an indication for cesarean delivery.

Active-Phase Arrest

Handa and Laros (1993) diagnosed active-phase arrest, defined as no dilation for 2 hours or more, in 5 percent of term nulliparas. This incidence has not changed since the 1950s (Friedman, 1978). Inadequate uterine contractions, defined as less than 180 Montevideo units, calculated as shown in Figure 23-1, were diagnosed in 80 percent of women with active-phase arrest. Hauth and coworkers (1986, 1991) reported that when labor is effectively induced or augmented with oxytocin, 90 percent of women achieve 200 to 225 Montevideo units, and 40 percent achieve at least 300 Montevideo units. These results suggest that certain minimums of uterine activity should be achieved before performing cesarean delivery for dystocia.

FIGURE 23-1

Montevideo units are calculated by subtracting the baseline uterine pressure from the peak contraction pressure for each contraction in a 10-minute window and adding the pressures generated by each contraction. In the example shown, there were five contractions, producing pressure changes of 52, 50, 47, 44, and 49 mm Hg, respectively. The sum of these five contractions is 242 Montevideo units.



Other criteria should also be met. First, the latent phase should be completed, and the cervix is dilated ≥4 cm. Also, a uterine contraction pattern of 200 Montevideo units or more in a 10-minute period has been present for 2 or more hours without cervical change. Rouse and associates (1999) challenged the "2-hour rule" on the grounds that a longer time, that is, at least 4 hours, is necessary before concluding that the active phase of labor has failed. We agree. The Consensus Committee (2016) has expanded the criteria, as described next.

Obstetric Care Consensus Committee

There are four recommendations by the Consensus Committee (2016) applicable to management of the first-stage labor. The first admonishes against cesarean delivery in the latent phase of labor. Specifically, a prolonged latent phase is not an indication for cesarean delivery. This guideline is not new and is traceable to the work of Friedman (1954), on which traditional tenets are based.

The second directive, too, is conventional practice. It recommends against cesarean delivery if labor is progressive but slow—a *protraction disorder*. This instance is typically managed with observation, assessment of uterine activity, and stimulation of contractions as needed.

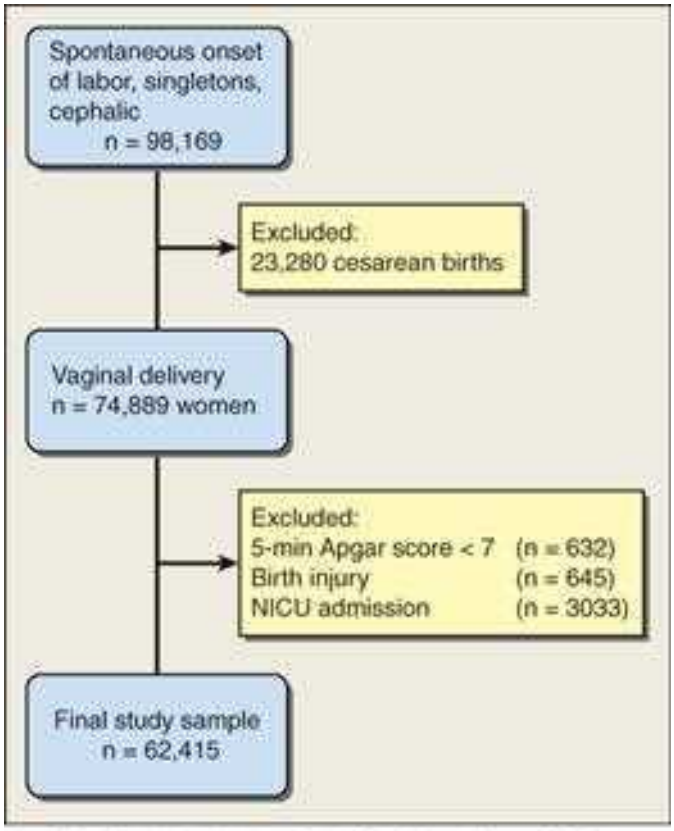
A third instruction addresses the cervical dilation threshold that serves to herald active labor. Namely, a cervical dilation of 6 cm—not 4 cm—is now the recommended threshold. Thus, before this threshold, standards for active-phase progress should not be applied.

A fourth stipulation notes that cesarean delivery for active-phase arrest "should be reserved for women at or beyond 6 cm of dilation with ruptured membranes who fail to progress despite 4 hours of adequate uterine activity, or at least 6 hours of oxytocin administration with inadequate contractions and no cervical change."

According to the Consensus Committee (2016), the "6-cm rule" stems from labor data from the Consortium on Safe Labor study (Zhang, 2010). This study derived its numbers from a retrospective observational dataset built from abstracted labor and delivery information from 19 hospitals across the United States. Various statistical methods and heavy manipulations of these numbers were used (Cohen, 2015b). As shown in Figure 23-2, a total of 62,415 women were analyzed after excluding all women with cesarean deliveries or asphyxiated newborns. The Consensus Committee (2016) was explicit that "the Consortium on Safe Labor data, rather than the standards proposed by Friedman should inform evidence-based labor management." Described in Chapter 21 (First Stage of Labor), the latter are labor curves that have been used since first proposed by Friedman (1955).

FIGURE 23-2

Study cohort for the analysis of spontaneous labor in the Consortium on Safe Labor study. NICU = neonatal intensive care unit. (Data from Zhang, 2010.)



Critics of the Consensus Committee (2016) recommendations note that the Consortium on Safe Labor data were derived from clinical settings with a net cesarean rate of 30 percent. Thus, adherence to the new recommendations may fail to achieve desired cesarean rate reductions. Also, the study lacked a focus on neonatal safety, given that all the asphyxiated neonates were excluded. Supporters note that the study of prolonged first-stage labors by Cheng and coworkers (2010) found higher rates of cesarean delivery and chorioamnionitis but not higher rates of neonatal morbidity. However, Harper and associates (2014) analyzed maternal and neonatal adverse outcomes related to first-stage labor lengths. In 5030 women, first-stage labor durations were divided into those <90th percentile or those ≥90th percentile, with incremental increases thereafter. These authors concluded that a longer first-stage labor was associated with maternal and neonatal complications and that these should be balanced against the risks of cesarean delivery. This concern for adverse fetal and maternal effects resulting from the new Consensus Committee guidelines was echoed by Cohen and Friedman (2015a,b).

Another caveat notes that the efficacy of these recommendations to achieve their primary goal is limited. In support, one retrospective cohort study of 200 women undergoing induction or augmentation before and 200 after guideline changes found a cesarean delivery rate drop from 35 to 25 percent (Wilson-Leedy, 2016). However, although the study was not powered to assess adverse neonatal outcomes, nonsignificant but higher rates of umbilical artery gases with pH <7 and base deficit >12 mmol/L were noted in the postguideline group (Marte, 2016). In another evaluation of outcomes before and after guideline implementation, cesarean delivery rates were unchanged. Overall, there were no associations between length of arrest and maternal or neonatal morbidity, but neonatal respiratory morbidity rates rose in newborns of women with longer periods of arrested dilation (Rosenbloom, 2017). Thus, additional studies are needed to define risks and benefits of the new guidelines.

Background for the 6-cm Rule

Review of selected publications helps explain the Consensus Committee (2016) evolution to a 6-cm rule. First, Zhang and coworkers (2002) compared study populations from one report by Friedman (1955) with one from 1992 to 1996 at Tripler Army Hospital, Hawaii (Table 23-3). The Friedman labor curves reflected women in spontaneous labor with infrequent use of neuraxial labor analgesia or oxytocin augmentation. In contrast, in the Tripler cohort, approximately 50 percent of women had neuraxial analgesia or augmentation. The rate of cervical change for the ensuing hour at each cervical dilation between 2 and 9 cm in the Tripler group is shown in Table 23-4. Progress is slow between 4 and 6 cm but accelerates thereafter. This could reasonably be interpreted as the active phase beginning at 6 cm. Shown in Figure 23-3 are the labor curves for Friedman (1955) compared to the Tripler cohort. These differ in a flattening of the active phase beginning at 3 to 4 cm in the Tripler group. This is consistent with the labor results obtained in the Safe Labor Consortium study (Zhang, 2010). Namely, the 6-cm rule for active labor derives from a slowing of the rate or flattening of the slope of cervical change in first-stage labor.

TABLE 23-3

Comparison of Study Populations Analyzed to Define Normal Labor Curves

	Friedman (n = 500)	Zhang[a] (n = 1162)
Year of data collection	Early 1950s	1992–1996
Caudal/epidural analgesia (%)	8	48
Oxytocin augmentation (%)	9	50

[a]Tripler Army Hospital.

Data from Friedman, 1955; Zhang, 2002.

TABLE 23-4

Rate of Change at Each Stage of Cervical Dilation

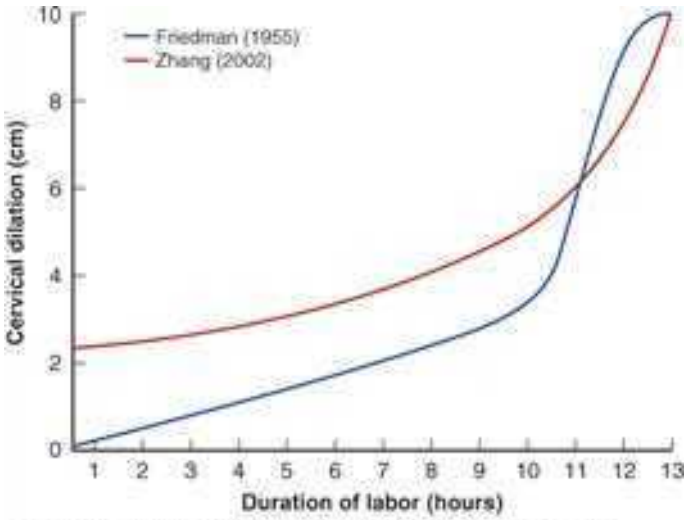
Cervical Dilation (cm)	Rate of Cervical Dilation (cm/h)[a]
2	0.3 (0.1, 1.8)
3	0.4 (0.1, 1.8)
4	0.6 (0.2, 1.8)
5	1.2 (0.3, 5.0)
6	1.7 (0.5, 6.3)
7	2.2 (0.7, 7.1)
8	2.4 (0.8, 7.7)
9	2.4 (0.7, 8.3)

[a]Median (5th and 95th percentiles).

Data from Zhang, 2002.

FIGURE 23-3

Cervical dilation curves. (From Friedman (1955) and Zhang (2002).)



Neuraxial analgesia delays the active phase of spontaneous labor and flattens the slope. For example, Gambling and associates (1998) compared combined spinal epidural (CSE) labor analgesia against intermittent intravenous (IV) boluses of 50 mg meperidine in 1223 nulliparas in spontaneous labor at term. The active phase of labor was diagnosed when cervical dilation was 4 cm in the presence of regular uterine contractions. As shown in Table 23-5, mean cervical dilation at first pain relief was 5 cm in both study groups. Oxytocin augmentation rates were significantly greater in the CSE group. Also, the first analgesia-to-delivery interval was lengthened (5 versus 4 hours). However, cesarean delivery rates did not differ significantly.

TABLE 23-5

Combined Spinal Epidural (CSE) Analgesia Compared with Meperidine for Nulliparas in Spontaneous Labor at Term

Labor Progress	CSE (n = 616)	Meperidine[a] (n = 607)	*p* value
Cervical dilation at first analgesia[b]	5	5	NS
Postanalgesia oxytocin augmentation[c]	132 (22%)	97 (16%)	.01
First analgesia to delivery (hr)[d]	5.0 ± 3.3	4.0 ± 3.1	.0001
Cesarean delivery[c]	39 (6%)	34 (6%)	NS

[a]Administered as intermittent intravenous boluses.

[b]Median value.

[c]Presented as number (%).

[d]Presented as mean ± standard deviation.

Data from Gambling, 1998.

Importantly, the effect of neuraxial analgesia to slow active-phase labor should not negatively affect use of neuraxial pain relief. As described in Chapter 25 (Effects on Labor), investigators at Parkland Hospital completed five randomized trials involving a total of 2703 nulliparas in spontaneous labor at term (Sharma, 2004). Various neuraxial techniques were compared with meperidine for pain relief. First-stage labor was significantly lengthened with neuraxial analgesia (8.1 versus 6.6 hours) but cesarean delivery rates for dystocia were unaffected (9.1 versus 8.1 percent).

In sum, neuraxial analgesia slows the active phase of first-stage labor. This currently is empirically corrected by augmentation of uterine contractions. Thus, recommendations of the Consensus Committee regarding protraction disorders are correct. Second, the Consensus Committee (2016) suggests that cesarean deliveries for dystocia are being done before 6 cm cervical dilation. However, there is good reason to believe that all of the Committee's first-stage recommendations are actually already empirically in use but are concurrent with an overall cesarean delivery rate in excess of 30 percent. For example, Table 23-6 lists labor characteristics in 9000 women with primary cesarean deliveries for dystocia at 13 university hospitals between 1999 and 2000 (Alexander, 2003). Notably, the median cervical dilation at the time of cesarean for dystocia was 6 cm. Moreover, Figure 23-4 depicts primary cesarean delivery rates for dystocia at Parkland Hospital between 1988 and 2017. The rate has not changed significantly in 28 years. Thus, Consensus Committee (2016) guidelines may fail to prevent additional cesareans for dystocia. Again, additional studies are needed.

TABLE 23-6

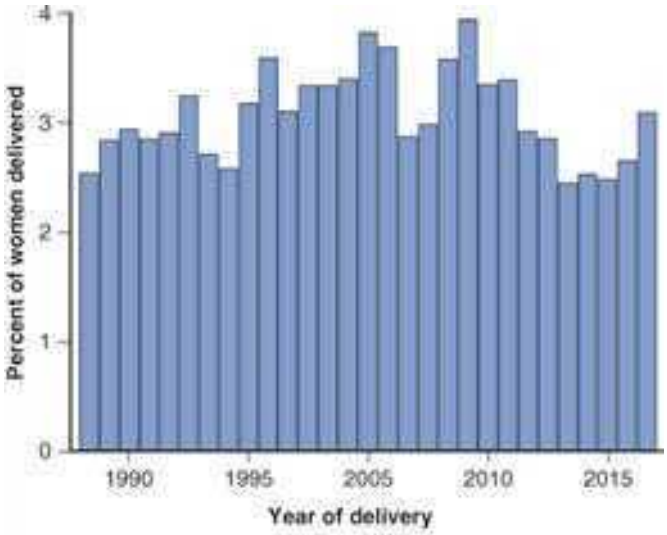
9000 Women Undergoing Primary Cesarean Delivery for Dystocia

Labor Characteristic	Percentage of Women with Noted Characteristic	Median (1st, 3rd quartiles)
Nulliparous	83%	—
Ruptured membranes	99%	—
Oxytocin stimulation	99%	—
Intrauterine pressure catheter	85%	—
≥200 Montevideo units	62%	—
Active phase labor (>4 cm dilation)	92%	—
Cervical dilation	—	6 cm (5, 8)
Augmentation to delivery time	—	9.3 hr (6, 13)

Data from Alexander, 2003.

FIGURE 23-4

Primary caesarean delivery rates for dystocia in low-risk women at term at Parkland Hospital from 1988 to 2017.



Second-Stage Descent Disorders

Fetal descent largely follows complete dilation. Moreover, the second stage incorporates many of the cardinal movements necessary for the fetus to negotiate the birth canal (Chap. 22, Descent). Accordingly, disproportion of the fetus and pelvis frequently becomes apparent during second-stage labor.

Similar to first-stage labor, time boundaries have been supported to limit second-stage duration to minimize adverse maternal and fetal outcomes. The second stage in nulliparas is limited to 2 hours and extended to 3 hours when regional analgesia is used. For multiparas, 1 hour is the limit, extended to 2 hours with regional analgesia.

Cohen (1977) investigated the fetal effects of second-stage labor length at Beth Israel Hospital. He included 4403 term nulliparas in whom electronic fetal heart rate monitoring was performed. The neonatal mortality rate was not increased in women whose second-stage labor exceeded 2 hours. Epidural analgesia was used commonly, and this likely accounted for the large number of pregnancies with a prolonged second stage. These data influenced decisions to permit an additional hour for the second stage when regional analgesia is used.

Menticoglou and coworkers (1995a,b) also challenged the prevailing dicta on second-stage duration. Their concern stemmed from grave neonatal injuries associated with forceps rotations to shorten second-stage labor. As a result, they allowed a longer second stage to decrease the operative vaginal delivery rate. Between 1988 and 1992, second-stage labor exceeded 2 hours in a fourth of 6041 nulliparas at term. Labor epidural analgesia was used in 55 percent. The length of the second stage, even in those lasting up to 6 hours or more, was not related to neonatal outcome. These results were attributed to careful use of electronic monitoring and

scalp pH measurements. These investigators concluded that there is no compelling reason to intervene with a possibly difficult forceps or vacuum extraction because a certain number of hours have elapsed. They observed, however, that after 3 hours in the second stage, delivery by cesarean or other operative method increased progressively. By 5 hours, the prospects for spontaneous delivery in the subsequent hour were only 10 to 15 percent.

Newer guidelines have been promoted by the Consensus Committee (2016) for second-stage labor. These recommend allowing a nullipara to push for at least 3 hours and a multipara to push for at least 2 hours before second-stage labor arrest is diagnosed. One caveat is that maternal and fetal status should be reassuring. These authors provide options to these times before cesarean delivery is performed. Namely, longer durations may be appropriate as long as progress is documented. Also, a specific maximal length of time spent in second-stage labor beyond which all women should undergo operative delivery has not been identified.

Intuitively, the goal to lower cesarean delivery rates is best balanced with one to ensure neonatal safety. And, it is problematic that no robust data on neonatal outcomes support the safety of allowing prolonged second-stage labor. Data from many evaluations reveal that serious newborn consequences attend second-stage labors longer than 3 hours (Allen, 2009; Bleich, 2012; Laughon, 2014; Leveno, 2016; Rosenbloom, 2017). Other data, when adjusted for labor variables, show no difference in neonatal complications for these longer second stages (Cheng, 2004; Le Ray, 2009; Rouse, 2009). Grobman and colleagues (2016) have argued that the absolute number of such adverse outcomes is small and "overall outcomes remain good." That said, some of the complications are severe. Thus, to fully ascertain specific effect of these guidelines on morbidity rates, randomized controlled trials are needed.

It is possible that prolonged first-stage labor presages that with the second stage. Nelson and associates (2013) studied the relationships between the lengths of the first and second stages of labor in 12,523 nulliparas at term delivered at Parkland Hospital. The second stage significantly lengthened concomitantly with increasing first-stage duration. The 95th percentile was 15.6 and 2.9 hours for the first and second stages, respectively. Women with first stages lasting longer than 15.6 hours (>95th percentile) had a 16-percent rate of second-stage labor lasting 3 hours (95th percentile). This compared with a 4.5-percent rate of prolonged second stages in women with first-stage labors lasting <95th percentile.

Maternal Pushing Efforts

With full cervical dilation, most women cannot resist the urge to "bear down" or "push" each time the uterus contracts (Chap. 22, Labor Management Protocols). The combined force created by contractions of the uterus and abdominal musculature propels the fetus downward. At times, force created by abdominal musculature is compromised sufficiently to slow or even prevent spontaneous vaginal delivery. Heavy sedation or regional analgesia may reduce the reflex urge to push and may impair the ability to contract abdominal muscles effectively. In other instances, the inherent urge to push is overridden by the intense pain created by bearing down. Two approaches to second-stage pushing in women with epidural analgesia have yielded contradictory results. The first advocates pushing forcefully with contractions after complete dilation, regardless of the urge to push. With the second, analgesia infusion is stopped and pushing begins only after the woman regains the sensory urge to bear down. Fraser and coworkers (2000) found that delayed pushing reduced difficult operative deliveries, whereas Manyonda and associates (1990) reported the opposite. Hansen and colleagues (2002) randomly assigned 252 women with epidural analgesia to one of the two approaches. No adverse maternal or neonatal outcomes were linked to delayed pushing despite significantly prolonging second-stage labor. Plunkett and coworkers (2003), in a similar study, confirmed these findings.

Fetal Station at Labor Onset

Descent of the leading edge of the presenting part to the level of the ischial spines (0 station) is defined as engagement. A higher station at the onset of labor is significantly linked with subsequent dystocia (Friedman, 1965, 1976; Handa, 1993). Roshanfekr and associates (1999) analyzed fetal station in 803 nulliparas at term in active labor. At admission, the third with the fetal head at or below 0 station had a 5-percent cesarean delivery rate. This compared with a 14-percent rate for those with higher stations. The prognosis for dystocia, however, was not related to incrementally higher fetal head stations above the pelvic midplane (0 station). Importantly, 86 percent of nulliparous women without fetal head engagement at diagnosis of active labor delivered vaginally. These observations apply especially for parous women because the head typically descends later in labor.

Risks for Uterine Dysfunction

Various labor factors have been implicated as causes of uterine dysfunction. As described, neuraxial analgesia can slow labor and has been associated with lengthening both first and second stages of labor and slowing the rate of fetal descent.

Chorioamnionitis is associated with prolonged labor, and some clinicians have suggested that this maternal intrapartum infection itself contributes to abnormal uterine activity. Satin and coworkers (1992) studied the effects of chorioamnionitis on oxytocin stimulation in 266 pregnancies. Infection diagnosed late in labor was found to be a marker of cesarean delivery performed for dystocia. Specifically, 40 percent of women developing chorioamnionitis after requiring oxytocin for dysfunctional labor later required cesarean delivery for dystocia. However, this was not a marker in women diagnosed as having chorioamnionitis early in labor. It is likely that uterine infection in this clinical setting is a consequence of dysfunctional, prolonged labor rather than a cause of dystocia.

PREMATURELY RUPTURED MEMBRANES AT TERM

Membrane rupture at term without spontaneous uterine contractions complicates approximately 8 percent of pregnancies. In the past, labor stimulation was initiated if contractions did not begin after 6 to 12 hours. Practice-changing research included that of Hannah (1996) and Peleg (1999) and their associates, who enrolled a total of 5042 pregnancies with ruptured membranes in a randomized investigation. They measured the effects of induction versus expectant management and also compared induction using intravenous oxytocin with that using prostaglandin E_2 gel. There were approximately 1200 pregnancies in each of the four study arms. They concluded that labor induction with intravenous oxytocin was preferred management. This was based on significantly fewer intrapartum and

postpartum infections in women whose labor was induced. There were no significant differences in cesarean delivery rates. Subsequent analysis by Hannah and coworkers (2000) indicated higher rates of adverse outcomes when expectant management at home was compared with in-hospital observation. Mozurkewich and associates (2009) reported lower rates of chorioamnionitis, metritis, and neonatal intensive care unit admissions for women with term ruptured membranes whose labors were induced compared with those managed expectantly. At Parkland Hospital, labor is induced soon after admission when ruptured membranes are confirmed at term. In those with hypotonic contractions or with advanced cervical dilation, oxytocin is selected to lower potential hyperstimulation risk. In those with an unfavorable cervix and no or few contraction, prostaglandin E_1 (misoprostol) is chosen to promote cervical ripening and contractions. The benefit of prophylactic antibiotics in women with ruptured membranes before labor at term is unclear (Passos, 2012). However, in those with membranes ruptured longer than 18 hours, antibiotics are instituted for group B streptococcal infection prophylaxis (Chap. 64, GBS Vaccine).

PRECIPITOUS LABOR AND DELIVERY

Labor can be too slow, but it also can be abnormally rapid. *Precipitous labor and delivery* is extremely rapid labor and delivery. It may result from an abnormally low resistance of the soft parts of the birth canal, from abnormally strong uterine and abdominal contractions, or rarely from the absence of painful sensations and thus a lack of awareness of vigorous labor.

Precipitous labor terminates in expulsion of the fetus in less than 3 hours. Using this definition, 25,260 live births—3 percent—were complicated by precipitous labor in the United States in 2013 (Martin, 2015). Despite this incidence, little published information describes maternal and perinatal outcomes.

For the mother, precipitous labor and delivery seldom are accompanied by serious maternal complications if the cervix is effaced appreciably and compliant, if the vagina has been stretched previously, and if the perineum is relaxed. Conversely, vigorous uterine contractions combined with a long, firm cervix and a noncompliant birth canal may lead to uterine rupture or extensive lacerations of the cervix, vagina, vulva, or perineum (Sheiner, 2004). It is in these latter circumstances that *amnionic-fluid embolism* most likely develops (Chap. 41, General Management). Precipitous labor is frequently followed by uterine atony. *The uterus that contracts with unusual vigor before delivery is likely to be hypotonic after delivery.* In one report of 99 term pregnancies, short labors were more common in multiparas who typically had contractions at intervals less than 2 minutes. Precipitous labors have been linked to cocaine abuse and associated with placental abruption, meconium, postpartum hemorrhage, and low Apgar scores (Mahon, 1994).

For the neonate, adverse perinatal outcomes from rapid labor may be increased considerably for several reasons. The tumultuous uterine contractions, often with negligible intervals of relaxation, prevent appropriate uterine blood flow and fetal oxygenation. Resistance of the birth canal may rarely cause intracranial trauma. Acker and coworkers (1988) reported that Erb or Duchenne brachial palsy was associated with such labors in a third of cases. Finally, during an unattended birth, the newborn may fall to the floor and be injured, or it may need resuscitation that is not immediately available.

As treatment, analgesia is unlikely to modify these unusually forceful contractions to a significant degree. The use of tocolytic agents such as magnesium sulfate or terbutaline is unproven in these circumstances. Use of general anesthesia with agents that impair uterine contractibility such as isoflurane is often excessively heroic. Certainly, any oxytocin being administered should be stopped immediately.

FETOPELVIC DISPROPORTION

Pelvic Capacity

Fetopelvic disproportion arises from diminished pelvic capacity, from abnormal fetal size or presentation, or more usually from both. The pelvic inlet, midpelvis, or pelvic outlet may be contracted solely or in combination. Any contraction of the pelvic diameters that diminishes pelvic capacity can create dystocia during labor. Normal pelvic dimensions are additionally discussed and illustrated in Chapter 2 (Planes and Diameters of the Pelvis).

Contracted Inlet

Using clinical measures, it is important to identify the shortest anteroposterior diameter through which the fetal head must pass. Before labor, the fetal biparietal diameter averages from 9.5 to as much as 9.8 cm. Therefore, it might prove difficult or even impossible for some fetuses to pass through a pelvic inlet that has an anteroposterior diameter <10 cm. Mengert (1948) and Kaltreider (1952), employing x-ray pelvimetry, demonstrated that the incidence of difficult deliveries rises when either the anteroposterior diameter of the inlet is <10 cm or the transverse diameter is <12 cm. As expected, when both diameters are contracted, dystocia rates are much greater than when only one is contracted. Either of these measures is used to consider a pelvis contracted.

The anteroposterior diameter of the inlet, which is the obstetrical conjugate, is commonly approximated by manually measuring the diagonal conjugate, which is approximately 1.5 cm greater. Ascertainment of these measures is described in Chapter 2 (Planes and Diameters of the Pelvis). Therefore, inlet contraction usually is defined as a diagonal conjugate <11.5 cm.

A small woman is likely to have a small pelvis, but she is also likely to have a small neonate. Thoms (1937) studied 362 nulliparas and found that the mean birthweight of their offspring was significantly lower—280 g—in women with a small pelvis than in those with a medium or large pelvis.

Normally, cervical dilation is aided by hydrostatic action of the unruptured membranes or after their rupture, by direct application of the presenting part against the cervix. In contracted pelves, however, because the head is arrested in the pelvic inlet, the entire force exerted by the uterus acts directly on the portion of membranes that contact the dilating cervix. Consequently, early spontaneous rupture of the membranes is more likely.

After membrane rupture, absent pressure by the head against the cervix and lower uterine segment predisposes to less effective contractions. Hence, further dilation may proceed very slowly or not at all. Cibils and Hendricks (1965) reported that the mechanical adaptation of the fetal passenger to the bony passage plays an

important part in determining the efficiency of contractions. The better the adaptation, the more efficient the contractions. Thus, cervical response to labor provides a prognostic view of labor outcome in women with inlet contraction.

A contracted inlet also plays an important part in the production of abnormal presentations. In nulliparas with normal pelvic capacity, the presenting part at term commonly descends into the pelvic cavity before labor onset. When the inlet is contracted considerably or there is marked asynclitism, descent usually does not take place until after labor onset, if at all. Cephalic presentations still predominate, but the head floats freely over the pelvic inlet or rests more laterally in one of the iliac fossae. Accordingly, very slight influences may cause the fetus to assume other presentations. In women with contracted pelves, face and shoulder presentations are encountered three times more frequently, and the cord prolapses four to six times more often.

Contracted Midpelvis

This finding is more common than inlet contraction. It frequently causes transverse arrest of the fetal head, which potentially can lead to a difficult midforceps operation or to cesarean delivery.

The obstetrical plane of the midpelvis extends from the inferior margin of the symphysis pubis through the ischial spines and touches the sacrum near the junction of the fourth and fifth vertebrae. A transverse line theoretically connecting the ischial spines divides the midpelvis into anterior and posterior portions (Fig. 2-16). The former is bounded anteriorly by the lower border of the symphysis pubis and laterally by the ischiopubic rami. The posterior portion is bounded dorsally by the sacrum and laterally by the sacrospinous ligaments, forming the lower limits of the sacrosciatic notch.

Average midpelvis measurements are as follows: *transverse,* or interischial spinous, 10.5 cm; *anteroposterior,* from the lower border of the symphysis pubis to the junction of S_{4-5}, 11.5 cm; and *posterior sagittal*, from the midpoint of the interspinous line to the same point on the sacrum, 5 cm. The definition of midpelvic contractions has not been established with the same precision possible for inlet contractions. Even so, the midpelvis is likely contracted when the sum of the interspinous and posterior sagittal diameters of the midpelvis—normally, 10.5 plus 5 cm, or 15.5 cm—falls to 13.5 cm or less. This concept was emphasized by Chen and Huang (1982) in evaluating possible midpelvic contraction. Midpelvic contraction is suspected whenever the interspinous diameter is <10 cm. When it measures <8 cm, the midpelvis is contracted.

Although no precise manual method permits measure of midpelvic dimensions, a suggestion of contraction sometimes can be inferred if the spines are prominent, the pelvic sidewalls converge, or the sacrosciatic notch is narrow. Moreover, Eller and Mengert (1947) noted that the relationship between the intertuberous and interspinous diameters of the ischium is sufficiently constant that narrowing of the interspinous diameter can be anticipated when the intertuberous diameter is narrow. A normal intertuberous diameter, however, does not always exclude a narrow interspinous diameter.

Contracted Outlet

This finding usually is defined as an interischial tuberous diameter of 8 cm or less. The pelvic outlet may be roughly likened to two triangles, with the interischial tuberous diameter constituting the base of both. The sides of the anterior triangle are the pubic rami, and its apex is the inferoposterior surface of the symphysis pubis. The posterior triangle has no bony sides but is limited at its apex by the tip of the last sacral vertebra—not the tip of the coccyx. Diminution of the intertuberous diameter with consequent narrowing of the anterior triangle must inevitably force the fetal head posteriorly. Floberg and associates (1987) reported that outlet contractions were found in almost 1 percent of more than 1400 unselected nulliparas with term pregnancies. A contracted outlet may cause dystocia not so much by itself but by an often-associated midpelvic contraction. *Outlet contraction without concomitant midplane contraction is rare.*

Although the disproportion between the fetal head and the pelvic outlet is not sufficiently great to give rise to severe dystocia, it may play an important part in perineal tears. With increased narrowing of the pubic arch, the occiput cannot emerge directly beneath the symphysis pubis but is forced farther down upon the ischiopubic rami. The perineum, consequently, becomes increasingly distended and thus exposed to risk of laceration.

Pelvic Fractures

Vallier (2012) reviewed experiences with pelvic fractures and pregnancy. Trauma from automobile collisions was the most common cause. Moreover, they note that fracture pattern, minor malalignment, and retained hardware are not absolute indications for cesarean delivery. In determining suitability for vaginal delivery, fracture healing requires 8 to 12 weeks and thus recent fracture merits cesarean delivery (Amorosa, 2013). A history of pelvic fracture warrants careful review of previous radiographs and possible imaging pelvimetry later in pregnancy.

Pelvic Capacity Estimation

The techniques for clinical evaluation using digital examination of the bony pelvis during labor are described in detail in Chapter 2 (Planes and Diameters of the Pelvis). The value of radiological imaging to assess pelvic capacity has also been examined. First, with x-ray pelvimetry alone, the prognosis for successful vaginal delivery in any given pregnancy with cephalic presentation cannot be established (Mengert, 1948). Similarly, one systematic review found insufficient evidence to support the use of x-ray pelvimetry with cephalic presentations (Pattinson, 2017).

Advantages of pelvimetry with computed tomography (CT) compared with those of conventional x-ray pelvimetry include greater accuracy and easier performance. With either method, costs are comparable, and x-ray exposure is small (Chap. 46, X-Ray Dosimetry). Depending on the machine and technique employed, fetal doses with CT pelvimetry may range from 250 to 1500 mrad (Moore, 1989).

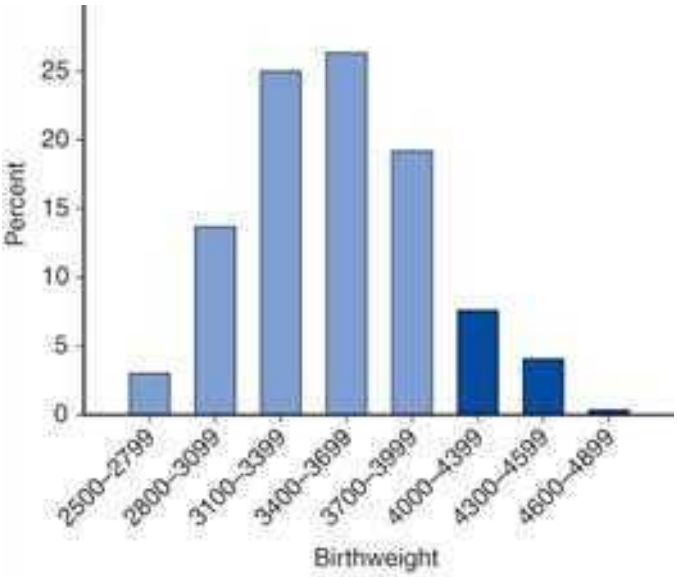
Advantages of magnetic resonance (MR) pelvimetry include lack of ionizing radiation, accurate measurements, complete fetal imaging, and the potential for evaluating soft tissue dystocia (McCarthy, 1986; Stark, 1985). Zaretsky and colleagues (2005) used MR imaging to measure pelvic and fetal head volume to identify those women at greatest risk of undergoing cesarean delivery for dystocia. Significant associations were found between some of the measures and cesarean delivery

for dystocia. However, these researchers could not with accuracy predict which individual woman would require cesarean delivery. Others have reported similar findings (Sporri, 1997).

Fetal Body and Head Size

Fetal size alone is seldom a suitable explanation for failed labor. Even with current technology, a fetal size threshold to predict fetopelvic disproportion is still elusive. Most cases of disproportion arise in fetuses whose weight is well within the range of the general obstetrical population. As shown in Figure 23-5, two thirds of neonates who required cesarean delivery after failed forceps delivery weighed <3700 g. Thus, other factors—for example, malposition of the head—obstruct fetal passage through the birth canal. These include asynclitism, occiput posterior position, and face or brow presentation.

FIGURE 23-5
Birthweight distribution of 362 newborns born by cesarean delivery after a failed forceps attempt at Parkland Hospital from 1989–1999. Only 12 percent (n = 44) of the newborns weighed >4000 g (*dark bars*).



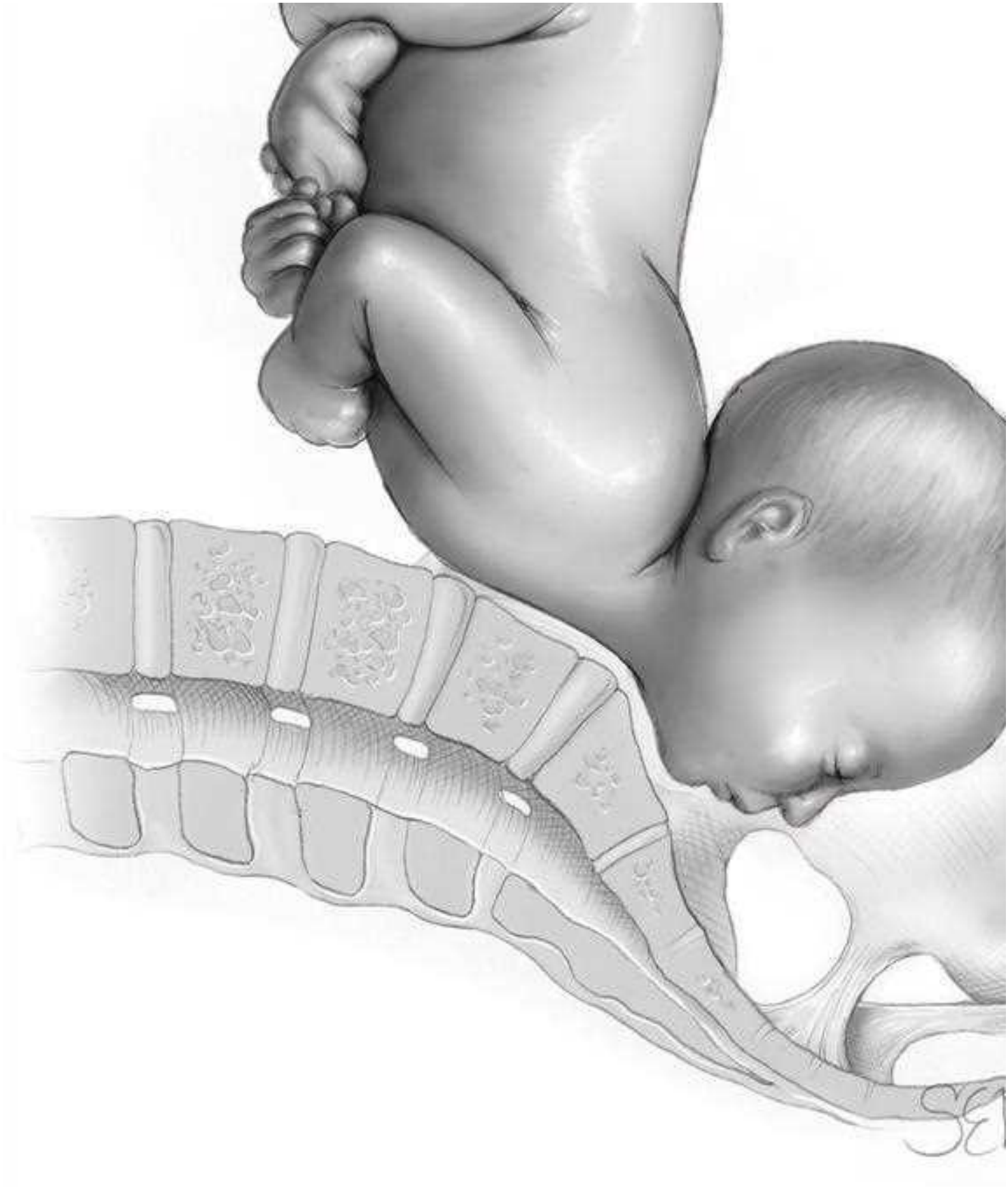
For fetal head size estimation, clinical and radiographical methods to predict fetopelvic disproportion have proved disappointing. Mueller (1885) and Hillis (1930) described a clinical maneuver to predict disproportion. The fetal brow and the suboccipital region are grasped through the abdominal wall with the fingers, and firm pressure is directed downward in the axis of the inlet. If no disproportion exists, the head readily enters the pelvis, and vaginal delivery can be predicted. Thorp and coworkers (1993) performed a prospective evaluation of this *Mueller-Hillis maneuver.* They found no relationship between failed descent during the maneuver and subsequent labor dystocia.

Measurements of fetal head diameters using plain radiographical techniques are not used because of parallax distortions. The biparietal diameter and head circumference can be measured sonographically, and investigators have attempted to use this information in the management of dystocia. Thurnau and colleagues (1991) used the *fetal-pelvic index* to identify labor complications. Unfortunately, the sensitivity of such measurements to predict cephalopelvic disproportion is poor (Ferguson, 1998; Korhonen, 2015). We believe that no current method of measurement satisfactorily predicts fetopelvic disproportion based on head size.

Face Presentation

With this presentation, the neck is hyperextended so that the occiput is in contact with the fetal back, and the chin (mentum) is presenting (Fig. 23-6). The fetal face may present with the chin (mentum) anteriorly or posteriorly, relative to the maternal symphysis pubis (Chap. 22, Diagnosis). Although some mentum posterior presentations persist, most convert spontaneously to anterior even in late labor (Duff, 1981). If not, the fetal brow (bregma) is pressed against the maternal symphysis pubis. This position precludes flexion of the fetal head necessary to negotiate the birth canal. Thus, a mentum posterior presentation is undeliverable except with a very preterm fetus.

FIGURE 23-6
Face presentation. The occiput is the longer end of the head lever. The chin is directly posterior. Vaginal delivery is impossible unless the chin rotates anteriorly.



Face presentation is diagnosed by vaginal examination and palpation of facial features. A breech may be mistaken for a face presentation. Namely, the anus may be mistaken for the mouth, and the ischial tuberosities for the malar prominences. Digital differentiation is described in Chapter 28 (Diagnosis). Radiographically, demonstration of the hyperextended head with the facial bones at or below the pelvic inlet is characteristic.

Cruikshank and White (1973) reported an incidence of 1 in 600, or 0.17 percent. As shown in Table 22-1, among more than 70,000 singleton newborns delivered at Parkland Hospital, approximately 1 in 2000 had a face presentation at delivery.

Etiology

Causes of face presentations are numerous and include conditions that favor extension or prevent head flexion. Preterm fetuses, with their smaller head dimensions, can engage before conversion to vertex position (Shaffer, 2006). In exceptional instances, marked enlargement of the neck or coils of cord around the neck may cause extension. Bashiri and associates (2008) reported that fetal malformations and hydramnios were risk factors for face or brow presentations. Anencephalic fetuses naturally present by the face.

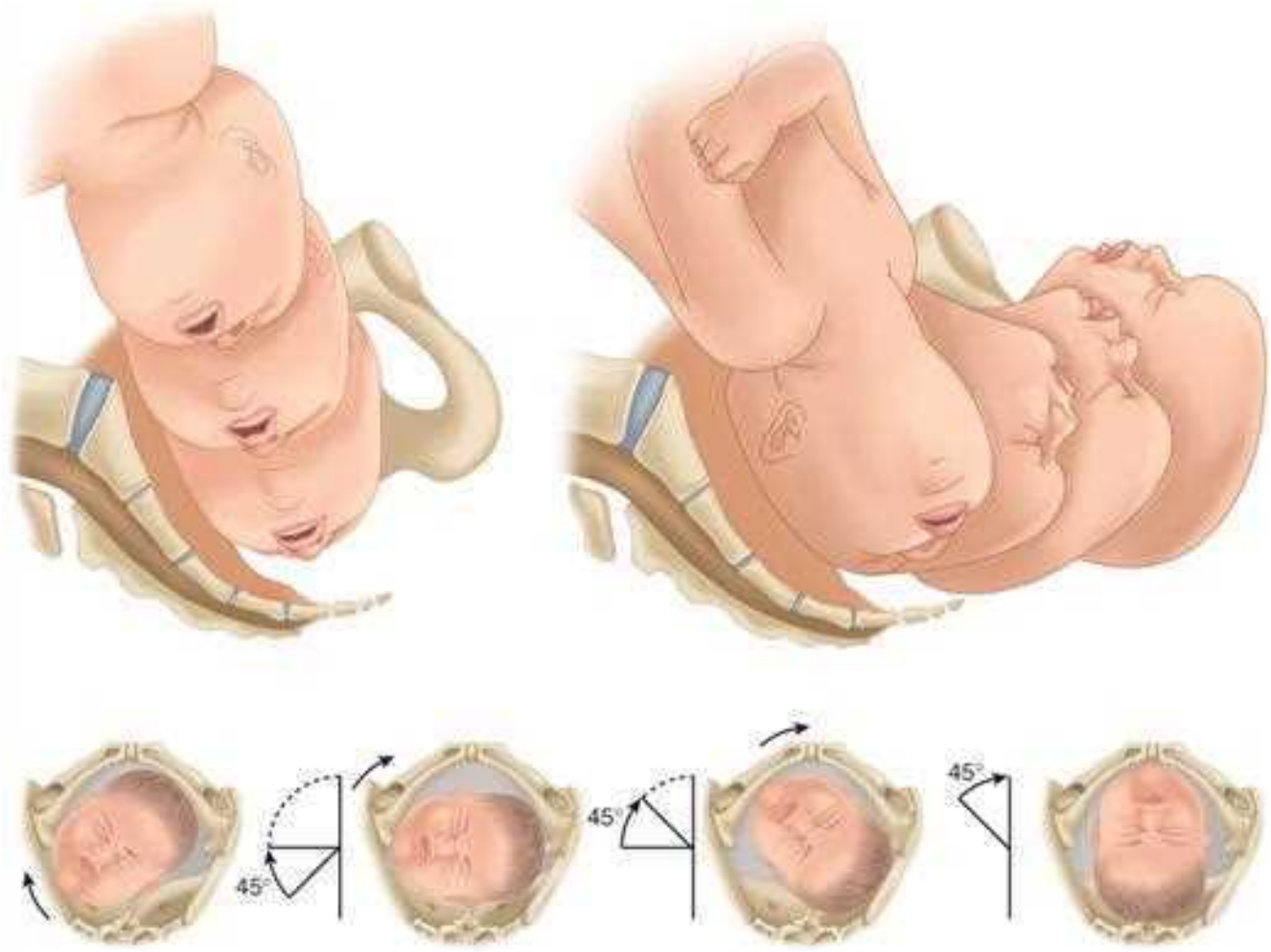
Extended neck positions develop more frequently when the pelvis is contracted or the fetus is very large. In a series of 141 face presentations studied by Hellman and coworkers (1950), the incidence of inlet contraction was 40 percent. This high incidence of pelvic contraction should be kept in mind when considering management.

High parity is a predisposing factor for face presentation (Fuchs, 1985). In these cases, a pendulous abdomen permits the back of the fetus to sag forward or laterally, often in the same direction in which the occiput points. This promotes extension of the cervical and thoracic spine.

Mechanism of Labor

Face presentations rarely are observed above the pelvic inlet. Instead, the brow generally presents early and is usually converted to present the face after further extension of the neck during descent. The mechanism of labor in these cases consists of the cardinal movements of descent, internal rotation, and flexion, and the accessory movements of extension and external rotation (Fig. 23-7). Descent is brought about by the same factors as in cephalic presentations. Extension results from the relation of the fetal body to the deflected head, which is converted into a two-armed lever, the longer arm of which extends from the occipital condyles to the occiput. When resistance is encountered, the occiput must be pushed toward the back of the fetus while the chin descends.

FIGURE 23-7
Mechanism of labor for right mentoposterior position with subsequent rotation of the mentum anteriorly and delivery.



The objective of internal rotation of the face is to bring the chin under the symphysis pubis. Only in this way can the neck traverse the posterior surface of the symphysis pubis. If the chin rotates directly posteriorly, the relatively short neck cannot span the anterior surface of the sacrum, which measures about 12 cm in length. Moreover, the fetal brow (bregma) is pressed against the maternal symphysis pubis. This position precludes flexion necessary to negotiate the birth canal.

Hence, as discussed earlier, birth of the head from a mentum posterior position is impossible unless the shoulders enter the pelvis at the same time, an event that is impossible except when the fetus is extremely small or macerated. Internal rotation results from the same factors as in vertex presentations.

After anterior rotation and descent, the chin and mouth appear at the vulva, the undersurface of the chin presses against the symphysis, and the head is delivered by flexion. The nose, eyes, brow (bregma), and occiput then appear in succession over the anterior margin of the perineum. After birth of the head, the occiput sags backward toward the anus. Next, the chin rotates externally to the side toward which it was originally directed, and the shoulders are born as in cephalic presentations.

Edema may sometimes significantly distort the face. At the same time, the skull undergoes considerable molding, manifested by an increase in length of the occipitomental diameter of the head.

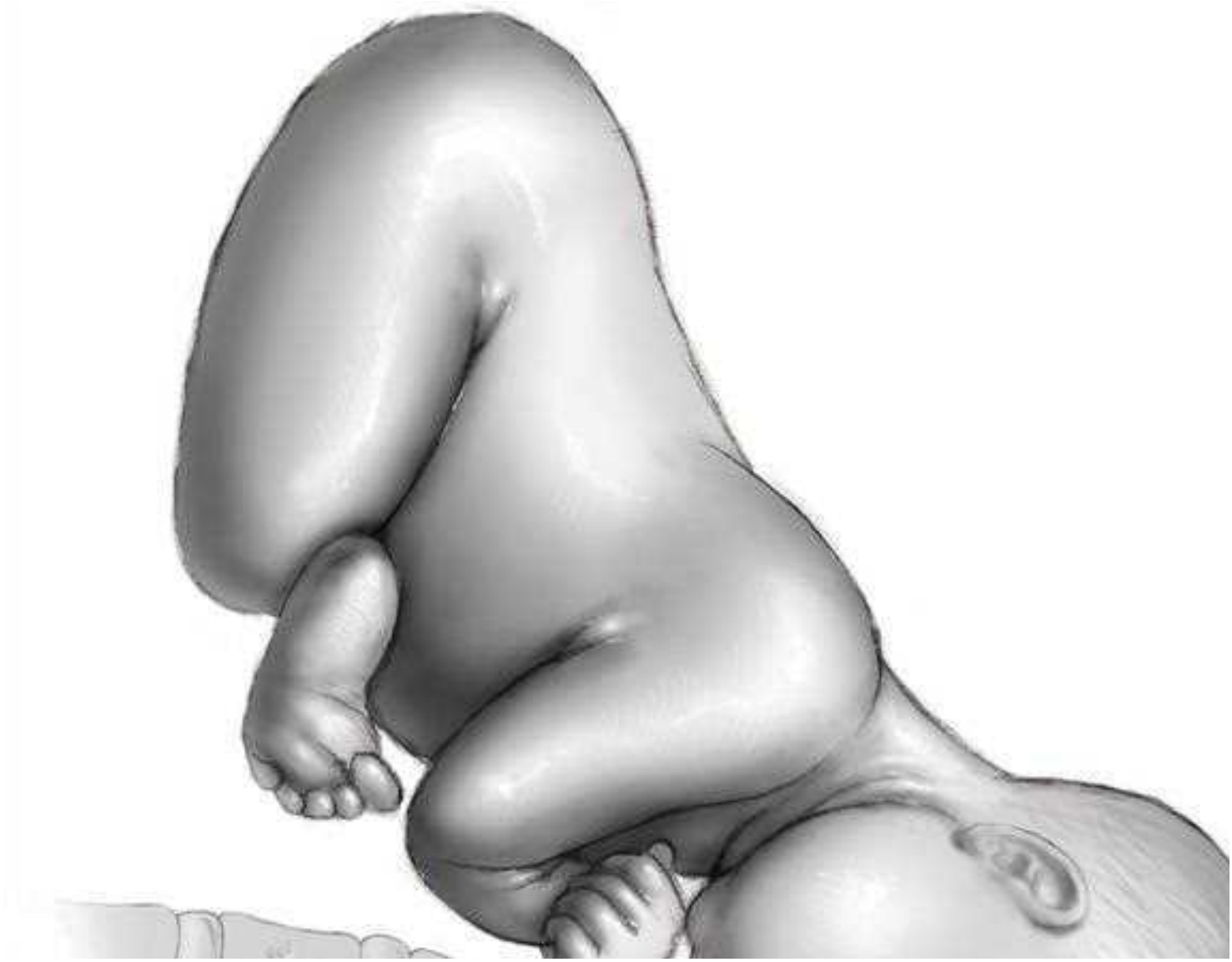
Management

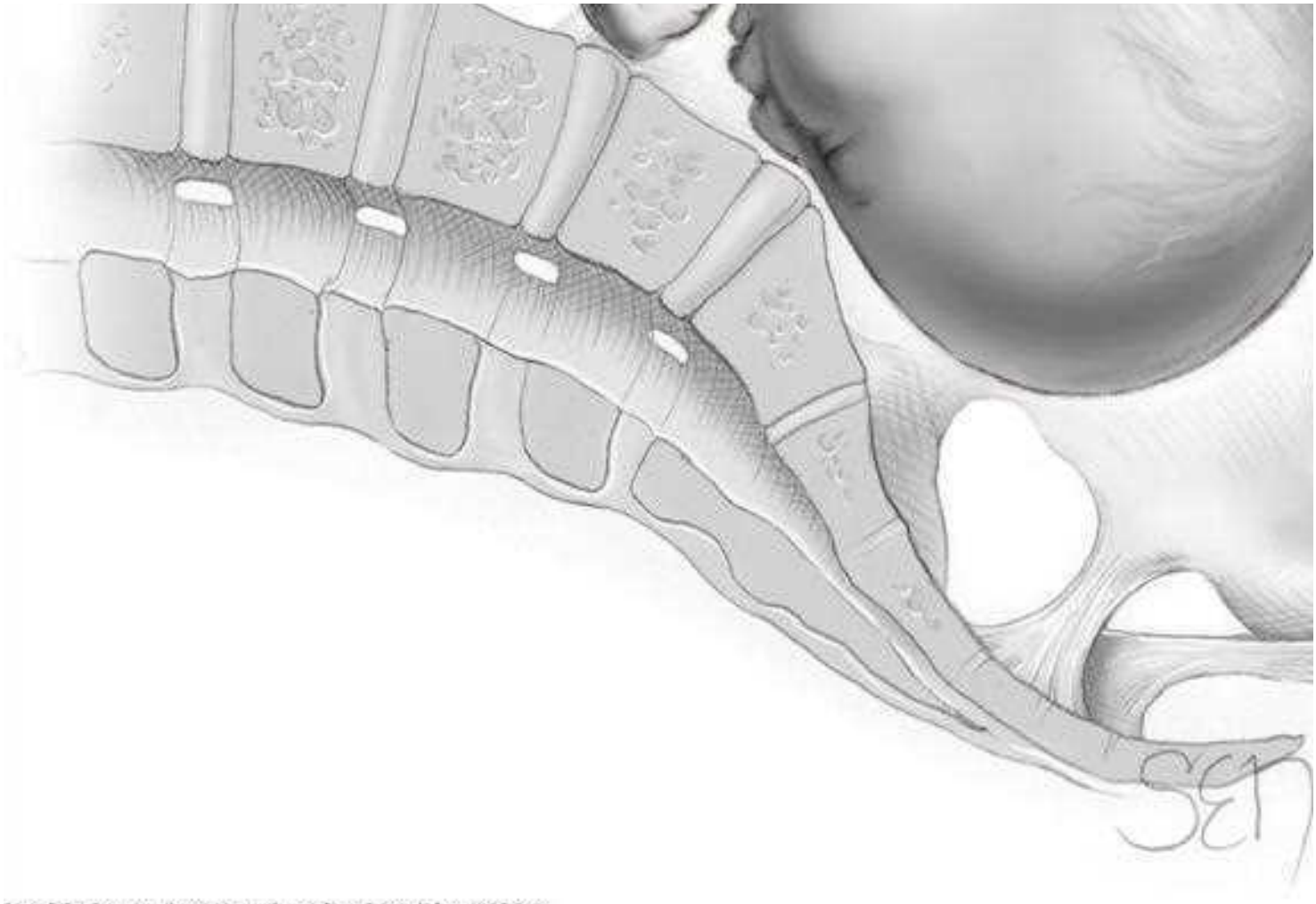
In the absence of a contracted pelvis and with effective labor, successful vaginal delivery usually will follow. Fetal heart rate monitoring is probably better done with external devices to avoid damage to the face and eyes. Because face presentations among term-size fetuses are more common when there is some degree of pelvic inlet contraction, cesarean delivery frequently is indicated. Attempts to convert a face presentation manually into a vertex presentation, manual or forceps rotation of a persistently posterior chin to a mentum anterior position, and internal podalic version and extraction are dangerous and should not be attempted. Low or outlet forceps delivery of a mentum anterior face presentation can be completed and is described in Chapter 29 (Vacuum Extraction).

Brow Presentation

This rare presentation is diagnosed when that portion of the fetal head between the orbital ridge and the anterior fontanel presents at the pelvic inlet. As shown in Figure 23-8, the fetal head thus occupies a position midway between full flexion (occiput) and extension (face). Except when the fetal head is small or the pelvis is unusually large, engagement of the fetal head and subsequent delivery cannot take place as long as the brow presentation persists.

FIGURE 23-8
Brow posterior presentation.





The causes of persistent brow presentation are the same as those for face presentation. A brow presentation is commonly unstable and often converts to a face or an occiput presentation (Cruikshank, 1973). The presentation may be recognized by abdominal palpation when both the occiput and chin can be palpated easily, but vaginal examination is usually necessary. The frontal sutures, large anterior fontanel, orbital ridges, eyes, and root of the nose are felt on vaginal examination, but neither the mouth nor the chin is palpable.

With a very small fetus and a large pelvis, labor is generally easy. With a larger fetus, it is usually difficult. This is because engagement is impossible until there is marked molding that shortens the occipitomental diameter or more commonly, until the neck either flexes to an occiput presentation or extends to a face presentation. The considerable molding essential for vaginal delivery of a persistent brow characteristically deforms the head. The caput succedaneum is over the forehead, and it may be so extensive that identification of the brow by palpation is impossible. In these instances, the forehead is prominent and squared, and the occipitomental diameter is diminished.

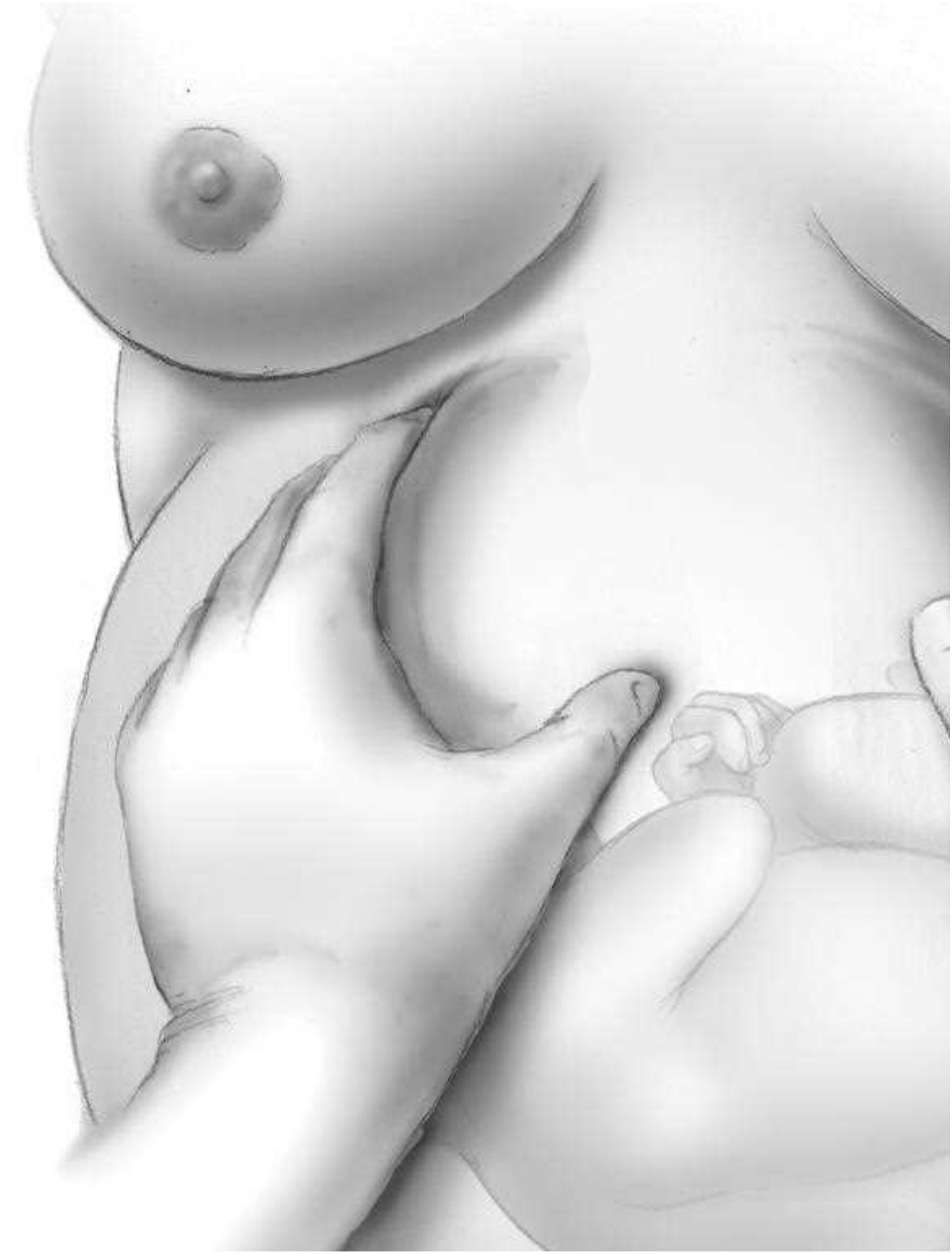
In transient brow presentations, the prognosis depends on the ultimate presentation. If the brow persists, prognosis is poor for vaginal delivery unless the fetus is small or the birth canal is large. Principles of management are the same as those for a face presentation.

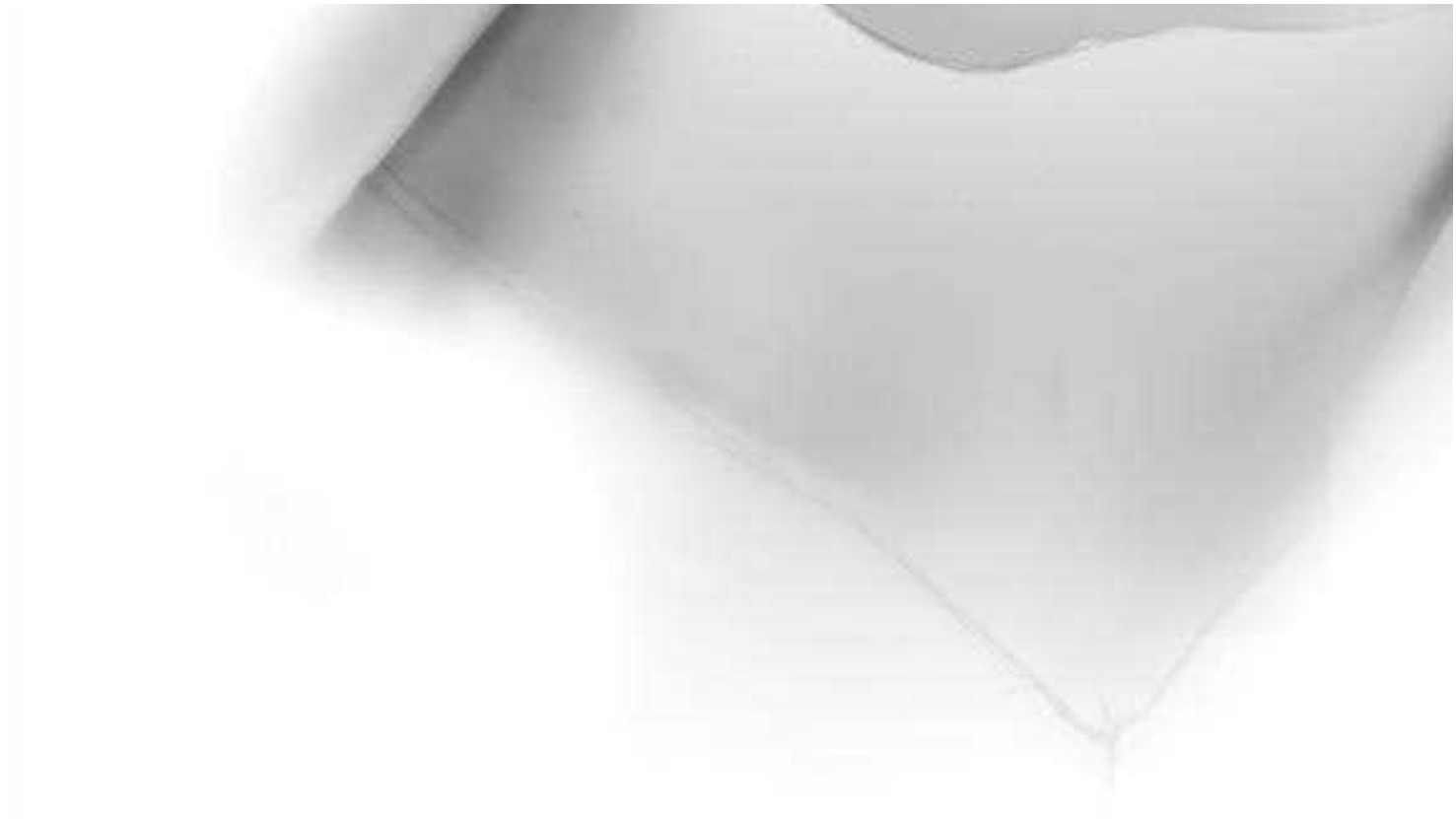
Transverse Lie

In this position, the long axis of the fetus is approximately perpendicular to that of the mother. When the long axis forms an acute angle, an *oblique lie* results. The latter is usually only transitory, because either a longitudinal or transverse lie commonly results when labor supervenes. For this reason, the oblique lie is called an *unstable lie* in Great Britain.

In a transverse lie, the shoulder is usually positioned over the pelvic inlet. The head occupies one iliac fossa, and the breech the other. This creates a *shoulder presentation* in which the side of the mother on which the acromion rests determines the designation of the lie as right or left acromial. And because in either position the back may be directed anteriorly or posteriorly, superiorly or inferiorly, it is customary to distinguish varieties as dorsoanterior and dorsoposterior (Fig. 23-9).

FIGURE 23-9
Leopold maneuver performed on a woman with a fetal transverse lie, right acromiodorsoanterior position.





A transverse lie is usually recognized easily, often by inspection alone. The abdomen is unusually wide, whereas the uterine fundus extends to only slightly above the umbilicus. No fetal pole is detected in the fundus, and the ballottable head is found in one iliac fossa and the breech in the other. The position of the back is readily identifiable. When the back is anterior, a hard resistance plane extends across the front of the abdomen. When it is posterior, irregular nodulations representing fetal small parts are felt through the abdominal wall.

On vaginal examination, in the early stages of labor, if the side of the thorax can be reached, it may be recognized by the "gridiron" feel of the ribs. With further dilation, the scapula and the clavicle are distinguished on opposite sides of the thorax. The position of the axilla indicates the side of the mother toward which the shoulder is directed.

Transverse lie was found once in 322 singleton deliveries (0.3 percent) at both the Mayo Clinic and the University of Iowa Hospital (Cruikshank, 1973; Johnson, 1964). This is remarkably similar to the incidence at Parkland Hospital of approximately 1 in 335 singleton fetuses.

Etiology

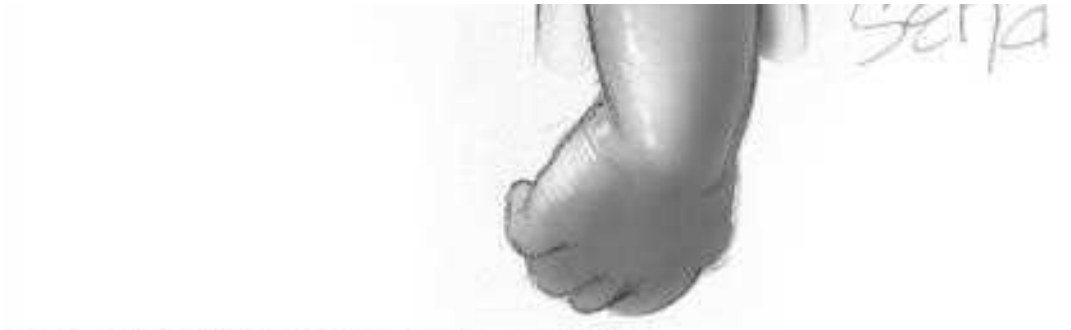
Some of the more common causes of transverse lie include: (1) abdominal wall relaxation from high parity, (2) preterm fetus, (3) placenta previa, (4) abnormal uterine anatomy, (5) hydramnios, and (6) contracted pelvis.

Women with four or more deliveries have a tenfold incidence of transverse lie compared with nulliparas. A relaxed and pendulous abdomen allows the uterus to fall forward, deflecting the long axis of the fetus away from the axis of the birth canal and into an oblique or transverse position. Placenta previa and pelvic contraction act similarly. A transverse or oblique lie occasionally develops in labor from an initial longitudinal position.

Mechanism of Labor

Spontaneous delivery of a fully developed newborn is impossible with a persistent transverse lie. After rupture of the membranes, if labor continues, the fetal shoulder is forced into the pelvis, and the corresponding arm frequently prolapses (Fig. 23-10). After some descent, the shoulder is arrested by the margins of the pelvic inlet. As labor continues, the shoulder is impacted firmly in the upper part of the pelvis. The uterus then contracts vigorously in an unsuccessful attempt to overcome the obstacle. With time, a retraction ring rises increasingly higher and becomes more marked. With this *neglected transverse lie,* the uterus will eventually rupture. Even without this complication, morbidity is increased because of the frequent association with placenta previa, the increased likelihood of cord prolapse, and the necessity for major operative efforts.

FIGURE 23-10
Neglected shoulder presentation. A thick muscular band forming a pathological retraction ring has developed just above the thin lower uterine segment. The force generated during a uterine contraction is directed centripetally at and above the level of the pathological retraction ring. This serves to stretch further and possibly to rupture the thin lower segment below the retraction ring.



If the fetus is small—usually <800 g—and the pelvis is large, spontaneous delivery is possible despite persistence of the abnormal lie. The fetus is compressed with the head forced against its abdomen. A portion of the thoracic wall below the shoulder thus becomes the most dependent part, appearing at the vulva. The head and thorax then pass through the pelvic cavity at the same time. The fetus, which is doubled upon itself and thus sometimes referred to as *conduplicato corpore*, is expelled.

Management

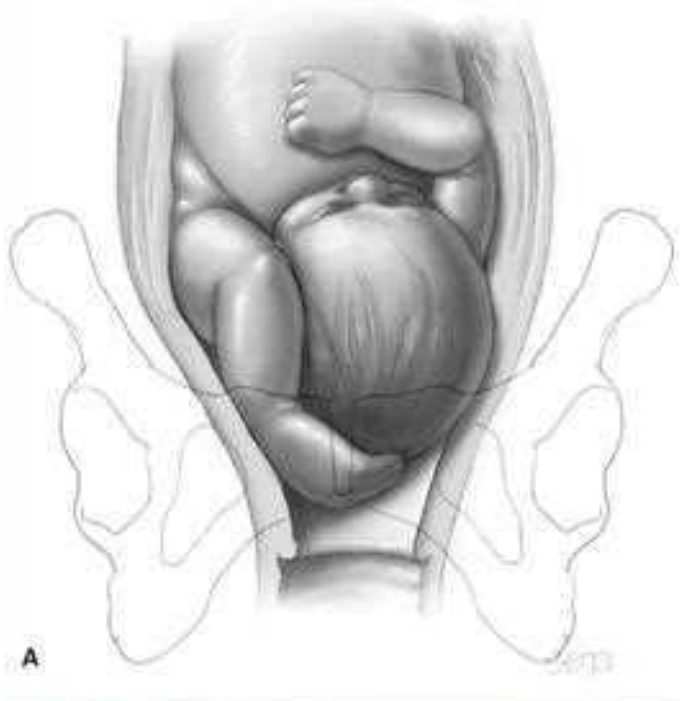
Active labor in a woman with a transverse lie is usually an indication for cesarean delivery. Before labor or early in labor, with the membranes intact, attempts at external version are worthwhile in the absence of other complications. If the fetal head can be maneuvered by abdominal manipulation into the pelvis, it should be held there during the next several contractions in an attempt to fix the head in the pelvis.

With cesarean delivery, because neither the feet nor the head of the fetus occupies the lower uterine segment, a low transverse incision into the uterus may lead to difficult fetal extraction. This is especially true of dorsoanterior presentations. Therefore, a vertical hysterotomy incision is often indicated.

Compound Presentation

With this, an extremity prolapses alongside the presenting part, and both present simultaneously in the pelvis (Fig. 23-11). Goplerud and Eastman (1953) identified a hand or arm prolapsed alongside the head once in every 700 deliveries. Much less common was prolapse of one or both lower extremities alongside a cephalic presentation or a hand alongside a breech. At Parkland Hospital, compound presentations were identified in only 68 of more than 70,000 singleton fetuses—an incidence of approximately 1 in 1000. Causes of compound presentations are conditions that prevent complete occlusion of the pelvic inlet by the fetal head, including preterm labor.

FIGURE 23-11
Compound presentation. **A.** The left hand is lying in front of the vertex. With further labor, the hand and arm may retract from the birth canal, and the head may then descend normally. **B.** Photograph of a small 34-week fetus with a compound presentation that delivered uneventfully with the hand presenting first. (Used with permission from Dr. Elizabeth Mosier.)



In most cases, the prolapsed part should be left alone, because most often it will not interfere with labor. If the arm is prolapsed alongside the head, the condition should be observed closely to ascertain whether the arm retracts out of the way with descent of the presenting part. If it fails to retract and if it appears to prevent descent of the head, the prolapsed arm should be pushed gently upward and the head simultaneously downward by fundal pressure.

In general, rates of perinatal mortality and morbidity are increased as a result of concomitant preterm delivery, prolapsed cord, and traumatic obstetrical procedures. Serious injury to the forearm is rare (Kwok, 2015; Tebes, 1999).

COMPLICATIONS WITH DYSTOCIA

Maternal Complications

Dystocia, especially if labor is prolonged, is associated with a higher incidence of several common obstetrical and neonatal complications. *Infection*, either intrapartum chorioamnionitis or postpartum pelvic infection, is more common with desultory and prolonged labors. *Postpartum hemorrhage* rates from atony are increased with prolonged and augmented labors. *Uterine tears with hysterotomy* also occur at greater incidence if the fetal head is impacted in the pelvis.

Uterine rupture is another risk. Abnormal thinning of the lower uterine segment creates a serious danger during prolonged labor, particularly in women of high parity and in those with a prior cesarean delivery. When disproportion is so pronounced that there is no engagement or descent, the lower uterine segment becomes increasingly stretched, and rupture may follow. In such cases, the normal *contraction ring* is usually exaggerated, like that shown in Figure 23-10.

Such pathological retraction rings are localized constrictions of the uterus that develop in association with prolonged obstructed labors. Seldom encountered today, the *pathological retraction ring of Bandl* is associated with marked stretching and thinning of the lower uterine segment. In contemporary practice, after birth of a

first twin, a pathological ring may still develop occasionally as an hourglass constriction of the uterus. The band may be seen clearly as a uterine indentation and signifies impending rupture of the lower uterine segment. The ring can sometimes be relaxed and delivery effected with appropriate general anesthesia, but occasionally prompt cesarean delivery offers a better prognosis for the second twin (Chap. 45, Vaginal Birth after Cesarean Delivery).

Fistula formation may result from dystocia, as the presenting part is firmly wedged into the pelvic inlet. Tissues of the birth canal lying between the leading part and the pelvic wall may be subjected to excessive pressure. Because of impaired circulation, necrosis can result and become evident several days after delivery as vesicovaginal, vesicocervical, or rectovaginal fistulas. Most often, pressure necrosis follows a very prolonged second stage. Such fistulas are rarely seen today except in undeveloped countries.

Pelvic floor injury during pregnancy and childbirth has gained recent attention. The pelvic floor is exposed to direct compression from the fetal head and to downward pressure from maternal expulsive efforts. These forces stretch and distend the pelvic floor, resulting in functional and anatomical alterations in the muscles, nerves, and connective tissues. Accumulating evidence suggests that such effects on the pelvic floor during childbirth can affect urinary or anal continence and pelvic support. These relationships are discussed in Chapter 30 (Cesarean Delivery Risks).

Lower extremity nerve injury in the mother can follow prolonged second-stage labor. Wong and colleagues (2003) reviewed neurological injury involving the lower extremities in association with labor and delivery. The most common mechanism is external compression of the common fibular (formerly common peroneal) nerve. This is usually caused by inappropriate leg positioning in stirrups, especially during prolonged second-stage labor. These and other injuries are discussed in Chapter 36 (Pain, Mood, and Cognition). Fortunately, symptoms resolve within 6 months of delivery in most women.

Perinatal Complications

Similar to the mother, the incidence of peripartum fetal sepsis rises with longer labors. *Caput succedaneum* and *molding* develop commonly and may be impressive (Fig. 22-16) (Buchmann, 2008). Mechanical trauma such as nerve injury, fractures, and cephalohematoma are also more frequent and are discussed further in Chapter 33 (Injuries of the Newborn).

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CHAPTER 24: Intrapartum Assessment

To study the forces exerted by labour, a rubber bag was inserted into the uterus which was connected with a manometer. In this way it was found that the intra-uterine pressure, in the intervals between the contractions, was represented by a column of mercury 20 millimeters high, 5 of which were due to the tonicity of the walls and 15 to its contents. During the pains, however, the mercury rose considerably, reaching a height of from 80 to 250 millimeters.

—J. Whitridge Williams (1903)

INTRODUCTION

Little is written in the first edition of this textbook concerning monitoring of the fetus during labor. Much later, periodic auscultation of the fetal heartbeat with a fetoscope was adopted. These practices were eclipsed in the late 1960s and early 1970s by the development of electronic fetal monitoring (Hon, 1958). It was hoped that the continuous graph-paper portrayal of the fetal heart rate was potentially diagnostic in assessing pathophysiological events affecting the fetus.

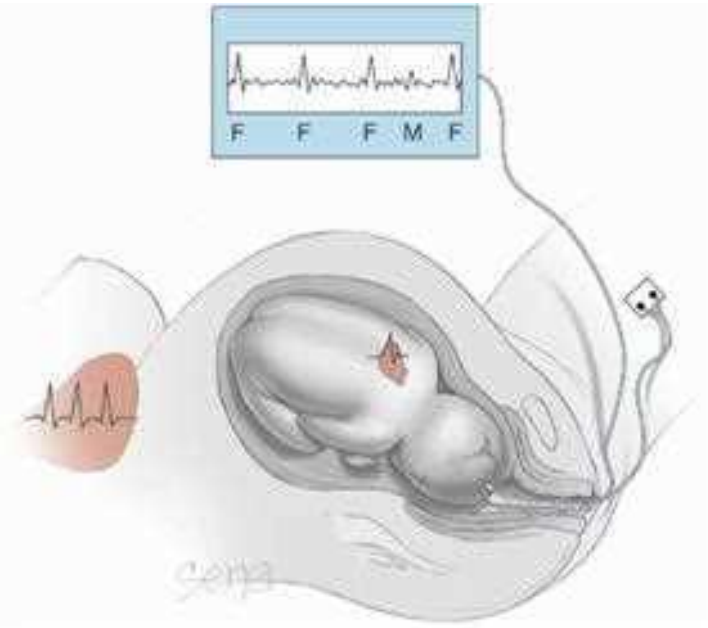
When first introduced, electronic fetal heart rate monitoring was used primarily in complicated pregnancies but gradually became used in most pregnancies. Now, more than 85 percent of all live births in the United States undergo electronic fetal monitoring (Ananth, 2013).

ELECTRONIC FETAL MONITORING

Internal (Direct) Electronic Monitoring

Direct fetal heart measurement is accomplished by attaching a bipolar spiral electrode directly to the fetus (Fig. 24-1). The wire electrode penetrates the fetal scalp, and the second pole is a metal wing on the electrode. The electrical fetal cardiac signal—P wave, QRS complex, and T wave—is amplified and fed into a cardiotachometer for heart rate calculation. The peak R-wave voltage is the portion of the fetal electrocardiogram (ECG) most reliably detected.

FIGURE 24-1
Internal electronic fetal monitoring. Schematic representation of a bipolar electrode attached to the fetal scalp for detection of fetal QRS complexes (F). Also shown is the maternal heart and corresponding electrical complex (M) that is detected.

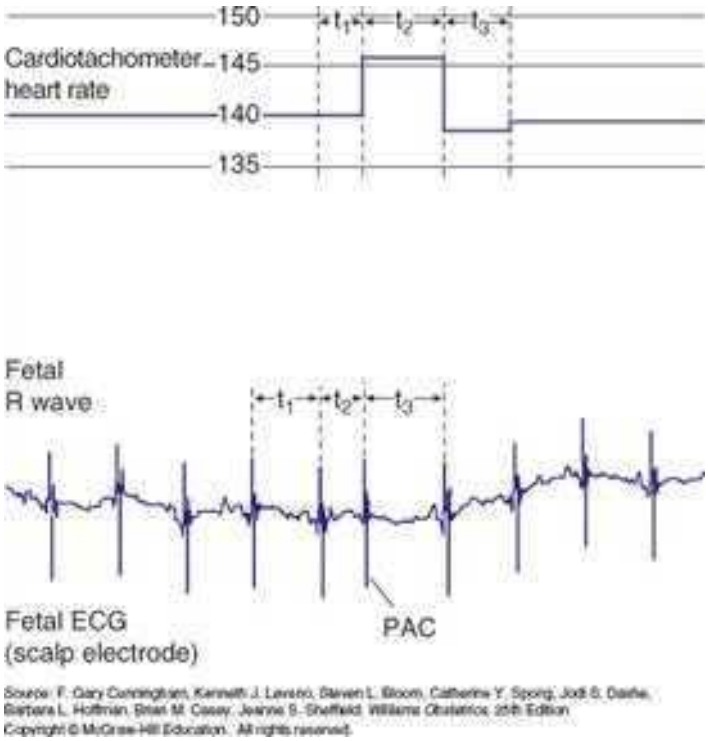


Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

An example of the method of fetal heart rate processing employed when a scalp electrode is used is shown in Figure 24-2. Time (t) in milliseconds between fetal R waves is fed into a cardiotachometer, where a new fetal heart rate is set with the arrival of each new R wave. As also shown in Figure 24-2, a premature atrial contraction is computed as a heart rate acceleration because the interval (t_2) is shorter than the preceding one (t_1). The phenomenon of continuous R-to-R wave fetal heart rate computation is known as *beat-to-beat variability.*

FIGURE 24-2

Schematic representation of fetal electrocardiographic signals used to compute continuing beat-to-beat heart rate with scalp electrodes. Time intervals (t_1, t_2, t_3) in milliseconds between successive fetal R waves are used by a cardiotachometer to compute instantaneous fetal heart rate. ECG = electrocardiogram; PAC = premature atrial contraction.



Electrical cardiac complexes detected by the electrode include those generated by the mother. However, the amplitude of the maternal ECG signal is diminished when recorded through the fetal scalp electrode and is masked by the fetal ECG. Shown in Figure 24-3 are simultaneous recordings of maternal chest wall ECG signals and fetal scalp electrode ECG signals. This fetus is experiencing premature atrial contractions, which cause the cardiotachometer to rapidly and erratically seek new heart rates, resulting in the "spiking" shown in the standard fetal monitor tracing. Importantly, when the fetus is dead, the maternal R waves are still detected by the scalp electrode as the next best signal and are counted by the cardiotachometer (Fig. 24-4).

FIGURE 24-3

The top tracing shows standard fetal monitor tracing of heart rate using a fetal scalp electrode. Spiking of the fetal rate in the monitor tracing is due to premature atrial contractions. The second panel displays accompanying contractions. The bottom two tracings represent cardiac electrical complexes detected from fetal scalp and maternal chest wall electrodes. ECG = electrocardiogram; F = fetus; M = mother; PAC = fetal premature atrial contraction.

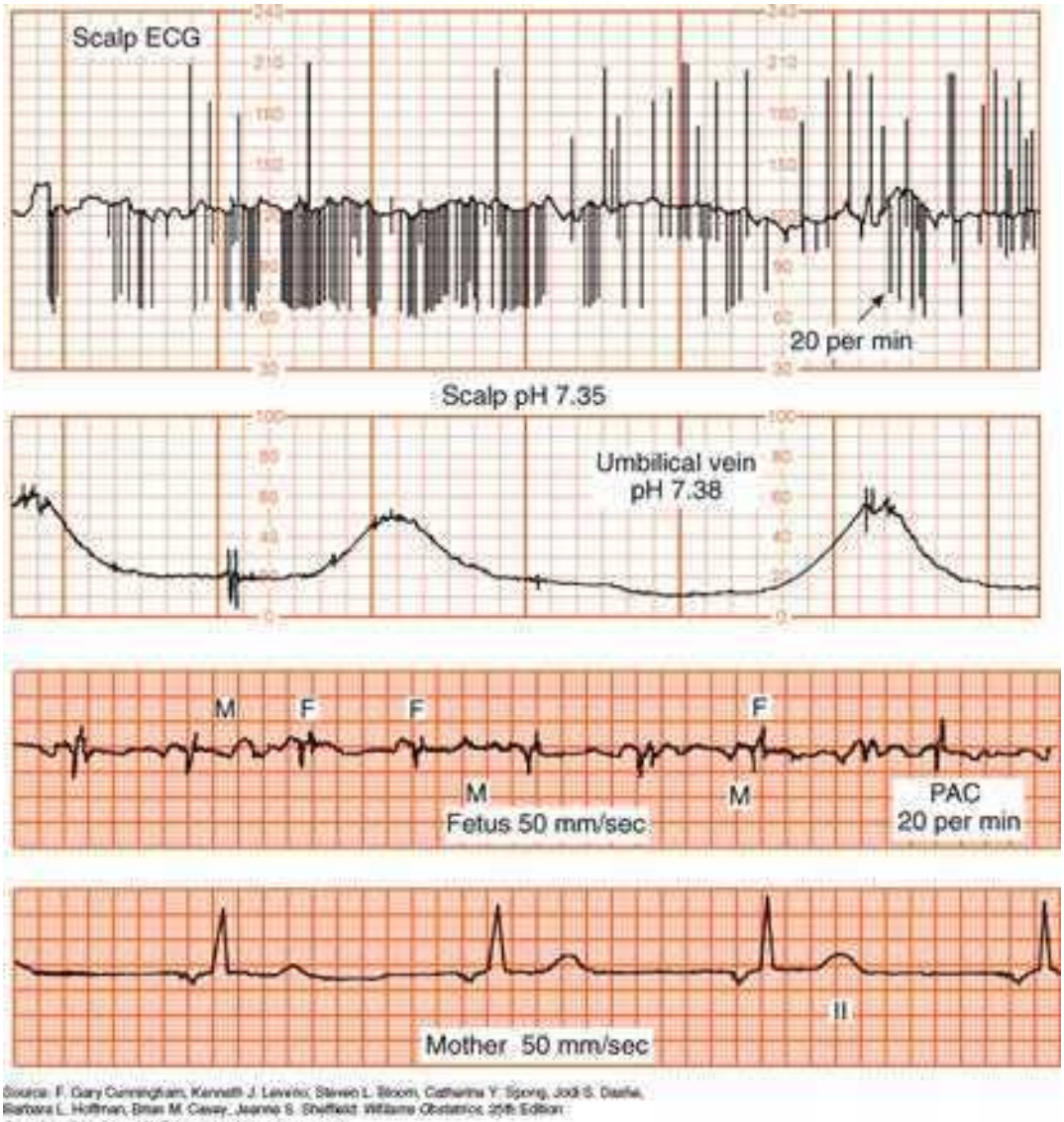
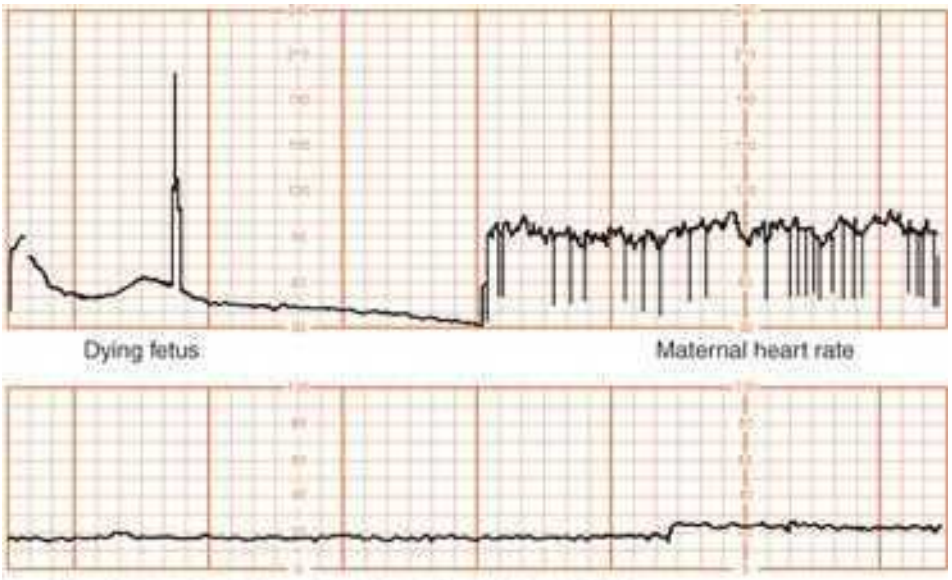


FIGURE 24-4

Placental abruption. In the upper panel, the fetal scalp electrode first detected the heart rate of the dying fetus. After fetal death, the maternal electrocardiogram complex is detected and recorded. The second panel displays an absence of uterine contractions.



External (Indirect) Electronic Monitoring

Although membrane rupture may be avoided, external monitoring does not provide the precision of fetal heart rate measurement afforded by internal monitoring (Nunes, 2014). In some women—for example, those who are obese—external monitoring may be difficult (Brocato, 2017).

With external monitoring, the fetal heart rate is detected through the maternal abdominal wall using the *ultrasound Doppler principle*. Ultrasound waves undergo a shift in frequency as they are reflected from moving fetal heart valves and from pulsatile blood ejected during systole (Chap. 10, Doppler). The unit consists of a transducer that emits ultrasound and a sensor to detect a shift in frequency of the reflected sound. The transducer is placed on the maternal abdomen at a site where fetal heart action is best detected. A coupling gel must be applied because air conducts ultrasound waves poorly. The device is held in position by an elastic belt. Correct positioning enhances differentiation of fetal cardiac motion from maternal arterial pulsations (Neilson, 2008).

Ultrasound Doppler signals are edited electronically before fetal heart rate data are printed onto monitor paper. Reflected ultrasound signals from moving fetal heart valves are analyzed through a microprocessor that compares incoming signals with the most recent previous signal. This process, called *autocorrelation*, is based on the premise that the fetal heart rate has regularity, whereas "noise" is random and without regularity. Several fetal heart motions must be deemed electronically acceptable by the microprocessor before the fetal heart rate is printed. Such electronic editing has greatly improved the tracing quality of the externally recorded fetal heart rate. Other features of current fetal monitors include the capability to monitor twin fetuses, monitor concurrent maternal heart rate, display the fetal ECG, and record maternal pulse oximetry values. Many fetal monitors are capable of interfacing with archival storage systems, which obviates maintaining actual paper tracings.

Technological advances now allow fetal heart rate monitoring from a remote, centralized location. Theoretically, the ability to monitor several patients simultaneously was hoped to improve neonatal outcomes. That said, only one study on centralized fetal monitoring has been reported. Anderson and colleagues (2011) measured the ability of 12 individuals to detect critical signals in fetal heart rate tracings on one, two, or four monitors. The results showed that detection accuracy declined as the number of displays increased.

Fetal Heart Rate Patterns

The interpretation of fetal heart rate patterns can be problematic without definitions and nomenclature. In one example, Blackwell and colleagues (2011) asked three Maternal-Fetal Medicine specialists to independently interpret 154 fetal heart rate tracings. Interobserver agreement was poor for the most ominous tracings and moderate for less severe patterns. The National Institute of Child Health and Human Development (NICHD) Research Planning Workshop (1997) brought together investigators with expertise in the field to propose standardized, unambiguous definitions for interpretation of fetal heart rate patterns during labor. This workshop reconvened in 2008. The definitions proposed as a result of this second workshop are used in this chapter and have been adopted by the American College of Obstetricians and Gynecologists (2017a) (Table 24-1). Importantly, interpretation of electronic fetal heart rate data is based on the visual pattern of the heart rate as portrayed on chart recorder graph paper. Thus, the choice of vertical and horizontal scaling greatly affects the appearance of the fetal heart rate. Scaling factors recommended by the NICHD Workshop are 30 beats per minute (beats/min or bpm) per vertical cm (range, 30 to 240 bpm) and 3 cm/min chart recorder paper speed. Fetal heart rate variation is falsely displayed at the slower 1 cm/min paper speed compared with that of the smoother baseline recorded at 3 cm/min. Thus, pattern recognition can be considerably distorted depending on the scaling factors used.

TABLE 24-1

Electronic Fetal Monitoring Definitions

Pattern	Definition
Baseline	• The mean FHR rounded to increments of 5 bpm during a 10-min segment, excluding: —Periodic or episodic changes —Periods of marked FHR variability —Segments of baseline that differ by more than 25 bpm • The baseline must be for a minimum of 2 min in any 10-min segment or the baseline for that time period is indeterminate. In this case, one may refer to the prior 10-min window for determination of baseline. • Normal FHR baseline: 110–160 bpm • Tachycardia: FHR baselines is greater than 160 beats per minute • Bradycardia: FHR baseline is less than 110 beats per minute
Baseline variability	• Fluctuations in the baseline FHR that are irregular in amplitude and frequency • Variability is visually quantified as the amplitude of peak-to-trough in beats per minute —Absent: amplitude range undetectable —Minimal: amplitude range detectable but 5 beats per minutes or fewer —Moderate (normal): amplitude range 6–25 beats per minute —Marked: amplitude range greater than 25 beats per minute
Acceleration	• A visually apparent abrupt increase (onset to peak in less than 30 seconds) in the FHR • At 32 weeks of gestation and beyond, an acceleration has a peak of 15 bpm or more above baseline, with a duration of 15 sec or more but less than 2 minutes from onset to return • Before 32 weeks, an acceleration has a peak of 10 bpm or more above baseline, with a duration of 10 seconds or more but less than 2 minutes from onset to return • Prolonged acceleration lasts 2 minutes or more but less than 10 minutes in duration • If an acceleration lasts 10 minutes or longer, it is a baseline change
Early deceleration	• Visually apparent usually symmetrical gradual decrease and return of the FHR associated with a uterine contraction • A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or more • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The nadir of the deceleration occurs at the same time as the peak of the contraction • In most cases the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively
Late deceleration	• Visually apparent usually symmetrical gradual decrease and return of the FHR associated with a uterine contraction • A gradual FHR decrease is defined as from the onset to the FHR nadir of 30 seconds or more • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction • In most cases the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively
Variable deceleration	• Visually apparent abrupt decrease in FHR • An abrupt FHR decrease is defined as from the onset of the deceleration to the beginning of the FHR nadir of less than 30 seconds • The decrease in FHR is calculated from the onset to the nadir of the deceleration • The decrease in FHR is 15 beats per minute or greater, lasting 15 seconds or greater, and less than 2 minutes in duration • When variable decelerations are associated with uterine contraction, their onset, depth, and duration commonly vary with successive uterine contractions
Prolonged deceleration	• Visually apparent decrease in the FHR below the baseline • Decrease in FHR from the baseline that is 15 beats per minute or more, and less than 2 minutes in duration • If a deceleration last 10 minutes or longer, it is a baseline change

Pattern	Definition
Sinusoidal pattern	• Visually apparent, smooth, sine wave-line undulating pattern in FHR baseline with a cycle frequency of 3–5 per minute which persists for 20 minutes or more

FHR = fetal heart rate.

Data from Macones, 2008.

Baseline Fetal Heart Activity

This refers to the modal characteristics that prevail apart from periodic accelerations or decelerations associated with uterine contractions. Descriptive characteristics of baseline fetal heart activity include *rate, beat-to-beat variability, fetal arrhythmia*, and distinct patterns such as *sinusoidal* or *saltatory* fetal heart rates.

Rate

With increasing fetal maturation, the heart rate decreases. This continues postnatally such that the average rate is 85 bpm by age 8 years (Tintinalli, 2016). Pillai and James (1990) reported that the baseline fetal heart rate declined an average of 24 bpm between 16 weeks' gestation and term, or approximately 1 bpm per week. This normal gradual slowing of the fetal heart rate is thought to correspond to maturation of parasympathetic (vagal) heart control (Renou, 1969).

The baseline fetal heart rate is the approximate mean rate rounded to increments of 5 bpm during a 10-minute tracing segment. In any 10-minute window, the minimum interpretable baseline duration must be at least 2 minutes. If the baseline fetal heart rate is less than 110 bpm, it is termed *bradycardia.* If the baseline rate is greater than 160 bpm, it is called *tachycardia.* The average fetal heart rate is considered the result of tonic balance between *accelerator* and *decelerator* influences on pacemaker cells. In this concept, the sympathetic system is the accelerator influence, and the parasympathetic system is the decelerator factor mediated by vagal slowing of heart rate (Dawes, 1985). Heart rate also is under the control of arterial chemoreceptors such that both hypoxia and hypercapnia can modulate rate. More severe and prolonged hypoxia, with a rising blood lactate level and severe metabolic acidemia, induces a prolonged fall in heart rate (Thakor, 2009).

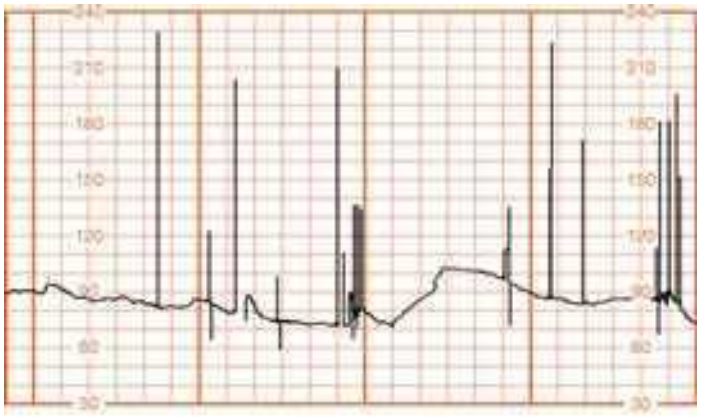
Bradycardia

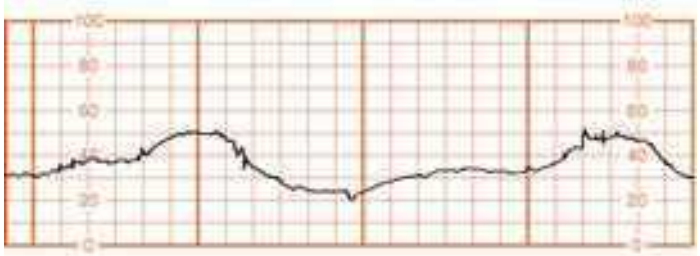
In the third trimester, the normal mean baseline fetal heart rate has generally been accepted to range between 120 and 160 bpm. But, pragmatically, a rate between 100 and 119 bpm, in the absence of other changes, usually is not considered to represent fetal compromise. Such low but potentially normal baseline heart rates also have been attributed to head compression from occiput posterior or transverse positions, particularly during second-stage labor (Young, 1976). Such mild bradycardias were observed in 2 percent of monitored pregnancies and averaged approximately 50 minutes in duration. Freeman and associates (2003) have concluded that bradycardia within the range of 80 to 120 bpm and with good variability is reassuring. Interpretation of rates less than 80 bpm is problematic, and such rates generally are considered nonreassuring.

Some causes of fetal bradycardia include congenital heart block and serious fetal compromise (Jaeggi, 2008; Larma, 2007). Figure 24-5 shows bradycardia in a fetus dying from placental abruption. Maternal hypothermia under general anesthesia for repair of a cerebral aneurysm or during maternal cardiopulmonary bypass for open-heart surgery can also cause fetal bradycardia. Sustained fetal bradycardia in the setting of severe pyelonephritis and maternal hypothermia also has been reported (Hankins, 1997). Involved fetuses apparently are not harmed by several hours of such bradycardia.

FIGURE 24-5

Fetal bradycardia measured with a scalp electrode (*upper panel*) in a pregnancy complicated by placental abruption and subsequent fetal death. Concurrent uterine contractions are shown in the lower panel.





Tachycardia

Fetal tachycardia is defined as a baseline heart rate greater than 160 bpm. The most common explanation for fetal tachycardia is maternal fever from chorioamnionitis, although fever from any source can produce this. In some cases, fetal tachycardia may precede overt maternal fever (Gilstrap, 1987). Fetal tachycardia caused by maternal infection typically is not associated with fetal compromise unless there are associated periodic heart rate changes or fetal sepsis.

Other causes of fetal tachycardia include fetal compromise, cardiac arrhythmias, and maternal administration of parasympathetic inhibiting (atropine) or sympathomimetic (terbutaline) drugs. Prompt relief of the compromising event, such as correction of maternal hypotension caused by epidural analgesia, can result in fetal recovery. The key feature to distinguish fetal compromise in association with tachycardia seems to be concomitant heart rate decelerations.

Wandering Baseline

This baseline rate is unsteady and “wanders” between 120 and 160 bpm (Freeman, 2003). This rare finding is suggestive of a neurologically abnormal fetus and may occur as a preterminal event. In contrast, changes of the normal baseline are common in labor and do not predict morbidity (Yang, 2017).

Beat-to-Beat Variability

Baseline variability is an important index of cardiovascular function and appears to be regulated largely by the autonomic nervous system (Kozuma, 1997). That is, a sympathetic and parasympathetic “push and pull” mediated via the sinoatrial node produces moment-to-moment or beat-to-beat oscillation of the baseline heart rate. Such heart rate change is defined as baseline variability. Variability can be further analyzed over the short term and long term, although these terms have fallen out of use. *Short-term variability* reflects the instantaneous change in fetal heart rate from one beat—or R wave—to the next. This variability is a measure of the time interval between cardiac systoles (Fig. 24-6). Short-term variability can most reliably be determined to be normally present only when electrocardiac cycles are measured directly with a scalp electrode. *Long-term variability* is used to describe the oscillatory changes during 1 minute and result in the waviness of the baseline (Fig. 24-7). The normal frequency of such waves is three to five cycles per minute (Freeman, 2003).

FIGURE 24-6

Schematic representation of short-term beat-to-beat variability measured by a fetal scalp electrode. t = time interval between successive fetal R waves. (Adapted with permission from Klavan M, Laver AT, Boscola MA: Clinical concepts of fetal heart rate monitoring. Waltham, Hewlett-Packard, 1977.)

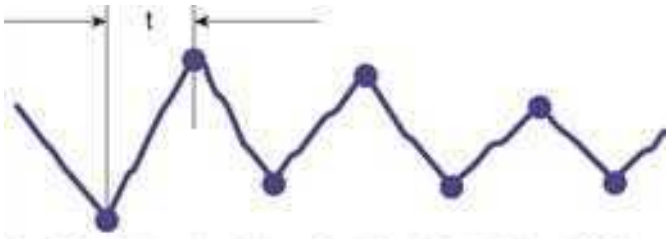
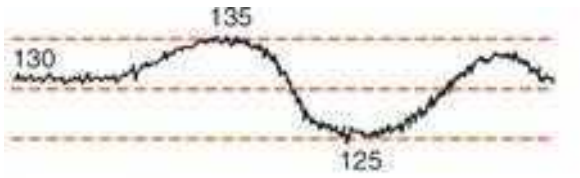


FIGURE 24-7

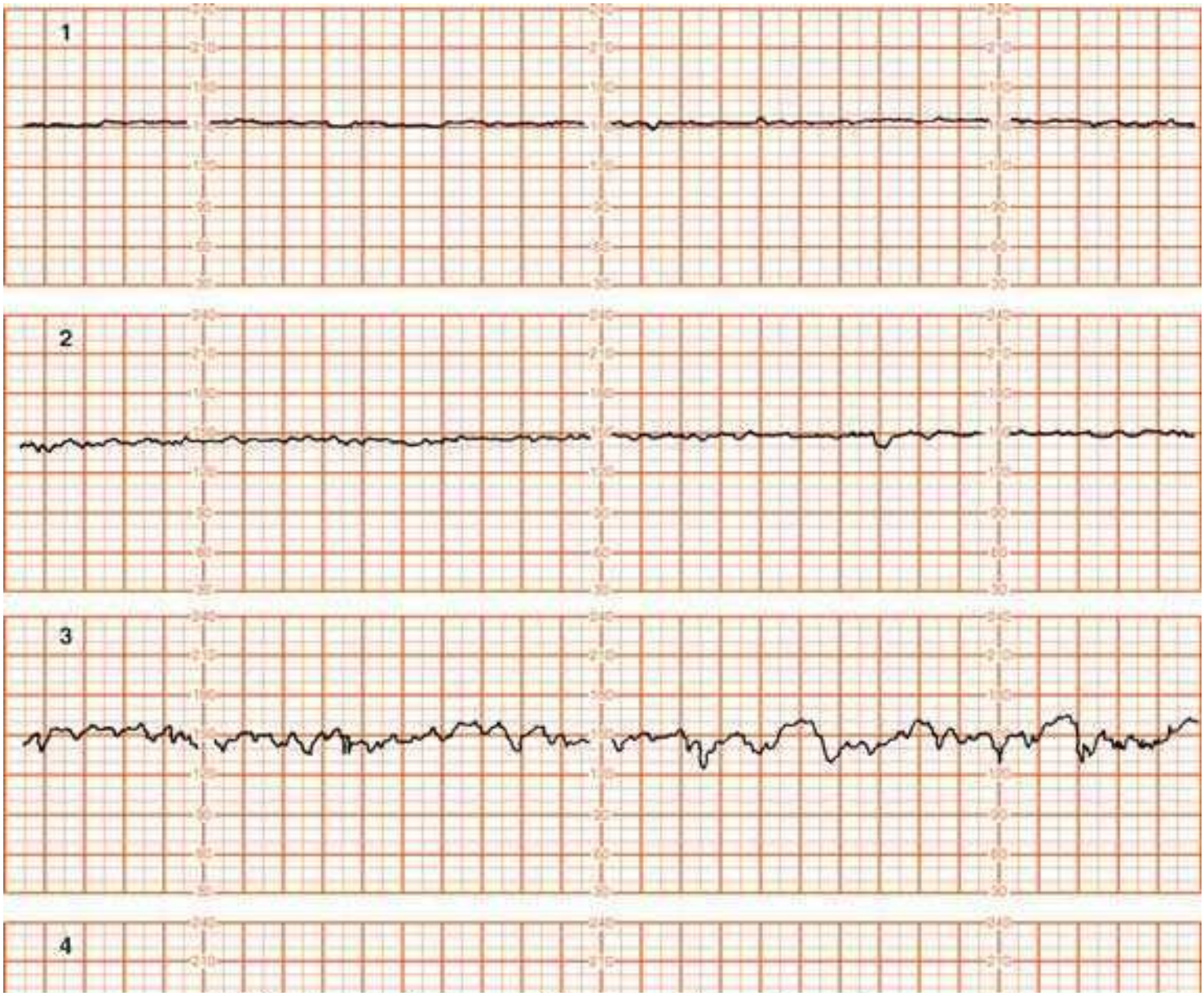
Schematic representation of long-term beat-to-beat variability of the fetal heart rate ranging between 125 and 135 bpm. (Adapted with permission from Klavan M, Laver AT, Boscola MA: Clinical concepts of fetal heart rate monitoring. Waltham, Hewlett-Packard, 1977.)

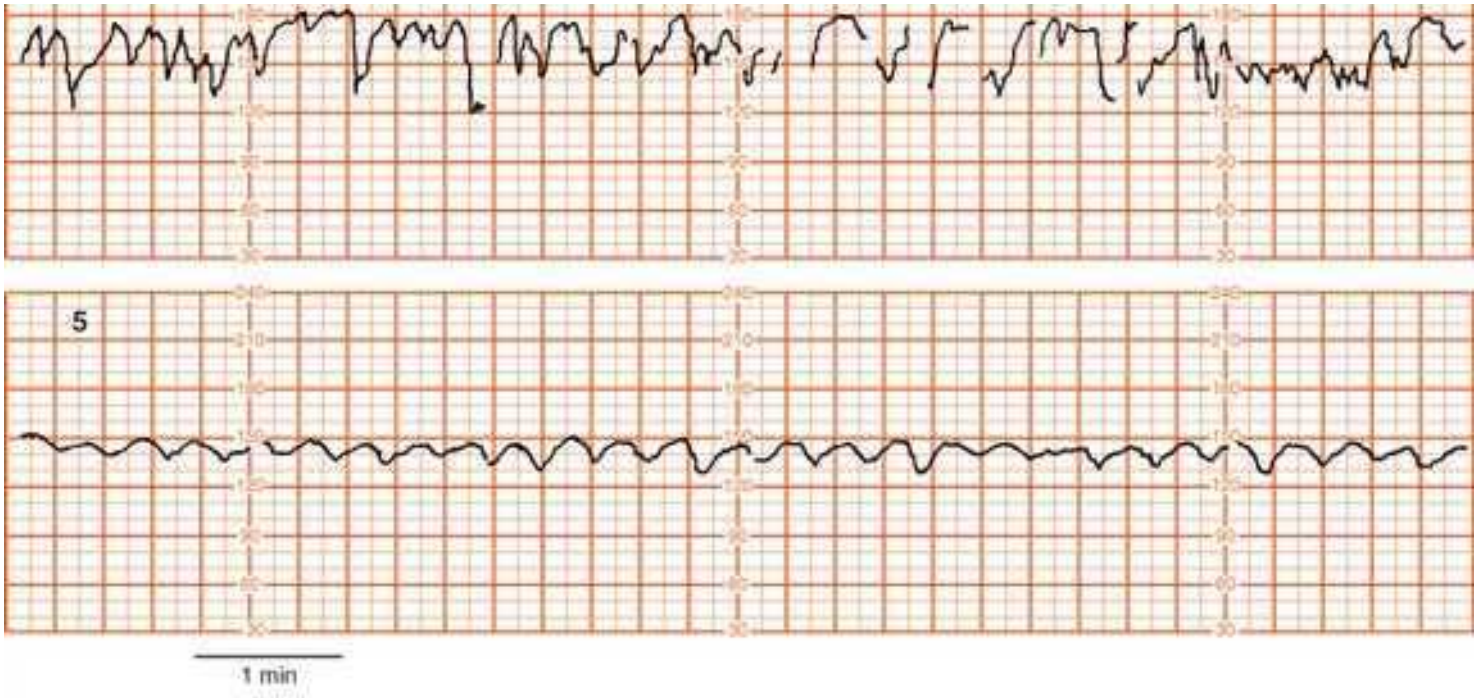


It should be recognized that precise quantitative analysis of both short- and long-term variability presents several frustrating problems due to technical and scaling factors (Parer, 1985). Thus, most clinical interpretation is based on visual analysis with subjective judgment of the smoothness or flatness of the baseline. According to Freeman and associates (2003), no evidence suggests that the distinction between short- and long-term variability has clinical relevance. Similarly, the NICHD Workshop (1997) did not recommend differentiating short- and long-term variability because in actual practice they are visually determined as a unit. The workshop panel defined baseline variability as those baseline fluctuations of two cycles per minute or greater. They recommended the criteria shown in Figure 24-8 for quantification of variability. Normal beat-to-beat variability was accepted to be 6 to 25 bpm.

FIGURE 24-8

Grades of baseline fetal heart rate variability shown in the following five panels. **1.** Undetectable, absent variability. **2.** Minimal variability, ≤5 bpm. **3.** Moderate (normal) variability, 6 to 25 bpm. **4.** Marked variability, >25 bpm. **5.** Sinusoidal pattern. This differs from variability in that it has a smooth, sinelike pattern of regular fluctuation and is excluded in the definition of fetal heart rate variability. (Adapted with permission from National Institute of Child Health and Human Development Research Planning Workshop, 1997.)





Increased Variability

Several physiological and pathological processes can affect beat-to-beat variability. Greater variability accompanies fetal breathing and body movements (Dawes, 1981; Van Geijn, 1980). Pillai and James (1990) reported increased baseline variability with advancing gestation. Up to 30 weeks, baseline characteristics were similar during both fetal rest and activity. After 30 weeks, fetal inactivity was associated with diminished baseline variability, but fetal activity enhanced it. Last, the baseline fetal heart rate becomes more physiologically fixed (less variable) as the rate rises. This phenomenon presumably reflects less cardiovascular physiological wandering as beat-to-beat intervals shorten with a higher heart rate.

Decreased Variability

A common cause of diminished beat-to-beat variability is administration of analgesic drugs during labor (Chap. 25, Analgesia and Sedation During Labor). Various central nervous system depressant drugs can cause transient diminished beat-to-beat variability. Included are narcotics, barbiturates, phenothiazines, tranquilizers, and general anesthetics. Corticosteroids also dampen variability (Knaven, 2017). As one specific example, variability regularly diminishes within 5 to 10 minutes following intravenous meperidine administration, and the effects may last up to 60 minutes or longer (Hill, 2003; Petrie, 1993). Butorphanol given intravenously has similar effects (Schucker, 1996). And, chronically administered buprenorphine suppresses fetal heart rate and movement (Jansson, 2017).

Magnesium sulfate, widely used in the United States for tocolysis or management of hypertensive gravidas, is associated with diminished beat-to-beat variability. In a study of nearly 250 term gestations, magnesium sulfate administration led to decreased variability but without evidence of adverse neonatal effects (Duffy, 2012). Others have echoed these findings (Hallak, 1999; Lin, 1988). With magnesium sulfate tocolysis of preterm labor, variability was also diminished in most reviewed studies (Nensi, 2014; Verdurmen, 2017).

Of greatest concern, diminished beat-to-beat variability can be an ominous sign indicating a seriously compromised fetus. Paul and coworkers (1975) reported that loss of variability in combination with decelerations was associated with *fetal acidemia*. Decreased variability was defined as an excursion of the baseline of ≤5 bpm (see Fig. 24-8). Severe *maternal acidemia* can also lower fetal beat-to-beat variability, for example, in a mother with diabetic ketoacidosis.

According to Dawes (1985), metabolic acidemia that causes depression of the fetal brainstem or the heart itself creates the loss of variability. Thus, diminished beat-to-beat variability, when it reflects fetal compromise, likely reflects acidemia rather than hypoxia. Indeed, mild degrees of fetal hypoxemia have been reported actually to *enhance* variability, at least initially (Murotsuki, 1997).

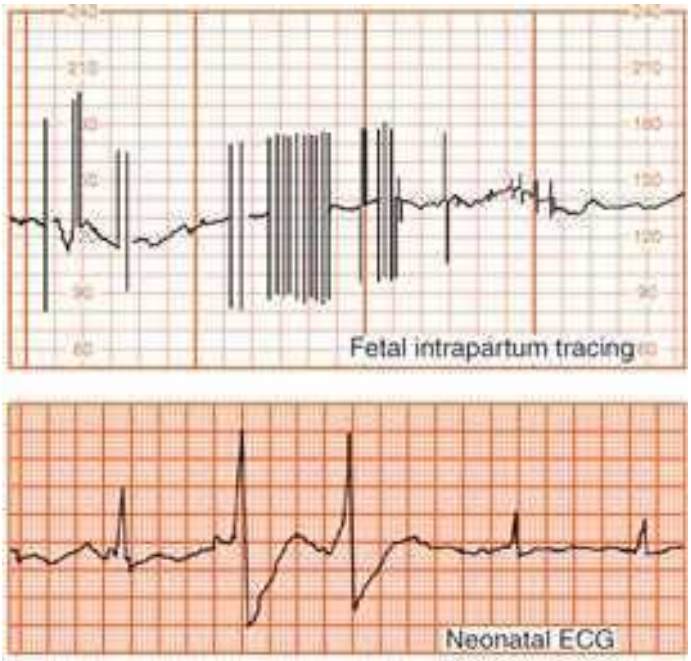
Reduced baseline heart rate variability is the single most reliable sign of fetal compromise. Smith and coworkers (1988) performed a computerized analysis of beat-to-beat variability in growth-restricted fetuses before labor. Diminished variability (≤4.2 bpm) maintained for 1 hour was diagnostic of developing acidemia and imminent fetal death. In contrast, Samueloff and associates (1994) evaluated variability in 2200 consecutive deliveries and concluded that variability by itself could not be used as the only indicator of fetal well-being. They also warned that good variability should not be interpreted as necessarily reassuring. Blackwell and associates (2011) found that even experts often disagreed as to whether variability was absent or minimal (≤5 bpm).

In sum, beat-to-beat variability is affected by fetal physiology, and its meaning differs depending on the clinical setting. Decreased variability in the absence of decelerations is unlikely to reflect fetal hypoxia (Davidson, 1992). A persistently flat fetal heart rate baseline—absent variability—within the normal baseline rate range and without decelerations may reflect a previous fetal insult that has resulted in neurological damage (Freeman, 2003).

Cardiac Arrhythmia

When fetal cardiac arrhythmias are first suspected using electronic monitoring, findings can include baseline bradycardia, tachycardia, or most commonly in our experience, *abrupt baseline spiking* (Fig. 24-9). An arrhythmia can only be documented, practically speaking, when scalp electrodes are used. Some fetal monitors can be adapted to output the scalp electrode signals into an ECG recorder. Because only a single lead is obtained, analysis and interpretation of rhythm and rate disturbances are severely limited.

FIGURE 24-9
Internal fetal monitoring at term demonstrated occasional abrupt beat-to-beat fetal heart rate spiking due to erratic extrasystoles shown in the corresponding fetal electrocardiogram. The normal newborn was delivered spontaneously and had normal cardiac rhythm in the nursery.



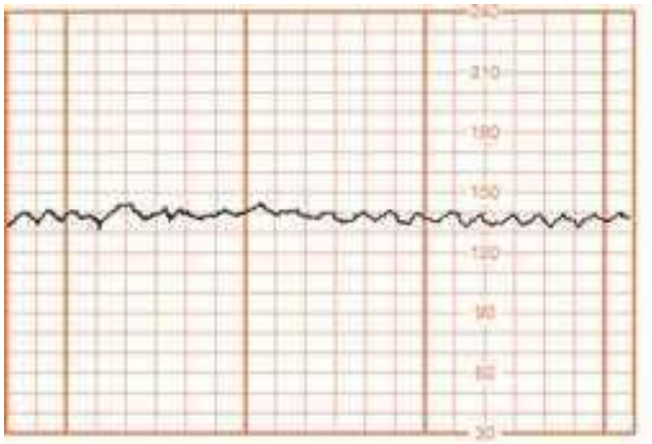
Southall and associates (1980) studied fetal cardiac rate and rhythm disturbances in 934 normal pregnancies between 30 and 40 weeks. Arrhythmias, episodes of bradycardia <100 bpm, or tachycardia >180 bpm were encountered in 3 percent. Most supraventricular arrhythmias are of little significance during labor unless there is coexistent fetal heart failure as evidenced by hydrops. Many supraventricular arrhythmias disappear in the immediate neonatal period, although some are associated with structural cardiac defects (Api, 2008). Intermittent baseline bradycardia is frequently due to congenital heart block. Conduction defects, most often complete atrioventricular (AV) block, usually are found in association with maternal connective tissue diseases (Chap. 59, Perinatal Mortality and Morbidity). Antepartum evaluation of the fetus with an identified arrhythmia and potential treatment options are discussed in Chapter 16 (Tachyarrhythmias).

Most fetal arrhythmias without comorbid fetal hydrops are inconsequential during labor, but they may hinder interpretation of fetal heart rate tracings. Sonographic evaluation of fetal anatomy and echocardiography can be useful. Generally, in the absence of fetal hydrops, neonatal outcome is not measurably improved by pregnancy intervention. At Parkland Hospital, intrapartum fetal cardiac arrhythmias, especially those associated with clear amnionic fluid, are typically managed conservatively.

Sinusoidal Heart Rate

A true sinusoidal pattern such as that shown in panel 5 of Figure 24-8 can be observed with fetal intracranial hemorrhage, with severe fetal asphyxia, and with severe fetal anemia. The last may stem from anti-D alloimmunization, fetomaternal hemorrhage, twin-twin transfusion syndrome, fetal parvoviral infection, or vasa previa with bleeding. Insignificant sinusoidal patterns have been reported following administration of meperidine, morphine, alphaprodine, and butorphanol (Angel, 1984; Egley, 1991; Epstein, 1982). Shown in Figure 24-10 is a sinusoidal pattern seen with maternal meperidine administration. An important characteristic of this pattern when due to narcotics is the sine frequency of 6 cycles per minute. A sinusoidal pattern also has been described with chorioamnionitis, fetal distress, and umbilical cord occlusion (Murphy, 1991). Young (1980a) and Johnson (1981) with their coworkers concluded that intrapartum sinusoidal fetal heart patterns were not generally associated with fetal compromise. Thus, management is usually dictated by the clinical setting. Modanlou and Freeman (1982), based on their extensive review, proposed adoption of a strict definition:

FIGURE 24-10
Sinusoidal fetal heart rate pattern associated with maternal intravenous meperidine administration. Sine waves are occurring at a rate of 6 cycles per minute.



1. Stable baseline heart rate of 120 to 160 bpm with regular oscillations
2. Amplitude of 5 to 15 bpm (rarely greater)
3. Long-term variability frequency of 2 to 5 cycles per minute
4. Fixed or flat short-term variability
5. Oscillation of the sinusoidal waveform above or below a baseline
6. Absent accelerations.

Although these criteria were selected to define a sinusoidal pattern that is most likely ominous, they observed that the pattern associated with alphaprodine is indistinguishable. Other investigators have proposed a classification of sinusoidal heart rate patterns into mild—amplitude 5 to 15 bpm, intermediate—16 to 24 bpm, and major—≥25 bpm to quantify fetal risk (Murphy, 1991; Neesham, 1993).

Some have defined intrapartum sine wavelike baseline variation with periods of acceleration as *pseudosinusoidal.* Murphy and colleagues (1991) reported that pseudosinusoidal patterns were seen in 15 percent of monitored labors. Mild pseudosinusoidal patterns were associated with use of meperidine and epidural analgesia. Intermediate pseudosinusoidal patterns were linked to fetal sucking or transient episodes of fetal hypoxia caused by umbilical cord compression. Egley and associates (1991) reported that 4 percent of fetuses demonstrated sinusoidal patterns transiently during normal labor. These authors observed patterns persisting for up to 90 minutes in some cases.

The pathophysiology of sinusoidal patterns is unclear, in part due to various definitions. There seems to be general agreement that *antepartum* sine wave baseline undulations portend severe fetal anemia. Still, few anti-D alloimmunized fetuses develop this pattern (Nicolaides, 1989). The sinusoidal pattern has been reported to develop or disappear after fetal transfusion (Del Valle, 1992; Lowe, 1984). Ikeda and associates (1999) proposed that the pattern is related to waves of arterial blood pressure, reflecting oscillations in the baroreceptor-chemoreceptor feedback mechanism.

Periodic Fetal Heart Rate Changes

These refer to deviations from baseline that are temporally related to uterine contractions. *Acceleration* refers to a rise in fetal heart rate above baseline, and *deceleration* is a drop below the baseline rate. The nomenclature most commonly used in the United States is based on the *timing* of the deceleration in relation to contractions—thus, *early, late,* or *variable*. The waveform of these decelerations is also significant for pattern recognition. In early and late decelerations, the slope of fetal heart rate change is gradual, resulting in a curvilinear and uniform or symmetrical waveform. With variable decelerations, the slope of fetal heart rate change is abrupt and erratic, giving the waveform a jagged appearance. The NICHD Workshop (1997) proposed that decelerations be defined as *recurrent* if they accompanied ≥50 percent of contractions in any 20-minute period.

Another system now used less often to describe decelerations is based on the pathophysiological events considered most likely to underlie the pattern. In this system, early decelerations are termed *head compression,* late decelerations are termed *uteroplacental insufficiency,* and variable decelerations are *cord compression patterns.*

Accelerations

These are abrupt heart rate increases above the fetal heart rate baseline and defined by an onset-to-peak rise within 30 seconds (American College of Obstetricians and Gynecologists, 2017a). At 32 weeks' gestation and beyond, an acceleration has a peak ≥15 bpm above baseline. Its duration is ≥15 sec but <2 minutes from onset to baseline return (see Table 24-1). Before 32 weeks, a peak ≥10 bpm for 10 seconds to 2 minutes is considered normal. Prolonged acceleration is defined as ≥2 minutes but <10 minutes.

According to Freeman and coworkers (2003), accelerations most often occur antepartum, in early labor, and in association with variable decelerations. Proposed mechanisms for intrapartum accelerations include fetal movement, stimulation by uterine contractions, umbilical cord occlusion, fetal stimulation during pelvic examination, scalp blood sampling, and acoustic stimulation. Accelerations are common during labor. These are virtually always reassuring and almost always confirm that the fetus is not acidemic at that time.

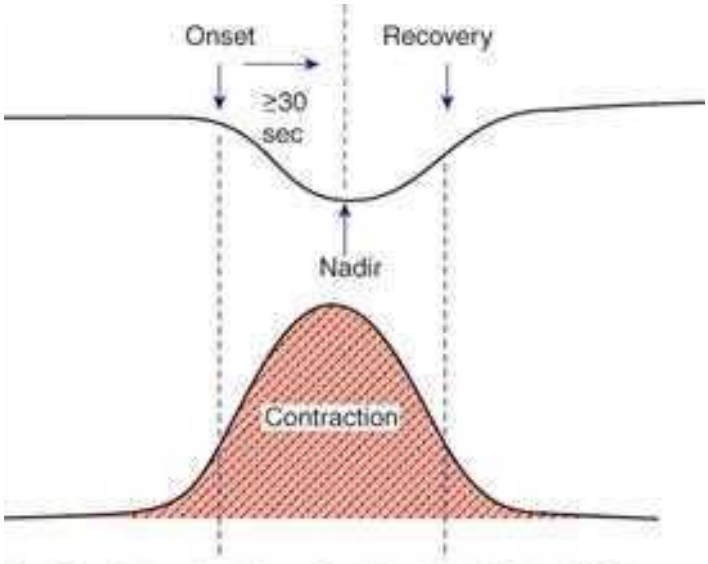
As with beat-to-beat variability, accelerations represent intact neurohormonal cardiovascular control mechanisms linked to fetal behavioral states. Krebs and colleagues (1982) analyzed electronic heart rate tracings in nearly 2000 fetuses and found sporadic accelerations during labor in 99.8 percent. Fetal heart rate accelerations during the first or last 30 minutes during labor, or both, were a favorable sign for fetal well-being. The absence of such accelerations during labor, however, is not necessarily an unfavorable sign unless coincidental with other nonreassuring changes. The chance of acidemia in the fetus that fails to respond to stimulation in the presence of an otherwise nonreassuring pattern approximates 50 percent (Clark, 1984; Smith, 1986).

Early Deceleration

This physiological response shows a gradual fetal heart rate decline and then return to baseline associated with a contraction (Fig. 24-11). Freeman and associates (2003) defined early decelerations as those generally seen in active labor between 4 and 7 cm cervical dilation. In their definition, the degree of deceleration is generally proportional to the contraction strength and rarely falls below 100 to 110 bpm or 20 to 30 bpm below baseline. Such decelerations are common during active labor and not associated with tachycardia, loss of variability, or other fetal heart rate changes. Importantly, early decelerations are not associated with fetal hypoxia, acidemia, or low Apgar scores.

FIGURE 24-11

Features of early fetal heart rate deceleration. Characteristics include a gradual decline in the heart rate with both onset and recovery coincident with the onset and recovery of the contraction. The nadir of the deceleration is 30 seconds or more after the deceleration onset.

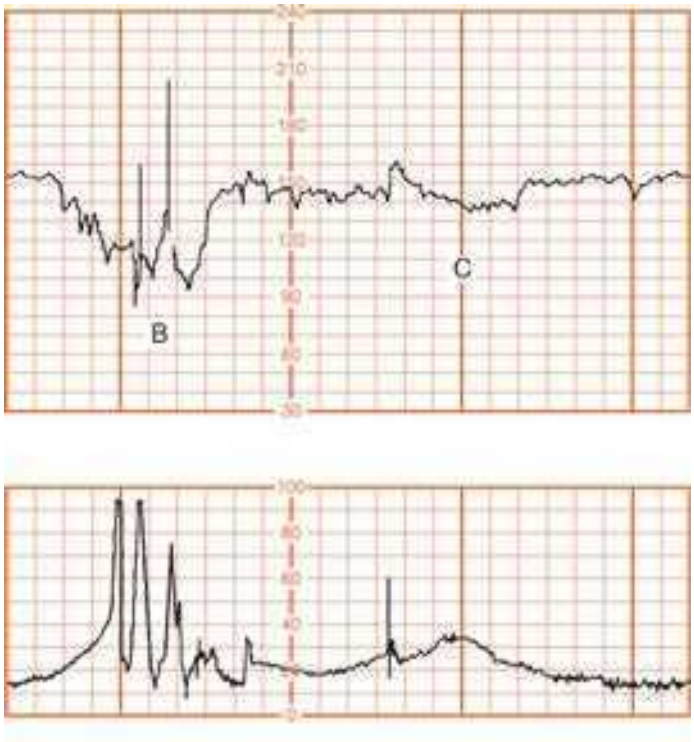


Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Head compression probably causes vagal nerve activation as a result of dural stimulation, and this mediates the heart rate deceleration (Paul, 1964). Ball and Parer (1992) concluded that fetal head compression is a likely cause not only of the deceleration shown in Figure 24-11 but also of those shown in Figure 24-12, which typically occur during second-stage labor. Indeed, they observed that head compression is the likely cause of many variable decelerations classically attributed to cord compression.

FIGURE 24-12

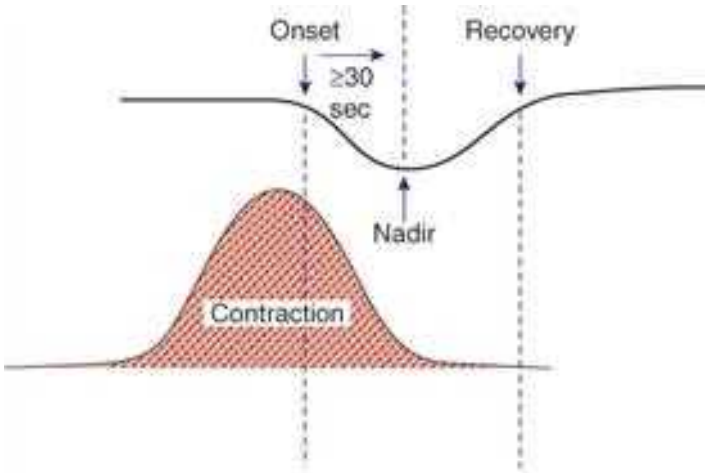
Two different fetal heart rate patterns during second-stage labor that are likely both due to head compression (*upper panel*). Maternal pushing efforts (*lower panel*) correspond to the spikes with uterine contractions. Fetal heart rate deceleration (*C*) is consistent with the pattern of head compression shown in Figure 24-11. Deceleration (*B*), however, is “variable” in appearance because of its jagged configuration and may alternatively represent cord occlusion.



Late Deceleration

The fetal heart rate response to uterine contractions can reflect uterine perfusion or placental function. A late deceleration is a smooth, gradual, symmetrical decline in fetal heart rate beginning at or after the contraction peak and returning to baseline only after the contraction has ended. This deceleration reaches its nadir within 30 seconds of its onset. In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively (Fig. 24-13). The magnitude of late decelerations is seldom more than 30 to 40 bpm below baseline and typically not more than 10 to 20 bpm. Late decelerations usually are not accompanied by accelerations. Myers and associates (1973) studied monkeys in which they compromised uteroplacental perfusion by lowering maternal aortic blood pressure. The interval or lag from the contraction onset until the late deceleration onset was directly related to basal fetal oxygenation. They demonstrated that the length of the lag was predictive of the fetal Po_2 but not fetal pH. The lower the fetal Po_2 before contractions, the shorter the lag to the onset of late decelerations. This lag reflected the time necessary for the fetal Po_2 to fall below a critical level necessary to stimulate arterial chemoreceptors, which mediated the decelerations.

FIGURE 24-13
Features of late fetal heart rate deceleration. Characteristics include gradual decline in the heart rate with the contraction nadir, and recovery occurring after the end of the contraction. The nadir of the deceleration occurs 30 seconds or more after the onset of the deceleration.



Murata and coworkers (1982) also showed that a late deceleration was the first fetal heart rate consequence of uteroplacental-induced hypoxia. During the course of progressive hypoxia that led to death over 2 to 13 days, monkey fetuses invariably exhibited late decelerations before development of acidemia.

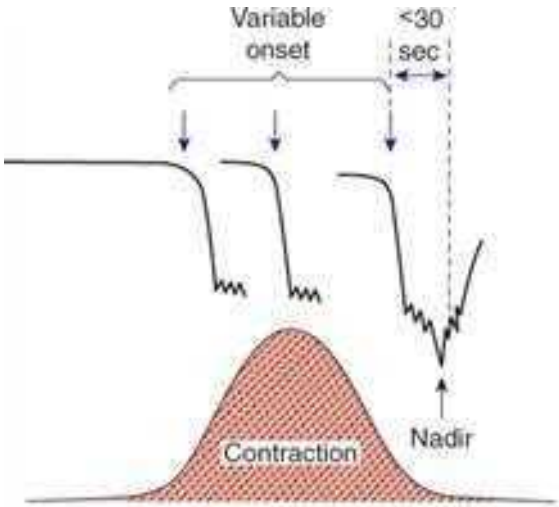
Variability of the baseline heart rate disappeared as acidemia developed.

Generally, any process that produces maternal hypotension, excessive uterine activity, or placental dysfunction can induce late decelerations. The two most common sources are hypotension from epidural analgesia and uterine hyperactivity from oxytocin stimulation. Maternal diseases such as hypertension, diabetes, and collagen vascular disorders can cause chronic placental dysfunction. Placental abruption can produce acute late decelerations.

Variable Deceleration

The most frequent deceleration patterns encountered during labor are variable decelerations attributed to umbilical cord occlusion. In a study of more than 7000 monitor tracings, variable decelerations were identified in 40 percent when labor had progressed to 5 cm dilation and in 83 percent by the end of first-stage labor (Melchior, 1985). A variable deceleration is defined as an abrupt drop in the fetal heart rate beginning with the onset of the contraction and reaching a nadir in less than 30 seconds. The decrease must last between 15 seconds and 2 minutes and must be ≥15 bpm in amplitude. The onset of deceleration typically varies with successive contractions (Fig. 24-14).

FIGURE 24-14
Features of variable fetal heart rate decelerations. Characteristics include an abrupt decline in the heart rate, and onset that commonly varies with successive contractions. The deceleration measures ≥15 bpm for ≥15 seconds and has an onset-to-nadir phase of <30 seconds. Total duration is <2 minutes.



Hon (1959) tested the effects of umbilical cord compression on fetal heart rate (Fig. 24-15). In experimental animals, complete occlusion of the umbilical cord produces abrupt, jagged-appearing deceleration of the fetal heart rate (Fig. 24-16). Concomitantly, fetal aortic pressure rises. Itskovitz and colleagues (1983) observed that variable decelerations in fetal lambs occurred only after umbilical blood flow was reduced by at least 50 percent.

FIGURE 24-15
A. The effects of 25-second cord compression compared with those of 40 seconds in panel **(B)**. (Redrawn with permission from Hon EH: The fetal heart rate patterns preceding death in utero, Am J Obstet Gynecol. 1959 Jul;78(1):47–56.)

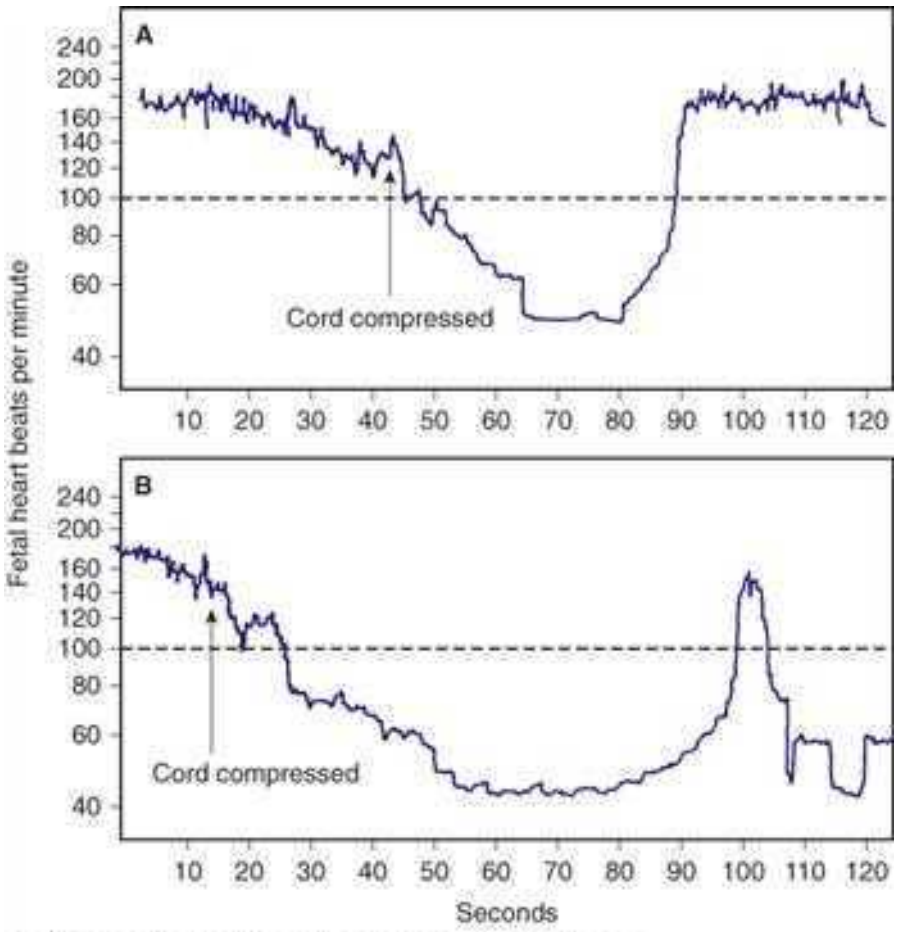
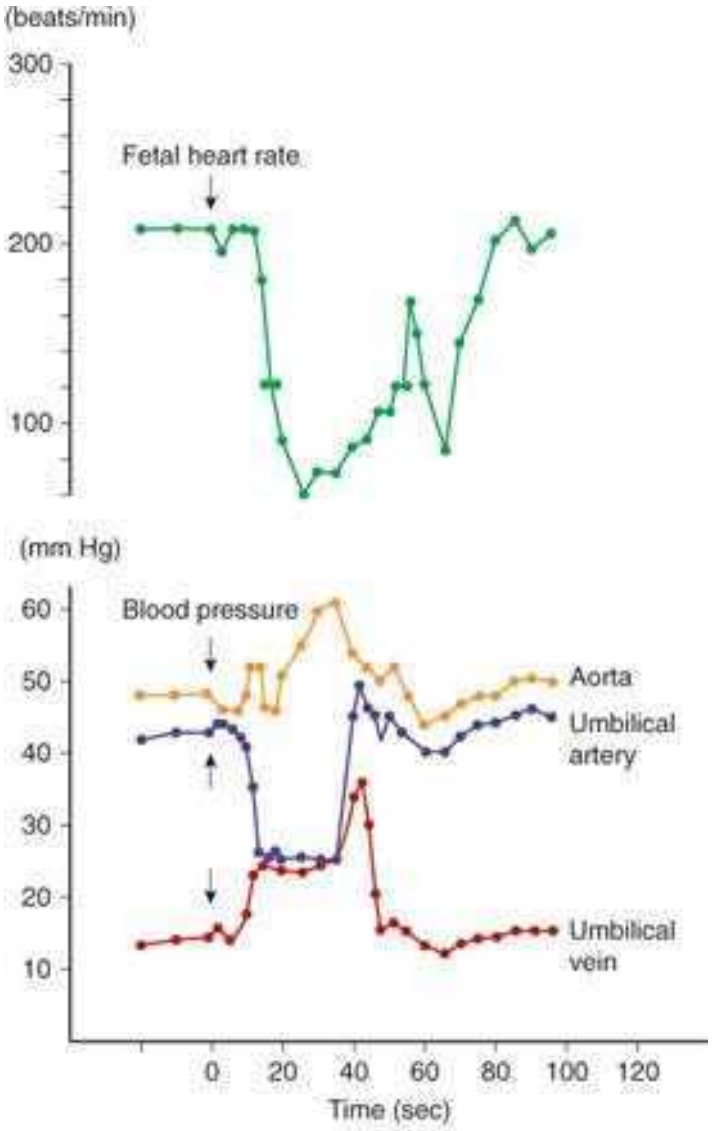


FIGURE 24-16

Total umbilical cord occlusion (*arrow*) in the sheep fetus is accompanied by an increase in fetal aortic blood pressure. Blood pressure changes in the umbilical vessels are also shown. (Redrawn with permission from Künzel W: Fetal heart rate alterations in partial and total cord occlusion. In Künzel W (ed): Fetal Heart Rate Monitoring: Clinical Practice and Pathophysiology. Berlin, Springer, 1985.)



Two types of variable decelerations are shown in Figure 24-17. The deceleration denoted by “A” is very much like that seen with complete umbilical cord occlusion in experimental animals (see Fig. 24-16). Deceleration “B,” however, has a different configuration because of the “shoulders” of acceleration before and after the deceleration component. Lee and coworkers (1975) proposed that this form of variable deceleration was caused by differing degrees of partial cord occlusion. In this physiological scheme, occlusion of only the vein reduces fetal blood return, thereby triggering a baroreceptor-mediated acceleration. With increasing intrauterine pressure and subsequent complete cord occlusion, fetal systemic hypertension develops due to obstruction of umbilical artery flow. This stimulates a baroreceptor-mediated deceleration. Presumably, the aftercoming shoulder of the acceleration represents the same events occurring in reverse (Fig. 24-18).

FIGURE 24-17
Varying (variable) fetal heart rate decelerations. Deceleration (*B*) exhibits “shoulders” of acceleration compared with deceleration (*A*).

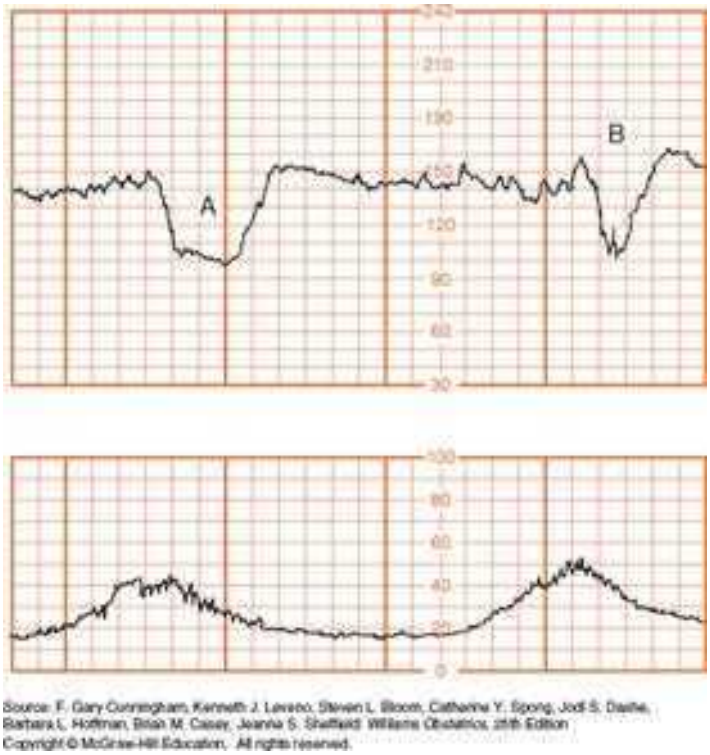


FIGURE 24-18

Schematic representation of the fetal heart rate effects with partial and complete umbilical cord occlusion. Uterine pressures generated early in a contraction cause cord compression predominantly of the thin-walled umbilical vein. The resulting decrease in fetal cardiac output leads to an initial compensatory rise in fetal heart rate. As cord compression intensifies, umbilical arteries are then also compressed. The resulting rise in fetal systolic blood pressure leads to a vagal-mediated fetal heart rate deceleration. As the contraction abates and compression is relieved first on the umbilical arteries, elevated fetal systolic blood pressures drop and the deceleration resolves. A final increase in fetal heart rate is seen as a result of persistent umbilical vein occlusion. With completion of the uterine contraction and cord compression, the fetal heart rate returns to baseline. BP = blood pressure. (Adapted with permission from Lee CV, DiLaretto PC, Lane JM: A study of fetal heart rate acceleration patterns, Obstet Gynecol. 1975 Feb;45(2):142–146.)

Ball and Parer (1992) concluded that variable decelerations are mediated vagally and that the vagal response may be due to chemoreceptor or baroreceptor activity or both. Partial or complete cord occlusion produces an increase in afterload (baroreceptor) and a drop in fetal arterial oxygen content (chemoreceptor). These both result in vagal activity leading to deceleration. In fetal monkeys, the baroreceptor reflexes appear to operate during the first 15 to 20 seconds of umbilical cord occlusion followed by decline in Po_2 at approximately 30 seconds, which then serves as a chemoreceptor stimulus (Mueller-Heubach, 1982).

Thus, variable decelerations represent fetal heart rate reflexes that reflect either blood pressure changes due to interruption of umbilical flow or changes in oxygenation. It is likely that most fetuses have experienced brief but recurrent periods of hypoxia due to umbilical cord compression during gestation. The frequency and inevitability of cord occlusions undoubtedly have provided the fetus with these physiological mechanisms as a means of coping. The great dilemma for the obstetrician in managing variable fetal heart rate decelerations is determining when variable decelerations are pathological. According to the American College of Obstetricians and Gynecologists (2017a), recurrent variable decelerations with minimal-to-moderate beat-to-beat variability are *indeterminate,* whereas those with absent variability are *abnormal*.

Other fetal heart rate patterns have been associated with umbilical cord compression. *Saltatory* baseline heart rate (Fig. 24-19) was first linked to umbilical cord complications during labor (Hammacher, 1968). The pattern consists of rapidly recurring couplets of acceleration and deceleration causing relatively large oscillations of the baseline fetal heart rate. We also observed a relationship between cord occlusion and the saltatory pattern in postterm pregnancies (Leveno, 1984). In the absence of other fetal heart rate findings, these do not signal fetal compromise. *Lambda* is a pattern involving an acceleration followed by a variable deceleration with no acceleration at the end of the deceleration. This pattern typically is seen in early labor and is not ominous (Freeman, 2003). This lambda pattern may result from mild cord compression or stretch. *Overshoot* is a variable deceleration followed by acceleration. The clinical significance of this pattern is controversial (Westgate, 2001).

FIGURE 24-19

Saltatory baseline fetal heart rate showing rapidly recurring couplets of acceleration combined with deceleration.

Prolonged Deceleration

This pattern, which is shown in Figure 24-20, is defined as an isolated deceleration ≥15 bpm that lasts ≥2 minutes but <10 minutes from onset to return to baseline. Prolonged decelerations are difficult to interpret because they are seen in many different clinical situations. Some of the more frequent causes are

cervical examination, uterine hyperactivity, cord entanglement, and maternal supine hypotension.

FIGURE 24-20
Prolonged fetal heart rate deceleration due to uterine hyperactivity. Approximately 3 minutes of the tracing are shown, but the fetal heart rate returned to normal after uterine hypertonus resolved. Vaginal delivery later ensued.

Epidural, spinal, or paracervical analgesia may induce a prolonged deceleration (Eberle, 1998). Hill and associates (2003) observed prolonged deceleration in 1 percent of women given epidural analgesia during labor at Parkland Hospital. Other causes of prolonged deceleration include maternal hypoperfusion or hypoxia from any cause, placental abruption, umbilical cord knots or prolapse, maternal seizures including eclampsia and epilepsy, application of a fetal scalp electrode, impending birth, or maternal Valsalva maneuver. In one example, Ambia and colleagues (2017) described prolonged decelerations lasting 2 to 10 minutes following an eclamptic seizure.

The placenta is effective in resuscitating the fetus if the original insult does not recur immediately. Occasionally, such self-limited prolonged decelerations are followed by loss of beat-to-beat variability, baseline tachycardia, and even a period of late decelerations, all of which resolve as the fetus recovers. Freeman and colleagues (2003) emphasize that the fetus may die during prolonged decelerations. Thus, management of prolonged decelerations can be extremely tenuous. Management of isolated prolonged decelerations is based on bedside clinical judgment, which inevitably will sometimes be imperfect given the unpredictability of these decelerations.

Fetal Heart Rate Patterns During Second-Stage Labor

Decelerations are virtually ubiquitous during the second stage of labor. In one study, only 1.4 percent of more than 7000 deliveries lacked decelerations during second-stage labor (Melchior, 1985). Both cord and fetal head compressions have been implicated as causes of decelerations and baseline bradycardia in this stage. Profound, prolonged fetal heart rate deceleration in the 10 minutes preceding vaginal delivery has been described (Boehm, 1975). And, similar prolonged second-stage decelerations were associated with a stillbirth and neonatal death (Herbert, 1981). These experiences attest to the unpredictability of the fetal heart rate during second-stage labor.

Spong and associates (1998) analyzed the characteristics of second-stage variable fetal heart rate decelerations in 250 deliveries. They found that as the total number of decelerations <70 bpm increased, the 5-minute Apgar score decreased. Of other patterns in second-stage labor, Picquard and coworkers (1988) reported that loss of beat-to-beat variability and baseline fetal heart rate <90 bpm predicted fetal acidemia. Krebs and associates (1981) also found that persistent or progressive baseline bradycardia or baseline tachycardia was associated with lower Apgar scores. Gull and colleagues (1996) observed that abrupt fetal heart rate deceleration to <100 bpm associated with loss of beat-to-beat variability for 4 minutes or longer was predictive of fetal acidemia. Thus, abnormal baseline heart rate—either bradycardia or tachycardia, absent beat-to-beat variability, or both—in the presence of deep second-stage decelerations is associated with a greater risk for fetal compromise (Fig. 24-21).

FIGURE 24-21
Cord-compression fetal heart rate decelerations in second-stage labor associated with tachycardia and loss of variability. The umbilical cord arterial pH was 6.9.

Admission Fetal Monitoring in Low-Risk Pregnancies

With this approach, women with low-risk pregnancies are monitored for a short time on admission for labor. In one study, 3752 low-risk women in spontaneous labor at admission were randomly assigned either to auscultation of the fetal heart or to 20 minutes of electronic fetal monitoring (Mires, 2001). Use of admission electronic fetal monitoring did not improve neonatal outcome. Moreover, its use resulted in a greater number of interventions, including operative delivery. A similar study echoed these neonatal outcomes (Impey, 2003). More than half of the women enrolled in these studies eventually required continuous monitoring. A review by Devane and associates (2017) found that admission fetal monitoring programs for low-risk pregnancy are associated with a higher risk for cesarean delivery. Somewhat related, with the increasing rate of scheduled cesarean deliveries in the United States, clinicians and hospitals must decide whether fetal monitoring is required before the procedure in low-risk women.

Computerized Interpretation

Fetal heart rate pattern interpretations are subjective. Thus, the potential for computer assistance to enhance the precision of identifying abnormal patterns appeared promising. The INFANT Collaborative Group (2017) studied whether the addition of computer-based decision-support software for interpretation of fetal heart rate patterns lowered the number of poor neonatal outcomes. In this trial, 23,515 women were randomized to computer-assisted interpretation compared with 23,055 women in a conventional clinical interpretation arm. Perinatal outcomes such as intrapartum stillbirth, early neonatal death, and neonatal encephalopathy were not improved by computer assistance. Cesarean delivery rates were similar in both groups. Moreover, a 2-year follow-up of a subset of the surviving children showed no differences in their neurological development.

OTHER INTRAPARTUM ASSESSMENT TECHNIQUES

Fetal Scalp Blood Sampling

According to the American College of Obstetricians and Gynecologists (2017a), measurements of the pH in capillary scalp blood may help identify the fetus in serious distress. However, this group also emphasizes that neither normal nor abnormal scalp pH results are predictive of neonatal outcome. Notably, the procedure is now used uncommonly and is not available at most hospitals in the United States.

With sampling, an illuminated endoscope is inserted through the dilated cervix after membrane rupture and is pressed firmly against the fetal scalp (Fig. 24-22). The skin is wiped clean with a cotton swab and coated with a silicone gel, which allows fetal blood to accumulate as discrete globules. An incision is made through the fetal scalp to a depth of 2 mm with a special blade on a long handle. As a drop of blood forms on the surface, it is immediately collected into a heparinized glass capillary tube. The pH of the blood is measured promptly.

FIGURE 24-22
The technique of fetal scalp sampling using an amnioscope. The end of the endoscope is displaced from the fetal vertex approximately 2 cm to show the disposable blade against the fetal scalp before incision.

The pH of fetal capillary scalp blood is usually lower than that of umbilical venous blood and approaches that of umbilical arterial blood. In one algorithm, if the pH is ≥7.25, labor is observed, and if between 7.20 and 7.25, the pH measurement is repeated within 30 minutes (Zalar, 1979). If the pH is <7.20, another scalp blood sample is collected immediately, and the mother is taken to an operating room and prepared for surgery. Delivery is performed promptly if the low pH is confirmed. Otherwise, labor is allowed to continue, and scalp blood samples are repeated periodically.

The only benefits reported for scalp blood pH testing are fewer cesarean deliveries for fetal distress (Young, 1980b). However, Goodwin and coworkers (1994) showed a decrease in the scalp pH sampling rate from approximately 1.8 percent in the mid-1980s to 0.03 percent by 1992. This drop in sampling rate was not associated with a higher cesarean delivery rate for fetal distress. They concluded that scalp blood pH sampling was unnecessary.

Kruger and colleagues (1999) have advocated the use of fetal scalp blood lactate concentration as an adjunct to pH. Wiberg-Itzel and associates (2008) randomly assigned 1496 fetuses to scalp blood pH analysis and 1496 to scalp blood lactate analysis. They found either to be equivalent in predicting fetal acidemia. The advantage of lactate measurement was that a smaller amount of blood was needed, which led to a lower procedural failure rate compared with scalp blood sampling for pH.

Scalp Stimulation

Clark and coworkers (1984) have suggested that fetal scalp stimulation is an alternative to scalp blood sampling. This proposal was based on the observation that heart rate acceleration in response to pinching the fetal scalp with an Allis clamp just before obtaining blood was invariably associated with a normal pH. Conversely, failure to provoke acceleration was not uniformly predictive of fetal acidemia. Later, Elimian and associates (1997) reported that of 58 cases in which the fetal heart rate accelerated >10 bpm after 15 seconds of gentle digital stroking of the scalp, 100 percent had a scalp blood pH of >7.20. Without an acceleration, however, only 30 percent had a scalp blood pH >7.20. Following a prospective cohort study, Tahir Mahmood and coworkers (2017) concluded that fetal scalp stimulation was a reliable alternative to scalp blood pH determination.

Vibroacoustic Stimulation

Fetal heart rate acceleration in response to vibroacoustic stimulation has been recommended as a substitute for fetal scalp blood sampling (Edersheim, 1987). The technique uses an electronic artificial larynx placed approximately 1 cm from or directly onto the maternal abdomen (Chap. 17, Acoustic Stimulation Tests). Response to vibroacoustic stimulation is considered normal if a fetal heart rate acceleration of at least 15 bpm for at least 15 seconds occurs within 15 seconds after the stimulation and with prolonged fetal movements (Sherer, 1994).

Lin and colleagues (2001) prospectively studied vibroacoustic stimulation in 113 women in labor with either moderate-to-severe variable or late fetal heart rate decelerations. They concluded that this technique is an effective predictor of fetal acidosis in the setting of variable decelerations. The predictability for fetal acidosis, however, is limited in the setting of late decelerations. Other investigators have reported that vibroacoustic stimulation in second-stage labor did not predict neonatal outcome or enhance labor management (Anyaegbunam, 1994).

Skupski and coworkers (2002) performed a metaanalysis of reports on intrapartum fetal stimulation tests published between 1966 and 2000. Four types of fetal stimulation were analyzed and included fetal scalp puncture for blood pH testing, Allis clamp pinching of the fetal scalp, vibroacoustic stimulation, and digital stroking of the fetal scalp. Results were similar for all four methods. These investigators concluded that intrapartum stimulation tests were useful to exclude fetal acidemia. They cautioned, however, that these tests are “less than perfect.”

Fetal Pulse Oximetry

Using technology similar to that of adult pulse oximetry, this instrumentation allows assessment of fetal oxyhemoglobin saturation once membranes are ruptured. A unique padlike sensor is inserted through the cervix and positioned against the fetal face. The transcervical device reliably registers fetal oxygen saturation in 70 to 95 percent of women throughout 50 to 88 percent of their labors (Yam, 2000). Using fetal pulse oximetry, the lower limit for normal fetal oxygen saturation is generally considered to be 30 percent (Gorenberg, 2003; Stiller, 2002). However, when measured in umbilical arterial blood, fetal oxygen saturation normally varies greatly, as shown in Figure 24-23. Bloom and associates (1999) reported that brief, transient fetal oxygen saturations <30 percent were common during labor because such values were observed in 53 percent of fetuses with normal outcomes. When persistent for 2 minutes or longer, however, saturation values <30 percent were associated with a greater risk of potential fetal compromise.

FIGURE 24-23
Frequency distribution of umbilical artery oxygen saturation values in 1281 vigorous newborn infants. Dotted line indicates normal distribution. (Redrawn with permission from Arikan GM, Scholz HS, Petru E, et al: Cord blood oxygen saturation in vigorous infants at birth: what is normal? BJOG. 2000 Aug;107(8):987–994.)

Garite and colleagues (2000) randomly assigned 1010 women with term pregnancies and in whom predefined abnormal fetal heart rate patterns developed. Patients received either conventional fetal monitoring alone or fetal monitoring plus continuous fetal pulse oximetry. The use of fetal pulse oximetry significantly reduced the cesarean delivery rate for nonreassuring fetal status from 10.2 to 4.5 percent. Alternatively, the cesarean delivery rate for dystocia rose significantly from 9 to 19 percent when pulse oximetry was used. No neonatal benefits or adverse effects were associated with fetal pulse oximetry. Based on these observations, the Food and Drug Administration approved marketing of the Nellcor N-400 Fetal Oxygen Monitoring System.

Since then, three other randomized trials have compared fetal pulse oximetry with standard care. In all three trials, neonatal outcomes were similar between the two study arms. East and coworkers (2006) reported that the addition of oximetry significantly reduced cesarean delivery rates for a nonreassuring fetal heart rate pattern. However, Bloom (2006) and Klauser (2005), each with their colleagues, found no difference in cesarean delivery rates between the two study groups. Because of these findings, in 2005, the manufacturer discontinued sale of the fetal oximeter system in the United States.

Fetal Electrocardiography

As fetal hypoxia worsens, the fetal ECG changes. Namely, the mature fetus exposed to hypoxemia develops an elevated ST segment and a progressive rise in the T-wave height that can be expressed as a T:QRS ratio (Fig. 24-24). Increasing T:QRS ratios are thought to reflect the fetal cardiac ability to adapt to hypoxia and appear before neurological damage. Further worsening of hypoxia then leads to progressively negative ST-segment deflection that takes on a biphasic form (Fig. 24-25). It is reasonable to consider that ST-segment abnormalities might occur late in the course of fetal compromise. Indeed, it has been hypothesized that ST-segment changes reflect myocardial tissue hypoxia.

FIGURE 24-24
A. ST segment changes in normal and hypoxic conditions. **B.** Generation of T:QRS ratios. (Redrawn with permission from Devoe L: ECG analysis: the next generation in electronic fetal monitoring? Contemporary Ob/Gyn, September 15, 2006.)

FIGURE 24-25
Biphasic ST-segment waveform with progressive fetal hypoxia. (Adapted with permission from Devoe L: ECG analysis: the next generation in electronic fetal monitoring? Contemporary Ob/Gyn, September 15, 2006.)

Because of these findings, several investigators have assessed the value of analyzing these parameters as an adjunct to conventional fetal monitoring. The technique requires internal fetal heart monitoring and special equipment to process the fetal ECG. In 2005, the manufacturer—Neoventa Medical—received Food and Drug Administration approval for their ST analysis program named the STAN system.

Several studies have evaluated ST-segment changes with fetal monitoring. In one randomized trial of 2400 pregnancies, neonatal outcomes were not improved compared with those in which conventional fetal monitoring alone was used (Westgate, 1993). However, the cesarean delivery rate for fetal distress declined in those with ST-segment analysis. Amer-Wåhlin and colleagues (2001, 2007) found that the addition of ST-segment analysis to conventional fetal monitoring significantly lowered cesarean delivery rates for fetal distress and reduced metabolic acidemia in umbilical artery blood.

Subsequently, Doria and associates (2007) introduced STAN as a clinical practice and reported no changes in the incidence of operative delivery or neonatal encephalopathy. And, one metaanalysis of five randomized trials comprising 15,352 patients found that ST-segment analysis did not lower rates of cesarean delivery or fetal metabolic acidemia at birth (Becker, 2012).

Last, in a trial by the NICHD, 5532 women were randomly assigned to an ST-segment analysis arm (the open group) and 5576 to standard intrapartum management (the masked group). The primary outcome was a composite of one or more of seven events associated with fetal compromise (Belfort, 2015). In the open group, clinical practice was directed to some degree by predetermined ST-segment analysis guidelines. These stipulated that intervention should be withheld, that is, expectant management adopted, for at least 60 minutes despite the presence of minimal variability; variable decelerations lasting ≥60 seconds or dropping to ≥60 bpm; recurrent late decelerations; or prolonged decelerations lasting >2 minutes, so long as no ST-event was present. These guidelines did not pertain to the standard usual management group. Notably, in the open group, 55 women were delivered when STAN guidelines indicated that labor should continue. This composed 20 percent of the total 287 cesarean deliveries performed for fetal distress in this group. Clearly, the attending physicians abandoned the open group protocol that stipulated nonintervention. They likely perceived the fetal heart rate patterns to reflect those formerly accepted in their usual practice as nonreassuring.

The results of this trial showed that STAN had no effect on neonatal outcome or cesarean delivery rates (Belfort, 2015). In their review, Neilson and colleagues (2015) reached similar conclusions. These results have essentially eliminated use of ST-segment analysis in the United States, but this technology is still used in Europe.

Intrapartum Doppler Velocimetry

Doppler interrogation of the umbilical artery has been studied as another potential adjunct to conventional fetal monitoring. Further described in Chapter 10 (Doppler), abnormal Doppler waveforms may signify pathological umbilical-placental vessel resistance. From their review, Farrell and associates (1999)

concluded that this technique, used intrapartum, was a poor predictor of adverse perinatal outcomes.

NONREASSURING FETAL STATUS

The term *fetal distress* is too broad and vague to be applied with any precision to clinical situations (American College of Obstetricians and Gynecologists, 2014). Uncertainty regarding the diagnosis based on interpretation of fetal heart rate patterns has given rise to descriptions such as *reassuring* or *nonreassuring.* The term "reassuring" suggests a restoration of confidence in the health of the fetus by a particular pattern. In contrast, a "nonreassuring" designation suggests inability to remove doubt. These patterns during labor are dynamic, and they can rapidly change from reassuring to nonreassuring and vice versa. *These assessments are subjective clinical judgments that are inevitably subject to imperfection and must be recognized as such.*

The difficulty in assigning a nonreassuring label to fetal heart rate patterns stems in part from the fact that these patterns are more a reflection of fetal physiology than of pathology. Physiological control of heart rate includes various interconnected mechanisms that depend on blood flow and oxygenation. Moreover, the activity of these control mechanisms is influenced by the preexisting state of fetal oxygenation, for example, as seen with chronic placental insufficiency. Importantly, the fetus is tethered by an umbilical cord, whereby blood flow is constantly in jeopardy. Moreover, normal labor is a process of increasing acidemia (Rogers, 1998). Thus, normal labor is a process of repeated fetal hypoxic events that can infrequently lead to significant acidemia.

Diagnosis

Identification of "fetal distress" based on fetal heart rate patterns is imprecise and controversial. Experts in interpretation of these patterns often disagree with each other. Ayres-de-Campos and colleagues (1999) investigated interobserver agreement of fetal heart rate pattern interpretation and found that agreement—or conversely, disagreement—was related to whether the pattern was normal, suspicious, or pathological. Specifically, experts agreed on 62 percent of normal patterns, 42 percent of suspicious patterns, and only 25 percent of pathological patterns. Keith and coworkers (1995) asked each of 17 experts to review 50 tracings on two occasions, at least 1 month apart. Approximately 20 percent changed their own interpretations, and approximately 25 percent did not agree with the interpretations of their colleagues.

To develop standardized and unambiguous definitions of fetal heart rate (FHR) tracings, the NICHD (1997) held a succession of workshops in 1995 and 1996 and published recommendations for interpreting these patterns. As previously shown in Table 24-1, a second workshop was convened to reevaluate these recommendations and clarify terminology (Macones, 2008). A major result was the recommendation of a three-tier system for classification of FHR patterns (Table 24-2). The American College of Obstetricians and Gynecologists (2017b) has recommended use of this tiered system.

TABLE 24-2

Three-Tier Fetal Heart Rate Interpretation System

Category I—Normal

Include all of the following:

- Baseline rate: 110–160 bpm
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

Category II—Indeterminate

Include all FHR tracings not categorized as Category I or III.

Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples include any of the following:

Baseline rate

- Bradycardia not accompanied by absent baseline variability
- Tachycardia

Baseline FHR variability

- Minimal baseline variability
- Absent baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations

- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations

- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, “overshoots,” or “shoulders”

Category III—Abnormal

Include either:

- Absent baseline FHR variability and any of the following:

Recurrent late decelerations

Recurrent variable decelerations

Bradycardia

- Sinusoidal pattern

bpm = beats per minute; FHR = fetal heart rate.

Reproduced with permission from Macones GA, Hankins GD, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol. 2008 Sep;112(3):661–666.

A few studies have assessed this three-tiered system. Jackson and coworkers (2011) studied 48,444 women in labor and found that category I (normal FHR) patterns were observed during labor in 99.5 percent of tracings. Category II (indeterminate FHR) patterns were found in 84.1 percent of tracings, and category III (abnormal FHR) patterns were seen in 0.1 percent (54 women). Most—84 percent of women—had a mix of categories during labor. Cahill and colleagues (2012) retrospectively correlated the incidence of umbilical cord acidemia (pH ≤7.10) with fetal heart rate characteristics during the 30 minutes preceding delivery. None of the three categories demonstrated a significant association with cord blood acidemia. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (2014) concluded that a category I or II tracing with a 5-minute Apgar score >7 or with normal arterial blood acid–base values was not consistent with an acute hypoxic-ischemic event.

Sholapurkar (2012) challenged the validity of the three-tier system because most abnormal fetal heart rate patterns fall into the indeterminate category II. It was further suggested that this resulted from most fetal heart rate decelerations being inappropriately classified as *variable* decelerations due to cord compression. A group of 19 experts led by Clark (2013) observed that more than 80 percent of fetuses have FHR patterns in tier II. They proposed a management algorithm for these fetuses, however, their hypothetical algorithm was not clinically tested.

Parer and King (2010) compared this situation in the United States with that of other countries in which a consensus on classification and management has been reached by several professional societies. Some of these include the Royal College of Obstetricians and Gynaecologists, the Society of Obstetricians and Gynaecologists of Canada, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the Japan Society of Obstetrics and Gynecology. These authors further comment that the NICHD three-tier system is inadequate because category II—an indeterminate FHR pattern—contains a vast heterogenous mixture of patterns that prevents development of a management strategy.

Parer and Ikeda (2007) had previously proposed a color-coded five-tier system for both FHR interpretation *and* management. Two subsequent reports have compared the five- and three-tier systems. Bannerman and associates (2011) found that the two systems were similar in fetal heart rate interpretations for tracings that were either very normal or very abnormal. Coletta and coworkers (2012) found that the five-tier system had better sensitivity than the three-tier system. Elliott and colleagues (2010) used computerization to measure the performance of a five-tier classification system but failed to successfully analyze and categorize 2472 fetal heart recordings.

It is apparent that, after 50 years of continuous electronic fetal heart rate monitoring use, there is not a consensus on interpretation and management recommendations for FHR patterns (Parer, 2011).

Meconium in the Amnionic Fluid

Obstetricians have long realized that meconium during labor is problematic in the prediction of fetal distress or asphyxia. Indeed, although 12 to 22 percent of labors are complicated by meconium, only a few are linked to neonatal mortality. In an investigation from Parkland Hospital, meconium was found to be a "low-risk" obstetrical hazard because the perinatal mortality rate attributable to meconium was only 1 death per 1000 live births (Nathan, 1994).

Three theories regarding fetal passage of meconium may explain, in part, the tenuous connection between its detection and neonatal mortality. First, fetuses may pass meconium in response to hypoxia, and meconium therefore signals fetal compromise (Walker, 1953). Second, in utero passage of meconium may represent normal gastrointestinal tract maturation under neural control (Mathews, 1979). A final theory posits that meconium passage follows vagal stimulation from common but transient umbilical cord entrapment with resultant increased bowel peristalsis (Hon, 1961).

Ramin and associates (1996) studied almost 8000 pregnancies with meconium-stained amnionic fluid delivered at Parkland Hospital. Meconium aspiration syndrome was significantly associated with fetal acidemia at birth. Other significant correlates of aspiration included cesarean delivery, forceps to expedite delivery, intrapartum heart rate abnormalities, depressed Apgar scores, and need for assisted ventilation at delivery. Analysis of the type of fetal acidemia based on umbilical blood gases suggested that the fetal compromise associated with meconium aspiration syndrome was an acute event. This is because most acidemic fetuses had abnormally increased P_{CO_2} values rather than a pure metabolic acidemia.

Dawes and coworkers (1972) observed that such hypercarbia in fetal lambs induces gasping and resultant increased amnionic fluid inhalation. Jovanovic and Nguyen (1989) observed that meconium gasped into the fetal lungs caused aspiration syndrome only in asphyxiated animals.

Ramin and colleagues (1996) hypothesized that the pathophysiology of meconium aspiration syndrome includes, but is not limited to, fetal hypercarbia, which stimulates fetal respiration leading to aspiration of meconium into the alveoli. Lung parenchymal injury is secondary to acidemia-induced alveolar cell damage. In this pathophysiological scenario, meconium in amnionic fluid is a fetal environmental hazard rather than a marker of preexistent compromise. This proposed pathophysiological sequence is not all-inclusive, because it does not account for approximately half of the cases of meconium aspiration syndrome in which the fetus is not acidemic at birth.

Thus, it was concluded that the high incidence of meconium observed in the amnionic fluid during labor often represents fetal passage of gastrointestinal contents in conjunction with normal physiological processes. Although normal, such meconium becomes an environmental hazard when fetal acidemia supervenes. Importantly, such acidemia occurs acutely, and therefore meconium aspiration is unpredictable and likely unpreventable. Moreover, Greenwood and colleagues (2003) showed that clear amnionic fluid was also a poor predictor. In a prospective study of 8394 women with clear amnionic fluid, they found that clear fluid was an unreliable sign of fetal well-being.

Growing evidence indicates that many newborns with meconium aspiration syndrome have suffered chronic hypoxia before birth (Ghidini, 2001). Blackwell and associates (2001) found that 60 percent of neonates diagnosed with meconium aspiration syndrome had umbilical artery blood pH ≥7.20, implying that the syndrome was unrelated to the neonatal condition at delivery. Similarly, markers of chronic hypoxia, such as elevated fetal erythropoietin levels and increased nucleated red blood cell counts in newborns, suggest that chronic hypoxia is involved in many meconium aspiration syndrome cases (Dollberg, 2001; Jazayeri, 2000).

In the recent past, routine obstetrical management of a newborn with meconium-stained amnionic fluid included intrapartum suctioning of the oropharynx and nasopharynx. In 2005, management guidelines were significantly modified. Now, the American College of Obstetricians and Gynecologists (2017c) recommends that newborns with meconium-stained amnionic fluid, regardless of their vigor, should no longer routinely receive intrapartum suctioning. Suctioning is reserved for those with airway obstruction. They also recommend that an appropriately credentialed team with full resuscitation skills be available (Chap. 32, Care in the Delivery Room).

Management Options

Principal management options for variant fetal heart rate patterns consist of correcting any fetal insult, if possible. Suggestions are listed in Table 24-3. The woman is moved to a lateral position, and supplemental oxygen is provided by mask. Correcting maternal hypotension caused by regional analgesia and discontinuing oxytocin both serve to improve uteroplacental perfusion. Vaginal examination excludes a prolapsed cord or impending delivery. Simpson and James (2005) assessed the benefits of three maneuvers in 52 women with fetal oxygen saturation sensors already in place. They used intravenous hydration —500 to 1000 mL of lactated Ringer solution given over 20 minutes; lateral versus supine positioning; and administration of supplemental oxygen at 10 L/min using a nonrebreathing mask. Each of these maneuvers significantly raised fetal oxygen saturation levels.

TABLE 24-3

Some Resuscitative Measures for Category II or Category III Tracings

Fetal Heart Rate Abnormality[a]	Interventions[b]
Recurrent late decelerations Prolonged decelerations or bradycardia Minimal or absent FHR variability	Lateral decubitus positioning; administer maternal oxygen; intravenous fluid bolus; reduce uterine contraction frequency
Tachysystole with category II or III tracing	Discontinue oxytocin or prostaglandins; Give tocolytics: terbutaline, magnesium sulfate
Recurrent variable decelerations Prolonged decelerations or bradycardia	Reposition mother; amnioinfusion; with cord prolapse, manually elevate the presenting part while preparing for immediate delivery

[a]Simultaneous evaluation of the suspected cause(s) is also an important step in management of abnormal FHR tracings.

[b]The combination of multiple interventions simultaneously may be appropriate and potentially more effective than doing them individually or serially.

FHR = fetal heart rate.

Tocolysis

Terbutaline sulfate given to relax the uterus can be a temporizing maneuver in the management of nonreassuring fetal heart rate patterns during labor. A single 250-µg intravenous or subcutaneous injection is used to inhibit uterine contractions and thereby improve fetal oxygenation. Cook and Spinnato (1994) described their 10-year experiences with terbutaline tocolysis in 368 pregnancies. Such resuscitation improved fetal scalp blood pH values, although all fetuses underwent cesarean delivery. These investigators concluded that although the studies were small and rarely randomized, most reported favorable results with terbutaline tocolysis for nonreassuring patterns. Small intravenous doses of nitroglycerin—60 to 180 µg—also have been reported to be beneficial (Mercier, 1997). Bullens and associates (2015) concluded in their review that tocolysis was beneficial. Still, the American College of Obstetricians and Gynecologists (2017b) cites that evidence is insufficient to recommend tocolysis for nonreassuring fetal heart rate patterns.

Amnioinfusion

Miyazaki and Taylor (1983) infused saline through an intrauterine pressure catheter in laboring women who had either variable or prolonged decelerations attributed to cord entrapment. Such therapy improved the heart rate pattern in half of the women studied. Later, Miyazaki and Nevarez (1985) randomly assigned 96 nulliparas in labor with cord compression patterns and found that those who were treated with amnioinfusion required cesarean delivery for fetal distress less often. Based on many of these early reports, transvaginal amnioinfusion has been extended into three clinical areas (Dad, 2016). These include: (1) treatment of variable or prolonged decelerations; (2) prophylaxis for women with oligohydramnios, as with prolonged ruptured membranes; and (3) attempts to dilute or wash out thick meconium (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy).

Many different amnioinfusion protocols have been reported, but most provide a 500- to 800-mL bolus of warmed normal saline followed by a continuous infusion of approximately 3 mL/min (Owen, 1990; Pressman, 1996). In another study, Rinehart and colleagues (2000) gave either a 500-mL bolus of normal saline at room temperature alone or a similar bolus plus a continuous infusion at 3 mL/min. Their study included 65 women with variable decelerations, and the investigators found neither method to be superior. Wenstrom and associates (1995) surveyed use of amnioinfusion in teaching hospitals in the United States. The procedure was used in 96 percent of the 186 centers surveyed, and it was estimated that 3 to 4 percent of all women delivered at these centers received such infusion. Potential complications of amnioinfusion are summarized in Table 24-4.

TABLE 24-4

Complications Associated with Amnioinfusion from a Survey of 186 Obstetrical Units

Complication	No. of Centers (%)
Uterine hypertonus	27 (14)
Abnormal fetal heart rate tracing	17 (9)
Chorioamnionitis	7 (4)
Cord prolapse	5 (2)
Uterine rupture	4 (2)
Maternal cardiac or respiratory compromise	3 (2)
Placental abruption	2 (1)
Maternal death	2 (1)

Data from Wenstrom, 1995.

For variable decelerations, Hofmeyr and Lawrie (2012) reviewed the effects of amnioinfusion in the management of fetal heart rate patterns associated with umbilical cord compression. They concluded that amnioinfusion appeared to be useful in reducing the occurrence of variable decelerations, improving neonatal outcome, and lowering cesarean delivery rates. The American College of Obstetricians and Gynecologists (2016) has concluded that amnioinfusion is a reasonable approach in the treatment of repetitive variable decelerations regardless of meconium status.

For oligohydramnios, amnioinfusion has been used prophylactically to avoid intrapartum fetal heart rate patterns from cord occlusion. Nageotte and coworkers (1991) found that this resulted in significantly fewer and less severe variable decelerations in labor. However, the cesarean delivery rate or condition of term newborn was not improved. In a randomized investigation, Macri and colleagues (1992) studied prophylactic amnioinfusion in 170 term and postterm pregnancies complicated by both thick meconium and oligohydramnios. Amnioinfusion significantly reduced meconium aspiration syndrome rates and cesarean delivery rates for fetal distress. In contrast, Ogundipe and associates (1994) randomly assigned 116 term pregnancies with an amnionic fluid index <5 cm to receive prophylactic amnioinfusion or standard obstetrical care. Overall cesarean delivery rates, delivery rates for fetal distress, or umbilical cord acid–base studies did not differ significantly between groups.

For meconium-stained amnionic fluid, Pierce and associates (2000) reviewed 13 prospective trials of intrapartum amnioinfusion for 1924 women with meconium-stained fluid. In the amnioinfusion group, newborns were significantly less likely to have meconium below the vocal cords, and meconium aspiration syndrome rates were lower. The cesarean delivery rate was also reduced in the amnioinfusion group. Similar results were reported by Rathore and coworkers (2002).

In contrast, several investigators were not supportive of amnioinfusion for meconium staining. For example, Usta and associates (1995) reported that amnioinfusion was not feasible in half of women with moderate or thick meconium who were randomized to this treatment. These investigators were unable to demonstrate improved neonatal outcomes with this treatment. Spong and coworkers (1994) also concluded that although prophylactic amnioinfusion did dilute meconium, it did not improve perinatal outcome. Last, Fraser and colleagues (2005) randomized amnioinfusion in 1998 women with thick meconium-stained amnionic fluid in labor and found no benefits. Hofmeyr and associates (2014) reported mixed results from their review. Because of these findings, the American College of Obstetricians and Gynecologists (2016) does not recommend amnioinfusion to dilute meconium-stained amnionic fluid.

Fetal Heart Rate Patterns and Brain Injury

Studies that have attempted to correlate fetal heart rate patterns with brain injury primarily have examined infants identified in medicolegal actions. Phelan and Ahn (1994) reported that among 48 fetuses later found to be neurologically impaired, a persistent nonreactive fetal heart rate tracing was already present at the time of admission in 70 percent. They concluded that fetal neurological injury occurred predominately before arrival to the hospital. When they looked retrospectively at heart rate patterns in 209 brain-injured newborns, they concluded that there was not a single unique pattern associated with fetal neurological injury (Ahn, 1996). Graham and associates (2006) reviewed the world literature published between 1966 and 2006 on the effect of fetal heart rate monitoring to prevent perinatal brain injury and found no benefit.

Fetal heart rate patterns necessary for perinatal brain damage have been studied in experimental animals. Myers (1972) described the effects of complete and partial asphyxia in rhesus monkeys. Complete asphyxia was produced by total occlusion of umbilical blood flow that led to prolonged deceleration (Fig.

24-26). Fetal arterial pH did not drop to 7.0 until approximately 8 minutes after complete cessation of oxygenation and umbilical flow. At least 10 minutes of such prolonged deceleration was required before there was evidence of brain damage in surviving fetuses.

FIGURE 24-26
Prolonged deceleration in a rhesus monkey shown with blood pressure and biochemical changes during total occlusion of umbilical cord blood flow. (Data from Myers, 1972.)

Myers (1972) also produced partial asphyxia in rhesus monkeys by impeding maternal aortic blood flow. This resulted in late decelerations due to uterine and placental hypoperfusion. He observed that several hours of these late decelerations did not damage the fetal brain unless the pH fell below 7.0. Indeed, Adamsons and Myers (1977) reported subsequently that late decelerations were a marker of partial asphyxia long before brain damage occurred.

The most common fetal heart rate pattern during labor—due to umbilical cord occlusion—requires considerable time to significantly affect the fetus in experimental animals. Clapp and colleagues (1988) partially occluded the umbilical cord for 1 minute every 3 minutes in fetal sheep. Rocha and associates (2004) totally occluded the umbilical cord for 90 seconds every 30 minutes for 3 to 5 hours a day for 4 days without producing necrotic brain cell injury. Results from such studies suggest that the effects of umbilical cord entrapment depend on the degree of occlusion—partial versus total, the duration of individual occlusions, and the frequency of such occlusions.

The contribution of intrapartum events to subsequent neurological handicaps has been greatly overestimated, as discussed in further detail in Chapter 33 (Neonatal Encephalopathy). It is clear that for brain damage to occur, the fetus must be exposed to much more than a brief period of hypoxia. Moreover, the hypoxia must cause profound, just barely sublethal metabolic acidemia. Because of this, the American College of Obstetricians and Gynecologists (2014) has recommended umbilical cord blood gases be obtained whenever cesarean delivery is performed for fetal compromise, a low 5-minute Apgar score, severe fetal-growth restriction, an abnormal fetal heart rate tracing, maternal thyroid disease, or multifetal gestation (Chap. 32, Umbilical Cord Blood Acid–Base Studies).

Until recently, the prognosis for moderately affected newborns with hypoxic-ischemic encephalopathy (HIE) was poor. This has stimulated research aimed at mitigating these consequences. Animal experiments beginning in the late 1990s suggested that reducing brain temperature after an inciting event could reduce the incidence of cerebral damage (Gunn, 1997, 2000; Nedelcu, 2000; Tooley, 2003; Wagner, 2002). These findings led to several studies worldwide that showed brain cooling administered to newborns suffering neonatal HIE could ameliorate the development of subsequent cerebral palsy. These studies are further described in Chapter 33 (Cerebral Palsy).

Benefits of Electronic Fetal Heart Rate Monitoring

Several false assumptions underlie the expectation of improved perinatal outcome with electronic monitoring. One is that fetal distress is a slowly developing phenomenon and that electronic monitoring permits early detection of the compromised fetus. Another presumption is that all fetal injury develops in the hospital. Within the past 20 years, attention has focused on the reality that most neurologically damaged fetuses suffered insults before arrival at labor units. The very term *fetal monitor* implies that this inanimate technology in some fashion "monitors." The assumption is made that if a dead or damaged fetus is delivered, the tracing strip must provide some clue, because this device was monitoring fetal condition. All of these assumptions led to great expectations and fostered the belief that all neonatal deaths or injuries were preventable.

By the end of the 1970s, questions regarding the efficacy, safety, and costs of electronic monitoring were being voiced from the Office of Technology Assessment, the United States Congress, and the Centers for Disease Control and Prevention. Banta and Thacker (2002) reviewed 25 years of the controversy on the benefits, or lack thereof, of electronic fetal monitoring. More recently, Alfirevic and colleagues (2017) reviewed 13 randomized trials involving more than 37,000 women. They concluded that electronic fetal monitoring was associated with fewer neonatal seizures but a higher rate of cesarean and operative vaginal deliveries. Importantly, rates of perinatal mortality or cerebral palsy did not decline. Grimes and Peipert (2010) wrote a *Current Commentary* on electronic fetal monitoring in *Obstetrics & Gynecology.* They summarized that such monitoring, although it has been used in 85 percent of the almost 4 million annual births in the United States, has failed as a public health screening program. They noted that the positive-predictive value of electronic fetal monitoring for fetal death in labor or cerebral palsy is near zero—meaning that "almost every positive test result is wrong."

There have been at least two attempts to study the epidemiological effects of electronic fetal monitoring in the United States. Chen and coworkers (2011) used 2004 data on more than 1.7 million singleton live births, 89 percent of which underwent electronic fetal monitoring. They reported that monitoring raised operative delivery rates but lowered early neonatal mortality rates. This benefit was gestational-age dependent, however, and the highest effect was seen in preterm fetuses. Later, Ananth and colleagues (2013) reported a similar but larger epidemiological study in the United States. They studied nearly 58 million nonanomalous singleton liveborn neonates delivered between 1990 and 2004. The temporal increase in fetal monitoring use was associated with a decline in neonatal mortality rates, especially in preterm gestations. In an accompanying editorial, Resnik (2013) cautioned that an epidemiological association between fetal monitoring and reduced neonatal death does not establish causation. He suggested that the limitations of the study by Ananth should make the reader skeptical of the findings.

At Parkland Hospital in July 1982, an investigation began to ascertain whether all women in labor should undergo electronic monitoring (Leveno, 1986). In alternating months, universal electronic monitoring was rotated with selective heart rate monitoring, which was the prevailing practice. During the 3-year investigation, more than 17,000 labors were managed using universal electronic monitoring, and these outcomes were compared with a similar-sized cohort of women selectively monitored electronically. No significant differences were found in any perinatal outcome. With universal monitoring, a small but

significant increase in the cesarean delivery rate for fetal distress was noted. Thus, greater application of electronic monitoring at Parkland Hospital did not improve perinatal results but did slightly raise the frequency of cesarean delivery for fetal distress. More recently, a Cochrane Database review found that intermittent auscultation had a higher cesarean delivery rate compared with continuous monitoring (Martis, 2017).

Current Recommendations

Methods most commonly used for intrapartum fetal heart rate monitoring include auscultation with a fetal stethoscope or a Doppler ultrasound device, or continuous electronic monitoring of the fetal heart rate and uterine contractions. No scientific evidence has identified the most effective method, including the frequency or duration of fetal surveillance that ensures optimum results. Summarized in Table 24-5 are the recommendations of the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017). Intermittent auscultation or continuous electronic monitoring is considered an acceptable method of intrapartum surveillance in both low- and high-risk pregnancies. The recommended interval between checking the heart rate, however, is longer in the uncomplicated pregnancy. When auscultation is used, it is recommended that it be performed after a contraction and for 60 seconds. It also is recommended that a 1-to-1 nurse–patient ratio be used if auscultation is employed. The position taken by the American College of Obstetricians and Gynecologists (2017b) acknowledges that available data do not show a clear benefit to the use of electronic monitoring over intermittent auscultation. At Parkland Hospital, all high-risk labors are continuously monitored electronically. In low-risk pregnancies, both intermittent auscultation and continuous electronic monitoring are used depending on clinical circumstances, including the woman's desire to ambulate.

TABLE 24-5

Guidelines for Methods of Intrapartum Fetal Heart Rate Monitoring

Surveillance	Low-Risk Pregnancies	High-Risk Pregnancies
Acceptable methods		
Intermittent auscultation	Yes	Yes[a]
Continuous electronic monitoring (internal or external)	Yes	Yes[b]
Evaluation intervals		
First-stage labor (active)	30 min	15 min[a,b]
Second-stage labor	15 min	5 min[a,c]

[a]Preferably before, during, and after a uterine contraction.

[b]Includes tracing evaluation and charting at least every 15 min.

[c]Tracing should be evaluated at least every 5 min.

Data from the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists, 2017.

INTRAPARTUM SURVEILLANCE OF UTERINE ACTIVITY

Analysis of electronically measured uterine activity permits some generalities concerning the relationship of certain contraction patterns and labor outcome. However, uterine muscle efficiency to bring about delivery varies greatly. Thus, caution should be exercised before diagnosing true labor or its absence solely from a monitor tracing.

With *internal monitoring* of contractions, amnionic fluid pressure is measured between and during contractions. In the past, a fluid-filled plastic catheter with its distal tip located above the presenting part was used (Fig. 24-27). The catheter was connected to a strain-gauge pressure sensor adjusted to the same level as the catheter tip in the uterus. The amplified electrical signal produced in the strain gauge by variation in pressure within the fluid system was recorded on a calibrated moving paper strip simultaneously with the fetal heart rate recording. Today, intrauterine pressure catheters are used that have the pressure sensor in the catheter tip, which obviates the need for the fluid column.

FIGURE 24-27

Placement of an intrauterine pressure catheter to monitor contractions and their pressures. The catheter, contained within the introducer, is inserted into the birth canal and placed along one side of the fetal head. The catheter is then gently advanced into the uterus, and the introducer is withdrawn.

With *external monitoring*, uterine contractions can be measured by a displacement transducer in which the transducer button, or "plunger," is held against the maternal abdominal wall. As the uterus contracts, the button moves in proportion to the strength of the contraction. This movement is converted into a measurable electrical signal that indicates the *relative* intensity of the contraction. It has generally been accepted that internal monitoring provided a more accurate measure of intensity. That said, Bakker and associates (2010) performed a randomized trial comparing internal versus external monitoring of uterine contractions in 1456 women. The two methods were equivalent in terms of operative delivery rates and neonatal outcomes.

Patterns of Uterine Activity

Caldeyro-Barcia and Poseiro (1960), from Montevideo, Uruguay, were pioneers in elucidating the patterns of spontaneous uterine activity throughout pregnancy. Contractile waves of uterine activity were usually measured using intraamnionic pressure catheters. But early in their studies, as many as four simultaneous intramyometrial microballoons were also used to record uterine pressure. Contraction intensity was defined as the rise in this pressure above a resting pressure baseline. These investigators also introduced the concept of *Montevideo units* to define uterine activity (Chap. 23, Active-Phase Protraction). With this definition, uterine performance is the product of contraction intensity in mm Hg multiplied by the number of contractions in a 10-minute span. For example, three contractions in 10 minutes, each of 50 mm Hg intensity, would equal 150 Montevideo units.

During the first 30 weeks of pregnancy, uterine activity is comparatively quiescent. Contractions are seldom greater than 20 mm Hg, and these have been equated with those first described by John Braxton Hicks. Uterine activity increases gradually after 30 weeks, and it is noteworthy that these *Braxton Hicks contractions* also increase in intensity and frequency. Uterine activity is further enhanced during the last weeks of pregnancy. During this phase, the cervix ripens (Chap. 21, Cervical Ripening).

According to Caldeyro-Barcia and Poseiro (1960), clinical labor usually commences when uterine activity reaches values between 80 and 120 Montevideo units. This translates into approximately three contractions of 40 mm Hg every 10 minutes. Importantly, no clear-cut division marks labor onset, which is a gradual and progressive transition.

In first-stage labor, uterine contractions progressively grow in intensity from approximately 25 mm Hg at labor commencement to 50 mm Hg at its end. At the same time, the frequency advances from three to five contractions per 10 minutes, and uterine baseline tone rises from 8 to 12 mm Hg. Uterine activity is further enhanced during second-stage labor, aided by maternal pushing. Indeed, contraction intensity of 80 to 100 mm Hg is typical, and the uterus contracts as frequently as five to six times each 10 minutes. Hauth and coworkers (1986) quantified uterine contraction pressures in 109 women at term who received oxytocin for labor induction or augmentation. Most of these women achieved 200 to 225 Montevideo units, and 40 percent had up to 300 units to effect delivery. The authors suggested that these levels of uterine activity should be sought before consideration of cesarean delivery for presumed dystocia (Chap. 23, Active-Phase Protraction).

Interestingly, the duration of uterine contractions—60 to 80 seconds—does not lengthen appreciably from early active labor through the second stage (Bakker, 2007; Pontonnier, 1975). Presumably, this duration constancy serves fetal respiratory gas exchange. During a uterine contraction, as the intrauterine pressure exceeds that of the intervillous space, respiratory gas exchange is halted. This leads to functional fetal "breath holding," which has a 60- to 80-second limit that remains relatively constant.

Caldeyro-Barcia and Poseiro (1960) also observed empirically that uterine contractions are clinically palpable only after their intensity exceeds 10 mm Hg. Moreover, until the intensity of contractions reaches 40 mm Hg, the uterine wall can readily be depressed by the finger. At greater intensities, the uterine wall then becomes so hard that it resists easy depression. Uterine contractions usually are not associated with pain until their strength exceeds 15 mm Hg. Presumably, this is the minimum pressure required to distend the lower uterine segment and cervix. It follows that Braxton Hicks contractions exceeding 15 mm Hg may be perceived as uncomfortable because distention of the uterus, cervix, and birth canal is generally thought to produce discomfort.

Hendricks (1968) observed that "the clinician makes great demands upon the uterus." The uterus is expected to remain well relaxed during pregnancy, to contract effectively but intermittently during labor, and then to remain in a state of almost constant contraction for several hours postpartum. Figure 24-28 demonstrates an example of normal uterine activity during labor. Uterine activity progressively and gradually rises from early through late labor. Interestingly, uterine contractions after birth are identical to those resulting in delivery of the newborn. Logically, the uterus that performs poorly before delivery is also prone to atony and puerperal hemorrhage.

FIGURE 24-28
Intrauterine pressure recorded through a single catheter. **A.** Prelabor. **B.** Early labor. **C.** Active labor. **D.** Late labor. **E.** Spontaneous activity ½ hour postpartum. **F.** Spontaneous activity 2½ hours postpartum. (Redrawn from Hendricks CH: Uterine contractility changes in the early puerperium, Clin Obstet Gynecol. 1968 Mar;11(1):125–144.)

Origin and Propagation of Contractions

The normal contractile wave of labor originates near the uterine end of one of the fallopian tubes. Thus, these areas act as "pacemakers" (Fig. 24-29). The right pacemaker usually predominates over the left and starts most contractile waves. Contractions spread from the pacemaker area throughout the uterus at 2 cm/sec, and the whole organ is depolarized within 15 seconds. This depolarization wave propagates downward toward the cervix. Intensity is greatest in the fundus, and it diminishes in the lower uterus. This phenomenon is thought to reflect the reduced myometrial thickness from the fundus to the cervix. Presumably, this descending pressure gradient serves to direct fetal descent toward the cervix and to efface the cervix. Importantly, all parts of the uterus are

synchronized and reach their peak pressure almost simultaneously, giving rise to the curvilinear waveform shown in Figure 24-29. Young and Zhang (2004) have shown that the initiation of each contraction is triggered by a tissue-level bioelectrical event.

FIGURE 24-29
Schematic representation of the normal contractile wave of labor. Large uterus on the left shows the four points at which intramyometrial pressure was recorded with microballoons. Four corresponding pressure tracings are shown in relation to each other by shading on the small uteri at top. (Adapted with permission from Caldeyro-Barcia R, Poseiro JJ: Physiology of the uterine contraction. Clin Obstet Gynecol 1960 3:386.)

The pacemaker theory also serves to explain the varying intensity of adjacent coupled contractions shown in panels A and B of Figure 24-28. Such coupling was termed *incoordination* by Caldeyro-Barcia and Poseiro (1960). A contractile wave begins in one cornual-region pacemaker but does not synchronously depolarize the entire uterus. As a result, another contraction begins in the contralateral pacemaker and produces the second contractile wave of the couplet. These small contractions alternating with larger ones appear to be typical of early labor. Indeed, labor may progress with such uterine activity, albeit at a slower pace. These authors also observed that labor would progress slowly if regular contractions were hypotonic—that is, contractions with intensity <25 mm Hg or frequency <2 per 10 minutes.

Uterine Contraction Terminology

Terms for the description and quantification of uterine contractions have been recommended by the American College of Obstetricians and Gynecologists (2017b). *Normal uterine activity* is defined as five or fewer contractions in 10 minutes, averaged during a 30-minute span. *Tachysystole* is more than five contractions in 10 minutes, averaged over 30 minutes. Tachysystole can be applied to spontaneous or induced labor. The term *hyperstimulation* was abandoned.

Stewart and associates (2012) prospectively studied uterine tachysystole in 584 women undergoing labor induction with misoprostol at Parkland Hospital. A higher rate of adverse neonatal outcomes was not associated with an increasing number of contractions per 10 minutes or per 30 minutes. Counts of six or more contractions in 10 minutes, however, were significantly associated with fetal heart rate decelerations.

Electronic Fetal Monitoring Complications

Electrodes for fetal heart rate evaluation and catheters for uterine contraction measurement are both associated with infrequent but potentially serious complications. Rarely, an intrauterine pressure catheter during placement may lacerate a fetal vessel in the placenta. Also with insertion, placental and possibly uterine perforation can cause hemorrhage, abruption, serious morbidity, and spurious recordings that have resulted in inappropriate management. Severe cord compression has been described from entanglement with the pressure catheter. Injury to the fetal scalp or breech by a heart rate electrode is rarely severe. However, application at some other site—such as the eye in face presentations—can be serious.

Both the fetus and the mother may be at greater risk of infection from internal monitoring (Faro, 1990). Scalp wounds from the electrode may become infected, and subsequent cranial osteomyelitis has been reported (Brook, 2005; Eggink, 2004; McGregor, 1989). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have recommended that certain maternal infections, including human immunodeficiency virus (HIV), herpes simplex virus, and hepatitis B and C virus, are relative contraindications to internal fetal monitoring.

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CHAPTER 25: Obstetrical Analgesia and Anesthesia

We are indebted to Sir James Y. Simpson, the discoverer of chloroform, for the introduction of anaesthesia into obstetrical practice. He employed ether for this purpose in 1847, and replaced it by chloroform. Every one agrees as to the marked benefits derived from anaesthesia when operative procedures are to be undertaken, but there is still considerable difference of opinion as to the advisability of its routine employment in normal labour.

—J. Whitridge Williams (1903)

INTRODUCTION

As cited by Williams, anesthetic techniques were a most welcome addition to obstetrics. That said, obstetrical anesthesia presents unique challenges. Labor begins without warning, and anesthesia may be required within minutes of a full meal. Vomiting with potential aspiration of the gastric contents is a constant threat due to delayed gastric emptying during pregnancy. Disorders of pregnancy such as preeclampsia, placental abruption, or sepsis further compound provision of obstetrical anesthesia.

Of all anesthesia-related deaths in the United States from 1995 to 2005, 3.6 percent were in pregnant women (Li, 2009). Creanga and colleagues (2017) analyzed deaths of women during or within 1 year of pregnancy in the United States from 2011 through 2013. Of these deaths, they found that 3 of 2009 (0.2 percent) were attributable to anesthesia complications. As shown in Table 25-1, between 1979 and 2002, anesthesia-related maternal mortality rates decreased nearly 60 percent, and currently approximately five deaths per million live births are attributed to anesthesia complications.

TABLE 25-1

Case-Fatality Rates and Rate Ratios of Anesthesia-Related Deaths During Cesarean Delivery by Type of Anesthesia in the United States, 1979–2002

	Case-Fatality Rates[a]		
Year	**General**	**Regional**	**Rate Ratios**
1979–1984	20.0	8.6	2.3 (95% CI 1.9–2.9)
1985–1990	32.3	1.9	16.7 (95% CI 12.9–21.8)
1991–1996	16.8	2.5	6.7 (95% CI 3.0–14.9)
1997–2002	6.5	3.8	1.7 (95% CI 0–4.6)

[a]Deaths per million general or regional anesthetics.

CI = confidence interval.

Data from Hawkins, 2011.

About two thirds of deaths associated with general anesthesia are caused by intubation failure or induction problems during cesarean delivery. Deaths associated with regional analgesia are caused by high spinal or epidural blocks—26 percent; respiratory failure—19 percent; and drug reaction—19 percent. The improved case-fatality rate for general anesthesia is especially notable considering that such anesthesia is now used for the highest-risk patients and the most hurried emergencies, that is, decision-to-incision intervals <15 minutes (Bloom, 2005).

The most significant factor linked to lower maternal mortality rates is the greater use of regional analgesia (Hawkins, 2011). In-house anesthesia coverage that is available around the clock is certainly another contributing factor. Logically, with increased use of regional analgesia, there are now reports of complications with these techniques. Indeed, compared to pre-1990 data, post-1990 obstetrical anesthesia was associated with more legal claims involving regional analgesia (Davies, 2009). In a recent analysis of 466,442 obstetrical hospital discharges, complications associated with regional analgesia accounted for 81 percent of anesthesia-related adverse events (Guglielminotti, 2015).

For the fetus, recent human studies suggest that single, relatively short exposure to general anesthetic and sedation is unlikely to have negative effects on subsequent behavior or learning. This evidence is presented in Chapter 46 (Medications and Surgeries). That said, in 2016, the Food and Drug Administration (FDA) warned that repeated or lengthy use of general anesthetic and sedation drugs in pregnant women during their third trimester may affect fetal brain development. Listed drugs include inhalation agents used in general anesthesia as well as lorazepam, ketamine, propofol, and midazolam. Notably, the American College of

Obstetricians and Gynecologists (2016a) and the Society for Obstetric Anesthesia and Perinatology (2017) have voiced concerns with this statement and cited the lack of significant human data, especially in pregnant women, to underpin this warning.

GENERAL PRINCIPLES

Obstetrical Anesthesia Services

The American College of Obstetricians and Gynecologists (2017a) recognizes that a woman's request for labor pain relief is sufficient medical indication for its provision. Identification of any of the risk factors shown in Table 25-2 should prompt consultation with anesthesia personnel to permit a joint management plan. This plan should include strategies to minimize the need for emergency anesthesia.

TABLE 25-2

Maternal Factors That May Prompt Anesthetic Consultation

Body mass index >30 kg/m^2
Short or thick neck or skeletal neck abnormality
Obstructive lesions: edema, anatomical abnormalities, trauma
Decreased range of motion in opening the mouth or small mandible
Thyromegaly or other neck tumor
Severe preeclampsia syndrome
Bleeding disorders
Obstetrical complications with a high risk of operative delivery
Maternal medical complications such as cardiopulmonary disease
Previous anesthetic complications

Goals for optimizing obstetrical anesthesia services have been established by the American College of Obstetricians and Gynecologists (2017a) and the American Society of Anesthesiologists (2016) and include:

1. Availability of a licensed practitioner who is credentialed to administer an appropriate anesthetic whenever necessary and to maintain support of vital functions in an obstetrical emergency.
2. Availability of anesthesia personnel to permit the start of a cesarean delivery within 30 minutes of the decision to perform the procedure.
3. Anesthesia personnel immediately available to perform an emergency cesarean delivery during the active labor of a woman attempting vaginal birth after cesarean (Chap. 31, Labor and Delivery Considerations).
4. Appointment of a qualified anesthesiologist to be responsible for all anesthetics administered.
5. Availability of a qualified physician with obstetrical privileges to perform operative vaginal or cesarean delivery during administration of anesthesia.
6. Availability of equipment, facilities, and support personnel equal to that provided in any surgical suite.
7. Immediate availability of personnel, other than the surgical team, to assume responsibility for resuscitation of a depressed newborn (Chap. 32, Transition to Air Breathing).

To meet these goals, 24-hour, in-house anesthesia coverage is usually necessary. Providing such service in smaller facilities is more challenging—a problem underscored by the fact that approximately a third of all hospitals providing obstetrical care perform fewer than 500 deliveries per year. The financial burden incurred to provide 24/7 obstetrical anesthesia coverage may result in cost deficits (Bell, 2000). Compounding this burden, some third-party payers have denied reimbursement for epidural analgesia in the absence of a specific medical indication—an approach repudiated by the American College of Obstetricians and Gynecologists (2017a).

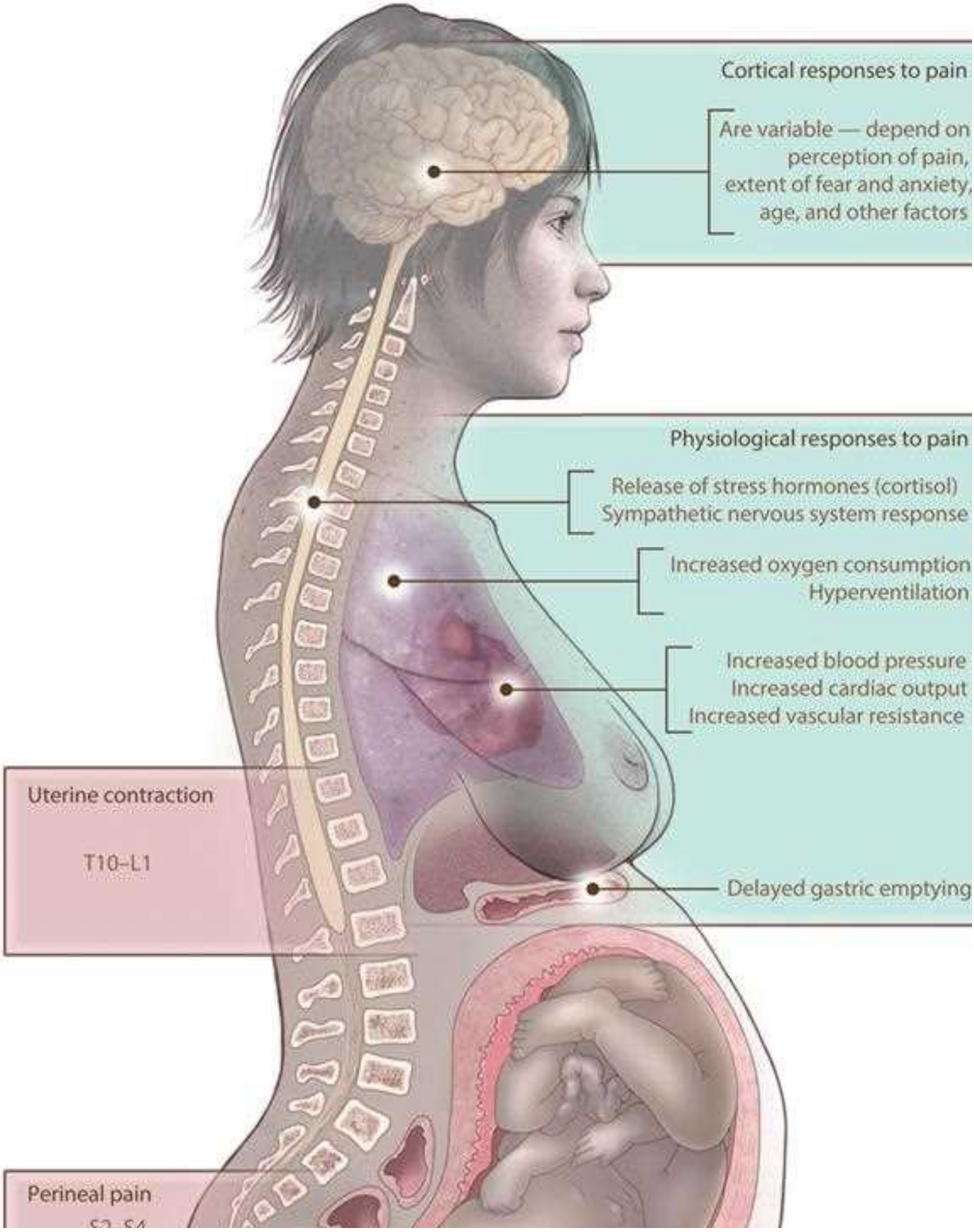
Regarding obstetricians, they should be proficient in local and pudendal analgesia. These may be administered in appropriately selected circumstances described in Central Nervous System Toxicity.

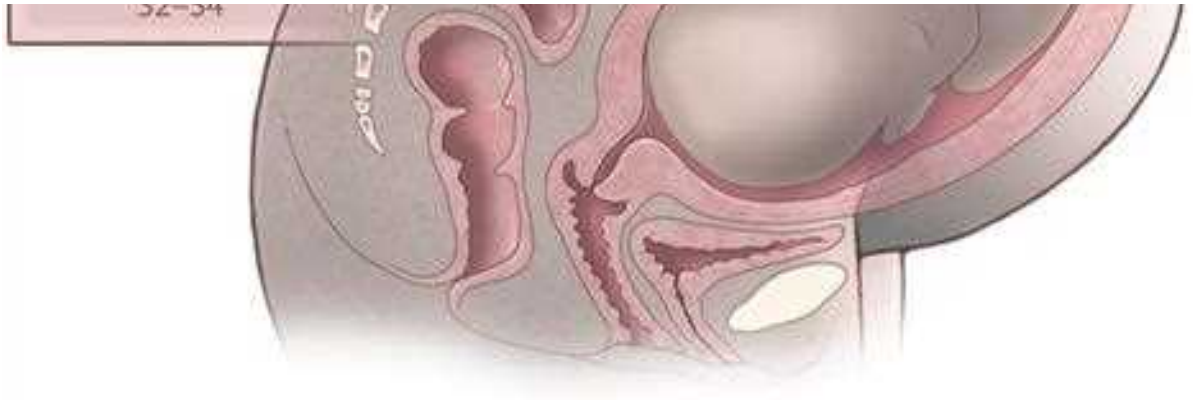
Pain Relief Principles

Hawkins (2010) emphasized that labor pain is a highly individual response to variable stimuli that are uniquely received and interpreted (Fig. 25-1). These stimuli are modified by emotional, motivational, cognitive, social, and cultural circumstances. Labor pain caused by uterine contractions and cervical dilation is transmitted through visceral afferent sympathetic nerves entering the spinal cord from T_{10} through L_1. Later in labor, perineal stretching transmits painful stimuli through the pudendal nerve and sacral nerves S_2 through S_4. Cortical responses to pain and anxiety during labor are complex and may be influenced by maternal expectations for childbirth, her age, preparation through education, emotional support, and other factors. Pain perception is heightened by fear and the need to move into various positions. A woman may be motivated to have a certain type of birthing experience, and these opinions will influence her judgment regarding pain management.

FIGURE 25-1

Sources of pain during labor and maternal physiological responses. (Reproduced with permission from Hawkins JL: Epidural analgesia for labor and delivery, N Engl J Med. 2010 Apr 22;362(16):1503–1510.)





Maternal physiological responses to labor pain can influence maternal and fetal well-being and labor progress. For example, hyperventilation may induce hypocarbia. A greater metabolic rate augments oxygen consumption. Increases in cardiac output and vascular resistance may raise maternal blood pressure. Pain, stress, and anxiety trigger release of stress hormones such as cortisol and β-endorphins. The sympathetic nervous system response to pain leads to a marked elevation in circulating catecholamines that can adversely affect uterine activity and uteroplacental blood flow. Effective analgesia attenuates or eliminates these responses.

ANALGESIA AND SEDATION DURING LABOR

If uterine contractions and cervical dilatation cause discomfort, pain relief is offered. If neuraxial analgesia is contraindicated or unavailable or is declined, a narcotic from Table 25-3 plus one of the tranquilizer-antiemetic drugs such as promethazine (Phenergan) is usually appropriate. With a successful program of analgesia and sedation, the mother ideally rests quietly between contractions. In this circumstance, discomfort usually is felt at the acme of an effective uterine contraction.

TABLE 25-3

Some Parenteral Analgesic Agents for Labor Pain

Agent	Usual Dose	Frequency	Onset	Neonatal Half-Life
Meperidine	25–50 mg (IV)	Q 1–2 hr	5 min (IV)	~18–20 hr
	50–100 mg (IM)	Q 2–4 hr	30–45 min (IM)	~60 hr
Fentanyl	50–100 µg (IV)	Q 1 hr	1 min	~5 hr
Morphine	2–5 mg (IV)	Q 4 hr	5 min (IV)	~7 hr
	10 mg (IM)		30–40 min (IM)	

IV = intravenously; IM = intramuscularly; Q = every.

Parenteral Agents

Meperidine and Promethazine

Meperidine, 50 to 100 mg, with promethazine, 25 mg, may be administered intramuscularly at intervals of 2 to 4 hours. A more rapid effect is achieved by giving meperidine intravenously in doses of 25 to 50 mg every 1 to 2 hours. Whereas analgesia is maximal 30 to 45 minutes after an intramuscular injection, it develops almost immediately following intravenous administration. Meperidine readily crosses the placenta and can have a prolonged half-life in the newborn (American College of Obstetricians and Gynecologists, 2017a). Its depressant effect in the fetus follows closely behind the peak maternal analgesic effect.

According to Bricker and Lavender (2002), meperidine is the most common opioid used worldwide for pain relief during labor. In one randomized study at Parkland Hospital, patient-controlled intravenous analgesia with meperidine was found to be an inexpensive and reasonably effective method for labor analgesia (Sharma, 1997). Women randomized to self-administered analgesia were given a 50-mg meperidine plus 25-mg promethazine dose intravenously as an initial bolus. Thereafter, an infusion pump was set to deliver 15 mg of meperidine every 10 minutes as needed until delivery. Neonatal sedation, as measured by the need for naloxone treatment in the delivery room, was identified in 3 percent of newborns. Both meperidine and its metabolite, normeperidine, are lipophilic and readily cross the placenta. Analgesia with meperidine was associated with lower Apgar scores in comparison to epidural analgesia (Sharma, 2004). Normeperidine is a strong respiratory depressant that has a significantly longer half-life than meperidine and is likely responsible for the fetal side effects of meperidine.

Butorphanol

This synthetic opioid receptor agonist–antagonist analgesic, given in 1- to 2-mg intravenous doses, compares favorably with 40 to 60 mg of meperidine. Its major side effects are somnolence, dizziness, and dysphoria. Neonatal respiratory depression is reported to be less than with meperidine. Importantly, the two drugs are not given contiguously because butorphanol antagonizes the narcotic effects of meperidine. Butorphanol has been associated with transient sinusoidal fetal heart rate patterns (Hatjis, 1986).

Nalbuphine

This is another mixed opioid receptor agonist–antagonist analgesic. It can be given intramuscularly, intravenously, or subcutaneously. The usual dose is 10 to 20 mg, administered every 4 to 6 hours irrespective of the route of administration. Small doses of nalbuphine may also be used to treat pruritus associated with neuraxial opioids.

Fentanyl

This short-acting and potent synthetic opioid may be given in doses of 50 to 100 µg intravenously every hour. Its main disadvantage is its short duration of action, which requires frequent dosing or use of a patient-controlled intravenous infusion pump.

Remifentanil

This is a synthetic opioid with an extremely rapid onset of action. It is hydrolyzed rapidly, resulting in a half-life of 3.5 minutes (Ohashi, 2016). Although it readily crosses the placenta, it is quickly metabolized or redistributed within the fetus (Kan, 1998). Various dosing regimens have been studied, and single boluses appear to mirror the periodic uterine contraction pattern. Infusions, on the other hand, have been reported to cause maternal apnea (Waring, 2007). Due to the aforementioned risks, only trained personnel should administer it, and only under strictly controlled circumstances.

Efficacy and Safety of Parenteral Agents

Hawkins and colleagues (1997) reported that four of 129 maternal anesthetic-related deaths were from parenteral sedation—one from aspiration, two from inadequate ventilation, and one from overdosage. Opioids used during labor may cause newborn respiratory depression. Naloxone is a narcotic antagonist capable of reversing this respiratory depression. It acts by displacing the narcotic from specific receptors in the central nervous system. Withdrawal symptoms may be precipitated in recipients who are physically dependent on narcotics. For this reason, naloxone is contraindicated in a newborn of a narcotic-addicted mother.

Nitrous Oxide

Inhaled nitrous oxide has a rapid onset and offset that provides analgesia during episodic contractions. It can be self-administered as a mixture of 50-percent nitrous oxide and 50-percent oxygen premixed in a single cylinder (Entonox) or using a blender that mixes the two gases from separate tanks (Nitronox). The gases are connected to a breathing circuit through a one-way valve that opens only during inspiration. The use of intermittent nitrous oxide for labor pain is generally regarded as safe for the mother and newborn, but pain control is less effective than epidural analgesia (Barbieri, 2014; Likis, 2014). In many cases, nitrous oxide simply serves to delay more definitive neuraxial analgesia. For maximal efficacy, nitrous oxide is inhaled 30 seconds prior to the start of a contraction, although this prevents adequate rest for the mother. Nitrous oxide is also associated with nausea and vomiting. The environmental and health risk of its use without proper scavenging remains to be carefully evaluated (King, 2014).

REGIONAL ANALGESIA

Various nerve blocks have been developed over the years to provide pain relief during labor and/or delivery. These include pudendal, paracervical, and neuraxial blocks such as spinal, epidural, and combined spinal-epidural techniques.

Anesthetic Agents

Some of the more commonly used nerve block anesthetics, along with their usual concentrations, doses, and durations of action, are summarized in Table 25-4. The dose of each agent varies widely and is dependent on the particular nerve block and physical status of the woman. The onset, duration, and quality of analgesia can be enhanced by raising the volume and/or concentration. This can be done safely only by incrementally administering small-volume boluses of the agent and by carefully monitoring early warning signs of toxicity. Administration of these agents must be followed by appropriate monitoring for adverse reactions. Equipment and personnel to manage these reactions must be immediately available.

TABLE 25-4

Local Anesthetic Agents Commonly Used in Obstetrics

Anesthetic Agent[a]	Usual Concentration (%)	Usual Volume (mL)	Onset	Average Duration (min)	Maximum Dose (mg)	Clinical Use
Aminoesters[b]						
2-Chloroprocaine	2 3	10–20 10–20	Rapid	30–60 30–60	800	Local infiltration or pudendal block Epidural *only* for cesarean
Aminoamides[b]						
Bupivacaine	0.0625–0.125 0.75	10–15 1.5–2	Slow	60–90 60–120	175	Epidural for labor Spinal for cesarean
Lidocaine	1–1.5 1.5–2 5	10–20 5–20 1.5–2	Rapid	30–60 60–90 45–60	300	Local infiltration or pudendal block Epidural for labor or cesarean Spinal for D&C or puerperal tubal
Ropivacaine	0.08–0.2 0.5–1	5–10 10–30	Slow	60–90 90–150	200 250	Epidural for labor Epidural for cesarean

[a]Without epinephrine.

[b]Esters are hydrolyzed by plasma cholinesterases and amides by hepatic clearance.

D&C = dilatation and curettage.

Data from Liu SS, Lin Y: Local anesthetics. In Barash P, Cullen B, Stoeling R, et al (eds): Clinical Anesthesia, 6th ed. Philadelphia, Lippincott Williams & Wilkins, 2009.

Most often, serious toxicity follows inadvertent intravenous injection. Systemic toxicity from local anesthetics typically manifests in the central nervous and cardiovascular systems. For this reason, when epidural analgesia is initiated, dilute epinephrine is sometimes added and given as a test dose. A sudden significant rise in the maternal heart rate or blood pressure immediately after administration suggests intravenous catheter placement. This should halt further injection and should prompt catheter repositioning. Local anesthetic agents are manufactured in more than one concentration and ampule size, which raises the potential for dosing errors.

Central Nervous System Toxicity

Early symptoms are those of *stimulation,* but as serum levels rise, *depression* follows. Symptoms may include light-headedness, dizziness, tinnitus, metallic taste, and numbness of the tongue and mouth. Patients may show bizarre behavior, slurred speech, muscle fasciculation and excitation, and ultimately, generalized convulsions, followed by loss of consciousness.

Cardiovascular Toxicity

These manifestations generally develop later than those of cerebral toxicity. Moreover, no symptoms may develop because signs are usually induced by higher serum drug levels. The notable exception is bupivacaine, which is associated with neurotoxicity and cardiotoxicity at virtually identical levels (Mulroy, 2002). Because of its toxicity risk, use of a 0.75-percent solution of bupivacaine for epidural injection has been proscribed by the FDA. Similar to neurotoxicity, cardiovascular toxicity is characterized first by stimulation and then by depression. Accordingly, hypertension and tachycardia are soon followed by hypotension, cardiac arrhythmias, and impaired uteroplacental perfusion.

Management of Local Anesthetic Systemic Toxicity

Seizures and severe ventricular arrhythmias can follow large doses of local anesthetics that are given inadvertently. Labor and delivery units should be stocked with a 20-percent lipid emulsion solution (Intralipid). It is administered as a rapid intravenous bolus followed by an infusion upon the first sign of local anesthetic systemic toxicity (Neal, 2012). Controlling seizures and securing the airway are essential to prevent aspiration and hypoxemia. Benzodiazepines, such as midazolam or lorazepam, may be used to help control seizures, particularly if lipid emulsions are not available. Magnesium sulfate also controls convulsions (Chap 40, Management of Eclampsia). Abnormal fetal heart rate patterns that include late decelerations or bradycardia can follow and stem from maternal hypoxia. With proper management, including supportive measures, the fetus usually recovers. Therefore, it is best for the fetus and mother to delay delivery until the mother is stabilized.

With proper treatment of local anesthetic systemic toxicity (LAST) with lipid emulsions, vital signs usually return to normal. The woman, however, should be monitored, placed in the lateral decubitus position to avoid aortocaval compression, and provided continued supportive care. Vasopressors can be used to support

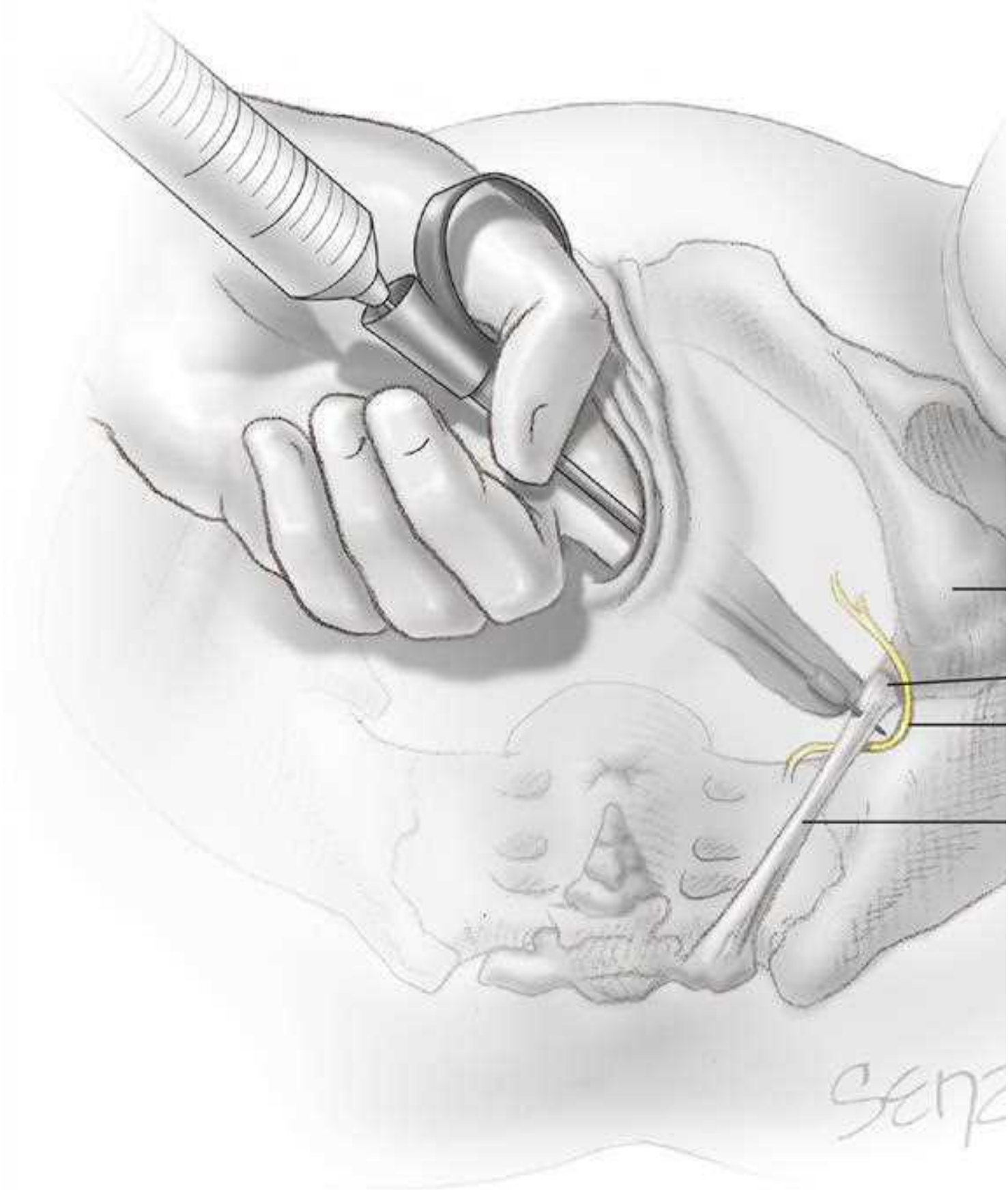
blood pressure. With cardiac arrest, emergency cesarean delivery is considered if maternal vital signs have not been restored within 5 minutes (Chap, 47, Cardiopulmonary Resuscitation). As with convulsions, however, the fetus is likely to recover more quickly in utero once maternal cardiac output is reestablished.

Pudendal Block

Pain with vaginal delivery arises from stimuli from the lower genital tract. These are transmitted primarily through the pudendal nerve, the peripheral branches of which provide sensory innervation to the perineum, anus, vulva, and clitoris. The pudendal nerve passes beneath the sacrospinous ligament just as the ligament attaches to the ischial spine. Sensory nerve fibers of the pudendal nerve are derived from ventral branches of the S_2 through S_4 nerves.

The pudendal nerve block is a relatively safe and simple method of providing analgesia for spontaneous delivery. As shown in Figure 25-2, a tubular introducer is used to sheathe and guide a 15-cm-long 22-gauge needle into position near the pudendal nerve. The end of the introducer is placed against the vaginal mucosa just beneath the tip of the ischial spine. The introducer allows 1.0 to 1.5 cm of needle to protrude beyond its tip, and the needle is pushed beyond the introducer tip into the mucosa. A mucosal wheal is made with 1 mL of 1-percent lidocaine solution or an equivalent dose of another local anesthetic (see Table 25-4). To guard against intravascular infusion, aspiration is attempted before this and all subsequent injections. The needle is then advanced until it touches the sacrospinous ligament, which is infiltrated with 3 mL of lidocaine. The needle is advanced farther through the ligament. As the needle pierces the loose areolar tissue behind the ligament, resistance against the plunger drops. Another 3 mL of solution is injected in this region. Next, the needle is withdrawn into the introducer, which is moved to a point just above the ischial spine. The needle is inserted through the mucosa and a final 3 mL is deposited. The procedure is then repeated on the other side.

FIGURE 25-2
Local infiltration of the pudendal nerve. Transvaginal technique showing the needle extended beyond the needle guard and passing through the sacrospinous ligament to reach the pudendal nerve.



Within 3 to 4 minutes of injection, a successful pudendal block will allow pinching of the lower vagina and posterior vulva bilaterally without pain. If delivery occurs before the pudendal block becomes effective and an episiotomy is indicated, then the fourchette, perineum, and adjacent vagina can be infiltrated with 5 to 10 mL of 1-percent lidocaine solution directly at the planned episiotomy site. By the time of repair, the pudendal block usually has become effective.

Pudendal block usually does not provide adequate analgesia when delivery requires extensive obstetrical manipulation. Moreover, such analgesia is usually inadequate for women in whom complete visualization of the cervix and upper vagina or manual exploration of the uterine cavity is indicated.

Infrequently, complications may follow this block. As previously described, intravascular injection of a local anesthetic agent may cause serious systemic toxicity. Hematoma formation from perforation of a blood vessel is most likely when there is a coagulopathy (Lee, 2004). Rarely, severe infection may originate at the injection site. The infection may spread posteriorly to the hip joint, into the gluteal musculature, or into the retropsoas space (Svancarek, 1977).

Paracervical Block

This block usually provides satisfactory pain relief during first-stage labor. However, because the pudendal nerves are not blocked during paracervical blockade, additional analgesia is required for delivery. For paracervical blockade, usually 5 to 10 mL of lidocaine (1 to 2 percent) or chloroprocaine (3 percent) is injected into the cervix laterally at 3 and 9 o'clock. Because these anesthetics are relatively short acting, this block may have to be repeated during labor.

Fetal bradycardia is a worrisome complication that occurs with approximately 15 percent of paracervical blocks (Rosen, 2002). Bradycardia usually develops within 10 minutes and may last up to 30 minutes. Doppler studies have shown a rise in the pulsatility index of the uterine arteries following paracervical blockade. These observations support the hypothesis of drug-induced arterial vasospasm as a cause of fetal bradycardia (Manninen, 2000). For these reasons, paracervical block is not used in situations of potential fetal compromise.

NEURAXIAL ANALGESIA

Epidural, spinal, or combined spinal-epidural techniques are the most common methods used for pain relief during labor and delivery. In the United States in 2008, epidural analgesia was used in nearly 70 percent of mothers during labor and had a success rate of 98.8 percent. Neuraxial analgesia was used even more often in operative vaginal deliveries and supported 84 percent of forceps deliveries and 77 percent of vacuum extractions (Osterman, 2011).

Spinal (Subarachnoid) Block

Anesthetic in this block can be given as a single dose, can be partnered with an epidural catheter as combined spinal-epidural analgesia, or can be administered as a continuous infusion. Injection of a local anesthetic into the subarachnoid space to effect analgesia has long been used for delivery. Advantages include rapid analgesia onset, short duration of action, and high success rate. The subarachnoid space during pregnancy is smaller, which likely results from internal vertebral venous plexus engorgement. Thus, in parturients, the same amount of anesthetic agent in the same volume of solution produces a much higher blockade than in nonpregnant women.

Vaginal Delivery

The first stage of labor requires a sensory block to the level of the umbilicus (T_{10}). During the second stage of labor and for operative vaginal delivery, a sensory block of S_2 through S_4 is usually adequate to cover pain from perineal stretching and/or instrumentation. Analgesic options include continuous lumbar epidural analgesia, combined spinal-epidural, continuous spinal analgesia, and other blocks such as pudendal and paracervical blocks.

Local anesthetic agents are usually given to establish a sensory block to the desired dermatome level. They are almost exclusively used in conjunction with neuraxial opioids. The mechanism of action is a function of the administration route and lipid solubility. Analgesia is induced by absorption into the vascular system (supraspinal), actions on the dorsal horns, and direct spread in the cerebrospinal fluid to the brainstem. Highly-soluble lipid opioids such as fentanyl and sufentanil have a rapid onset of action. But, because they are absorbed into lipid membranes and the epidural vasculature, their duration of action is short. Hydrophilic solutions such as morphine, on the other hand, provide extended analgesia (Lavoie, 2013). The major advantages of using such a combination are the rapid onset of pain relief, a decrease in shivering, and less dense motor blockade. Side effects are common and include pruritus and urinary retention. Nalbuphine, 2.5 to 5 mg intravenously, can be used to treat pruritis without diminishing the analgesic effect.

Cesarean Delivery

A level of sensory blockade extending to the T_4 dermatome is desired for cesarean delivery. Depending on maternal size, 10 to 12 mg of bupivacaine in a hyperbaric solution or 50 to 75 mg of lidocaine hyperbaric solution is administered. The addition of opioid increases the rapidity of blockade onset, reduces shivering, and minimizes referred pain and other symptoms such as nausea and vomiting. The addition of a preservative-free morphine (Duramorph or Astramorph), 0.1 to 0.3 mg intrathecal or 2 to 4 mg epidural, provides pain control up to 24 hours postoperatively.

Complications

Hypotension

Shown in Table 25-5 are some of the more common adverse events associated with neuraxial analgesia. Importantly, obese women have significantly impaired ventilation, and thus close clinical monitoring is imperative (Vricella, 2011).

TABLE 25-5

Complications of Regional Analgesia

Complication
Not infrequent
Hypotension
Fever Postdural puncture headache
Breakthrough pain
Uncommon
Inadvertant intrathecal, subdural, or intravascular injection of local anesthetic drugs
Neurologic injury

Hypotension is a common complication that may develop soon after injection of the local anesthetic agent. It is the consequence of vasodilatation from sympathetic blockade and is compounded by obstructed venous return due to uterine compression of the great vessels. In the supine position, even in the absence of maternal hypotension measured in the brachial artery, placental blood flow may still be significantly reduced. Treatment includes uterine displacement by left lateral patient positioning, intravenous crystalloid hydration, and intravenous bolus injections of ephedrine or phenylephrine.

Ephedrine is a sympathomimetic drug that binds to α- and β-receptors but also indirectly enhances norepinephrine release. It raises blood pressure by raising heart rate and cardiac output and by variably elevating peripheral vascular resistance. In early animal studies, ephedrine preserved uteroplacental blood flow during pregnancy compared with α_1-receptor agonists. Accordingly, it had been the preferred vasopressor for obstetrical use. Phenylephrine is a pure α-agonist and elevates blood pressure solely through vasoconstriction. A metaanalysis of seven randomized trials by Lee (2002a) suggests that the safety profiles of ephedrine and phenylephrine are comparable. Following their systematic review of 14 reports, Lee (2002b) questioned whether routine prophylactic ephedrine is needed for elective cesarean delivery. Although fetal acidemia has been reported with prophylactic ephedrine use, this was not observed with prophylactic phenylephrine use (Ngan Kee, 2004).

High or Total Spinal Blockade

Most often, high or total spinal blockade follows administration of an excessive dose of local anesthetic or inadvertent injection into the subdural or subarachnoid space. Subdural injection manifests as a high but patchy block even with a small dose of local anesthetic agent, whereas subarachnoid injection typically leads to complete spinal blockade with hypotension and apnea. These conditions must be immediately treated to prevent cardiac arrest. In the undelivered woman: (1) the uterus is immediately displaced laterally to minimize aortocaval compression; (2) effective ventilation is established, preferably with tracheal intubation; and (3) intravenous fluids and vasopressors are given to correct hypotension. If chest compressions are to be performed, the woman is placed in the left-lateral position to allow left uterine displacement.

Postdural Puncture Headache

Leakage of cerebrospinal fluid (CSF) from the dura mater puncture site can lead to postdural puncture or “spinal headache.” Presumably, when the woman sits or stands, the diminished CSF volume creates traction on pain-sensitive central nervous system structures. Another mechanism may be the compensatory cerebral vasodilation in response to the loss of CSF—the Monro-Kellie doctrine (Mokri, 2001).

Rates of this complication can be reduced by using a small-gauge spinal needle and avoiding multiple punctures. In a prospective, randomized study of five different spinal needles, Vallejo and associates (2000) concluded that Sprotte and Whitacre needles had the lowest risks of postdural puncture headaches. Sprigge and Harper (2008) reported that the incidence of postdural puncture headache was 1 percent in more than 5000 women undergoing spinal analgesia. Postdural puncture headaches are much less frequent with epidural blockade because the dura mater is not intentionally punctured. The incidence of inadvertent dural puncture with epidural analgesia approximates 0.2 percent (Introna, 2012; Katircioglu, 2008). There is no good evidence that placing a woman absolutely flat on her back for several hours is effective in preventing this headache.

Once headache develops, it is managed aggressively, as expectant management increases hospital-stay lengths and subsequent emergency-room visits (Angle, 2005). Conservative management, such as fluid administration and bed rest, is largely ineffective. If not effectively treated, postdural puncture headache can persist as a chronic headache (Webb, 2012).

Epidural blood patch is considered the gold standard for treatment. Typically, 10 to 20 mL of autologous blood obtained aseptically by venipuncture is injected into the epidural space. Further CSF leakage is halted by either mass effect or coagulation. Relief is almost always immediate, and complications are uncommon. The initial success rate of an epidural blood patch ranges from 61 to 73 percent (Paech, 2011). Performing a “prophylactic” blood patch is debatable and is thought not to be as effective as if performed after the headache develops (Scavone, 2004, 2015).

If a headache does not have the pathognomonic postural characteristics or persists despite treatment with a blood patch, other diagnoses are considered. Chisholm and Campbell (2001) described a case of superior sagittal sinus thrombosis that manifested as a postdural headache. Smarkusky and colleagues (2006) described pneumocephalus, which caused immediate cephalgia. Finally, intracranial and intraspinal subarachnoid hematomas have developed after spinal analgesia (Dawley, 2009; Liu, 2008).

Convulsions

In rare instances, postdural puncture cephalgia is associated with temporary blindness and convulsions. Shearer and associates (1995) described eight such cases associated with 19,000 regional analgesic procedures done at Parkland Hospital. It is presumed that these too are caused by CSF hypotension. Immediate treatment of seizures and a blood patch were usually effective in these cases.

Bladder Dysfunction

With neuraxial analgesia, bladder sensation is likely to be obtunded and bladder emptying impaired for several hours after delivery. As a consequence, bladder distention is a frequent postpartum complication, especially if appreciable volumes of intravenous fluid are given. Millet and colleagues (2012) randomized 146 women with neuraxial analgesia to either intermittent or continuous bladder catheterizations and found that the intermittent method was associated with significantly higher rates of bacteriuria. That said, we do not recommend routine postpartum use of indwelling catheters following uncomplicated vaginal delivery.

Arachnoiditis and Meningitis

Local anesthetics are no longer preserved in alcohol, formalin, or other toxic solutes, and disposable equipment is usually used. These practices, coupled with aseptic technique, have made meningitis and arachnoiditis rare (Centers for Disease Control and Prevention, 2010).

Contraindications to Neuraxial Analgesia

Shown in Table 25-6 are absolute contraindications. Obstetrical complications that are associated with maternal hypovolemia and hypotension—for example, severe hemorrhage—are contraindications (Kennedy, 1968).

TABLE 25-6

Absolute Contraindications to Neuraxial Analgesia

Refractory maternal hypotension
Maternal coagulopathy
Thrombocytopenia (variously defined)
Low-molecular-weight heparin within 12 hours
Untreated maternal bacteremia
Skin infection over site of needle placement
Increased intracranial pressure caused by a mass lesion

Disorders of coagulation and defective hemostasis also preclude neuraxial analgesia use. Although no randomized studies guide the management of anticoagulation at the time of delivery, consensus opinion suggests that women given subcutaneous unfractionated heparin or low-molecular-weight heparin should be instructed to stop therapy when labor begins (Krivak, 2007). Subarachnoid puncture is also contraindicated if cellulitis involves the planned needle entry site. Many consider neurological disorders to be a contraindication, if for no other reason than that exacerbation of the neurological disease might be erroneously attributed to the anesthetic agent. Other maternal conditions, such as aortic stenosis or pulmonary hypertension, are also relative contraindications (Chap. 49, Physiological Considerations in Pregnancy).

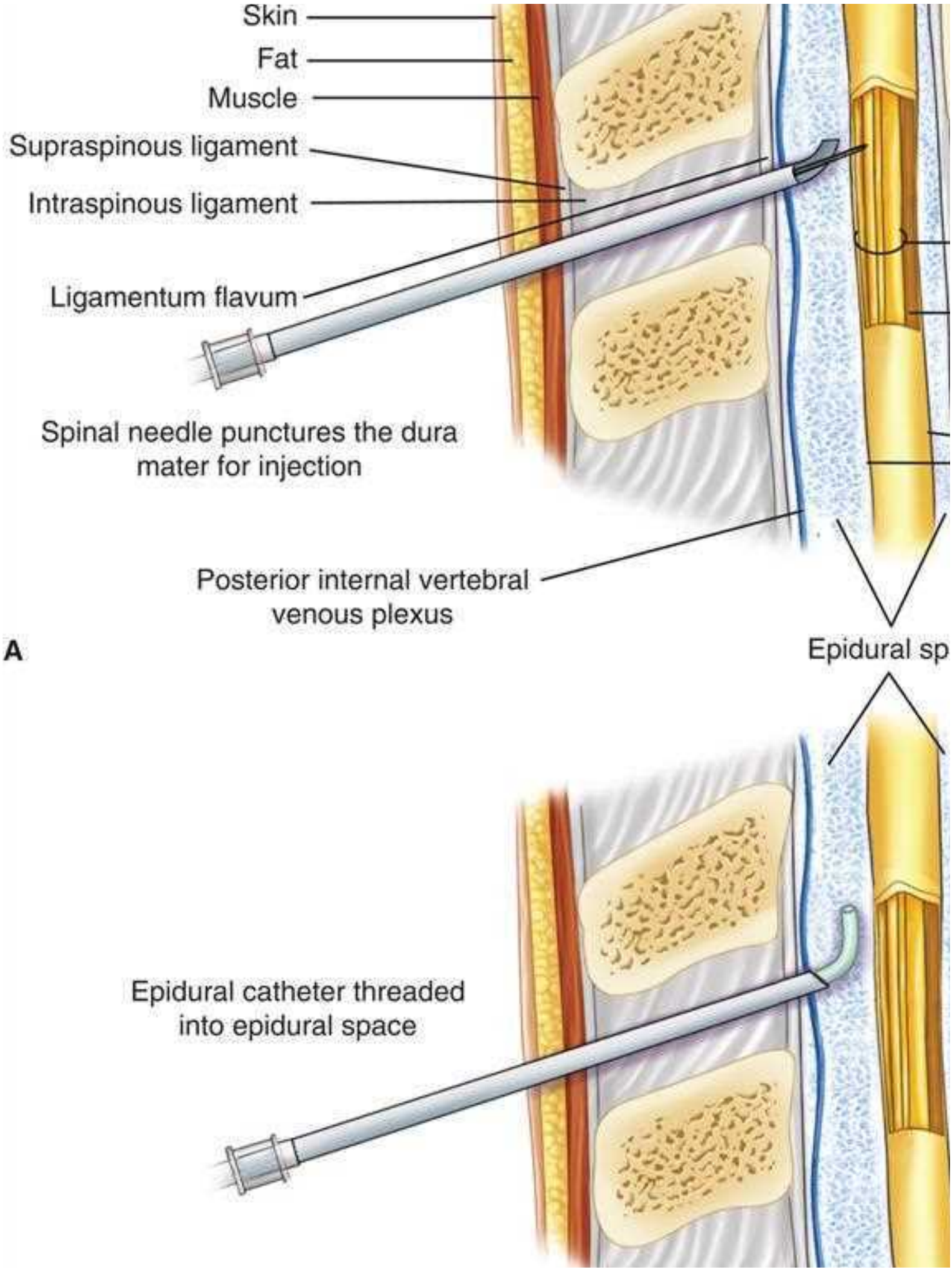
Severe preeclampsia is another comorbid condition in which markedly decreased blood pressure can be predicted when neuraxial analgesia is used. Wallace and associates (1995) randomly assigned 80 women with severe preeclampsia undergoing cesarean delivery at Parkland Hospital to receive general anesthesia or either epidural or combined spinal-epidural analgesia. Maternal and neonatal outcomes did not differ. Still, 30 percent of women given epidural analgesia and 22 percent of those given spinal-epidural blockade developed hypotension. The average reduction in mean arterial pressure ranges between 15 and 25 percent.

Epidural Analgesia

Relief of labor and childbirth pain, including cesarean delivery, can be accomplished by injection of a local anesthetic agent into the epidural or peridural space (Fig. 25-3). This potential space contains areolar tissue, fat, lymphatics, and the internal vertebral venous plexus. This plexus becomes engorged during pregnancy such that the volume of the epidural space is appreciably reduced. Entry for obstetrical analgesia is usually through a lumbar intervertebral space. Although only one injection may be elected, usually an indwelling catheter is placed for subsequent agent boluses or infusion via a volumetric pump. The American College of Obstetricians and Gynecologists (2017a) concludes that under appropriate physician supervision, labor and delivery nursing personnel who have been specifically trained in the management of epidural infusions should be able to adjust dosage and also discontinue infusions.

FIGURE 25-3

Neuraxial analgesia: **A.** Combined spinal-epidural analgesia. **B.** Epidural analgesia.


Skin
Fat
Muscle
Supraspinous ligament
Intraspinous ligament
Ligamentum flavum
Spinal needle punctures the dura mater for injection
Posterior internal vertebral venous plexus
Epidural sp
A
Epidural catheter threaded into epidural space

Continuous Lumbar Epidural Block

Complete analgesia for the pain of labor and vaginal delivery necessitates a block from the T_{10} to the S_5 dermatomes (see Fig. 25-1). For cesarean delivery, a block extending from the T_4 to the S_1 dermatomes is desired. The effective spread of anesthetic depends on the catheter tip location; the dose, concentration, and volume of anesthetic agent used; and whether the mother is head-down, horizontal, or head-up (Setayesh, 2001). Individual variations in anatomy or presence of synechiae may preclude a completely satisfactory block. Finally, the catheter tip may migrate from its original location during labor.

Technique

One example of the sequential steps and techniques for performance of epidural analgesia is detailed in Table 25-7. Before injection of the local anesthetic therapeutic dose, a test dose is given. The woman is observed for features of toxicity from intravascular injection and for signs of high or total blockade from subdural or subarachnoid injection. If these are absent, only then is a full dose given. Analgesia is maintained by intermittent boluses of similar volume or by small volumes delivered continuously by infusion pump (Halpern, 2009). Current pumps used for epidural analgesia offer a programmed intermittent epidural bolus (PIEB) mode, which reduces the required concentration of local anesthetics, the degree of lower extremity motor blockade, and rates of operative vaginal delivery (Capogna, 2011). The addition of small doses of a short-acting narcotic—fentanyl or sufentanil—has been shown to improve analgesic efficacy while avoiding motor blockade (Chestnut, 1988). As with spinal blockade, close monitoring, including the level of analgesia, is imperative and must be performed by trained personnel. Appropriate resuscitation equipment and drugs must be available during administration of epidural analgesia.

TABLE 25-7

Technique for Labor Epidural Analgesia

Informed consent is obtained, and the obstetrician consulted
Monitoring includes the following:
Blood pressure every 1 to 2 minutes for 15 minutes after giving a bolus of local anesthetic
Continuous maternal heart rate monitoring during analgesia induction
Continuous maternal pulse oximetry
Continuous fetal heart rate monitoring
Continual verbal communication
Hydration with 500 to 1000 mL of lactated Ringer solution
The woman assumes a lateral decubitus or sitting position
The epidural space is identified with a loss-of-resistance technique
The epidural catheter is threaded 3 to 5 cm into the epidural space
A test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine or 3 mL of 0.25% bupivacaine with 1:200,000 epinephrine is injected after careful aspiration to avert intravascular injection and after a uterine contraction. This minimizes the chance of confusing tachycardia that results from labor pain with tachycardia from intravenous injection of the test dose.
If the test dose is negative, 10–15 mL of 0.0625–0.125% bupivacaine are injected to achieve a sensory T_{10} level.
After 15 to 20 minutes, the block is assessed using loss of sensation to cold or pinprick. If no block is evident, the catheter is replaced. If the block is asymmetrical, the epidural catheter is withdrawn 0.5 to 1.0 cm and an additional 5 to 10 mL of 0.0625–0.125% bupivacaine is injected. If the block remains inadequate, the catheter is replaced.
The woman is positioned in the lateral or semilateral position to avoid aortocaval compression.
Subsequently, maternal blood pressure is recorded every 5 to 15 minutes. The fetal heart rate is monitored continuously.
The level of analgesia and intensity of motor blockade are assessed at least hourly.

Reproduced with permission from Glosten B: Local anesthetic techniques. In Chestnut DH (ed): Obstetric Anesthesia: Principles and Practice, 2nd ed. St Louis, Mosby, 1999.

Complications

Higher or Total Spinal Blockade

In general, complications with epidural analgesia are similar to those with spinal analgesia (see Table 25-5). Dural puncture with inadvertent subarachnoid injection may cause total spinal blockade. Sprigge and Harper (2008) cited an incidence of 0.91 percent recognized accidental dural punctures at the time of epidural analgesia in more than 18,000 women. Personnel and facilities must be immediately available to manage this complication as described earlier (Cesarean Delivery). In other aspects, however, complications are unique and inherent to epidural analgesia use.

Ineffective Analgesia

Using currently popular continuous epidural infusion regimens such as 0.125-percent bupivacaine with 2-µg/mL fentanyl, 90 percent of women rate their pain relief as good to excellent (Sharma, 1997). Alternatively, a few women find epidural analgesia to be inadequate for labor. In a study of almost 2000 parturients, Hess and associates (2001) found that approximately 12 percent complained of three or more episodes of pain or pressure. Risk factors for such breakthrough pain included nulliparity and heavier fetal weights. Dresner and colleagues (2006) also reported that epidural analgesia was more likely to fail as body mass index increased. If epidural analgesia is allowed to dissipate before another injection of anesthetic drug, subsequent pain relief may be delayed, incomplete, or both.

In some women, epidural analgesia is insufficient for cesarean delivery. For example, in a Maternal Fetal Medicine Units (MFMU) Network study, 4 percent of women initially given epidural analgesia required a general anesthetic for cesarean delivery (Bloom, 2005). Also at times, perineal analgesia for delivery is difficult to obtain, especially with the lumbar epidural technique. When this situation is encountered, pudendal block or systemic analgesia or rarely general anesthesia may be added.

Hypotension

Sympathetic blockade from epidurally injected analgesic agents can cause hypotension and decreased cardiac output. Despite precautions, hypotension is the most frequent side effect and is severe enough to require treatment in a third of women (Sharma, 1997). According to Miller and coworkers (2013), hypotension is more common—20 percent—in women with an admission pulse pressure <45 mm Hg, compared with 6 percent in those whose pulse pressure is >45 mm Hg. In normal gravidas, hypotension induced by epidural analgesia usually can be prevented by rapid infusion of 500 to 1000 mL of crystalloid solution as described for spinal analgesia. Maintaining a lateral position also minimizes hypotension.

Maternal Fever

Fusi and colleagues (1989) observed that the mean temperature rose in laboring women given epidural analgesia. Subsequently, several randomized and retrospective cohort studies have confirmed that some women develop intrapartum fever following this procedure. Many studies are limited by inability to control for other risk factors such as labor length, duration of ruptured membranes, and number of vaginal examinations. With this in mind, the frequency of intrapartum fever associated with epidural analgesia was found by Lieberman and O'Donoghue (2002) to be 10 to 15 percent above the baseline rate.

The two general theories concerning the etiology of maternal hyperthermia are *maternal-fetal infection* or *dysregulation of body temperature*. Dashe and coworkers (1999) studied placental histopathology in laboring women given epidural analgesia and identified intrapartum fever only when there was placental inflammation. This suggests that fever is due to infection. The other proposed mechanisms include alteration of the hypothalamic thermoregulatory set point; impairment of peripheral thermoreceptor input to the central nervous system, with selective blockage of warm stimuli; or imbalance between heat production and heat loss. Sharma (2014) randomized 400 nulliparas with labor epidural analgesia to receive cefoxitin 2 g prophylactically versus placebo. It was hypothesized that epidural-related fever was due to infection and that prophylactic antimicrobial use should significantly reduce the rate of fever. Approximately equal proportions—about 40 percent—of women developed fever >38°C during labor. This suggests that infection is unlikely to be the cause of fever.

Back Pain

An association between epidural analgesia and subsequent back pain has been reported by some but not all. In a prospective cohort study, Butler and Fuller (1998) reported that back pain after delivery was common with epidural analgesia, however, persistent pain was uncommon. Based on their systematic review, Lieberman and O'Donoghue (2002) concluded that available data do not support an association between epidural analgesia and development of de novo, long-term backache.

Miscellaneous Complications

A spinal or epidural hematoma is a rare complication of an epidural catheter (Grant, 2007). Epidural abscesses are equally infrequent (Darouiche, 2006). And uncommonly, the plastic epidural catheter can be sheared off (Noblett, 2007).

Effects on Labor

Most studies, including the five from Parkland Hospital, report that epidural analgesia prolongs labor and increases the use of oxytocin stimulation (Table 25-8). Alexander and associates (2002) examined the effects of epidural analgesia on the Friedman (1955) labor curve described in Chapter 22 (First Stage of Labor). Compared with original Friedman criteria, epidural analgesia prolonged the active phase of labor by 1 hour. As further shown in Table 25-8, epidural analgesia also increased the need for operative vaginal delivery because of prolonged second-stage labor. But importantly, this led to no greater rates of adverse neonatal effects.

TABLE 25-8

Selected Labor Events in 2703 Nulliparous Women Randomized to Epidural Analgesia or Intravenous Meperidine Analgesia

Event[a]	Epidural Analgesia *n* = 1339	Intravenous Meperidine *n* = 1364	*p* value
Labor outcomes			
First-stage duration (hr)[b]	8.1 ± 5	7.5 ± 5	0.011
Second-stage duration (min)	60 ± 56	47 ± 57	<0.001
Oxytocin after analgesia	641 (48)	546 (40)	<0.001
Type of delivery			
SVD	1027 (77)	1122 (82)	<0.001
Forceps	172 (13)	101 (7)	<0.001
Cesarean	140 (10.5)	141 (10.3)	0.92

[a]Data are presented as n (%) or mean ± SD.

[b]First stage = initiation of analgesia to complete cervical dilatation.

SVD = spontaneous vaginal delivery.

Adapted with permission from Sharma SK, McIntire DD, Wiley J, et al: Labor analgesia and cesarean delivery. An individual patient meta-analysis of nulliparous women, Anesthesiology. 2004 Jan;100(1):142–148.

This association among epidural analgesia and prolonged second-stage labor and operative vaginal delivery has been attributed to anesthesia-induced motor blockade and resultant impaired maternal expulsive efforts. Craig and colleagues (2015) randomized 310 nulliparous women with labor epidural analgesia to bupivacaine plus fentanyl or fentanyl alone during second-stage labor. Epidural bupivacaine analgesia did cause motor blockade during the second stage, however, the duration of the second stage was not increased.

Fetal Heart Rate

Hill and associates (2003) examined the effects of epidural analgesia with 0.25-percent bupivacaine on fetal heart rate patterns. Compared with intravenous meperidine, no deleterious effects were identified. Reduced beat-to-beat variability and fewer accelerations were more frequent sequelae in fetuses whose mothers received meperidine (Chap. 24, Cardiac Arrhythmia). Based on their systematic review, Reynolds and coworkers (2002) reported that epidural analgesia was associated with improved neonatal acid-base status compared with meperidine.

Cesarean Delivery Rates

A contentious issue in the past was whether epidural analgesia increased the risk for cesarean delivery. Supporting evidence for this view came from the era when dense blocks of local anesthetic agents were used that impaired motor function and therefore likely did contribute to higher cesarean delivery rates. As techniques were refined, however, many investigators came to believe that epidural administration of *dilute* anesthetic solutions did not increase cesarean delivery rates.

Several studies conducted at Parkland Hospital were designed to answer this and related questions. From 1995 to 2002, a total of 2703 nulliparas at term and in spontaneous labor were enrolled in five trials to evaluate epidural analgesia techniques compared with methods of intravenous meperidine administration. The results from these are summarized in Figure 25-4 and show that epidural analgesia does not significantly raise cesarean delivery rates.

FIGURE 25-4

Results of five studies comparing the incidence of cesarean delivery in women given either epidural analgesia or intravenous meperidine. The individual odds ratios (ORs) with 95-percent confidence intervals (CIs) for each randomized study, as well as overall crude and adjusted ORs with 95-percent CIs, are shown. An OR <1.0 favored epidural over meperidine analgesia. (Reproduced with permission from Sharma SK, McIntire DD, Wiley J, et al: Labor analgesia and cesarean delivery. An individual patient meta-analysis of nulliparous women, Anesthesiology. 2004 Jan;100(1):142–148.)

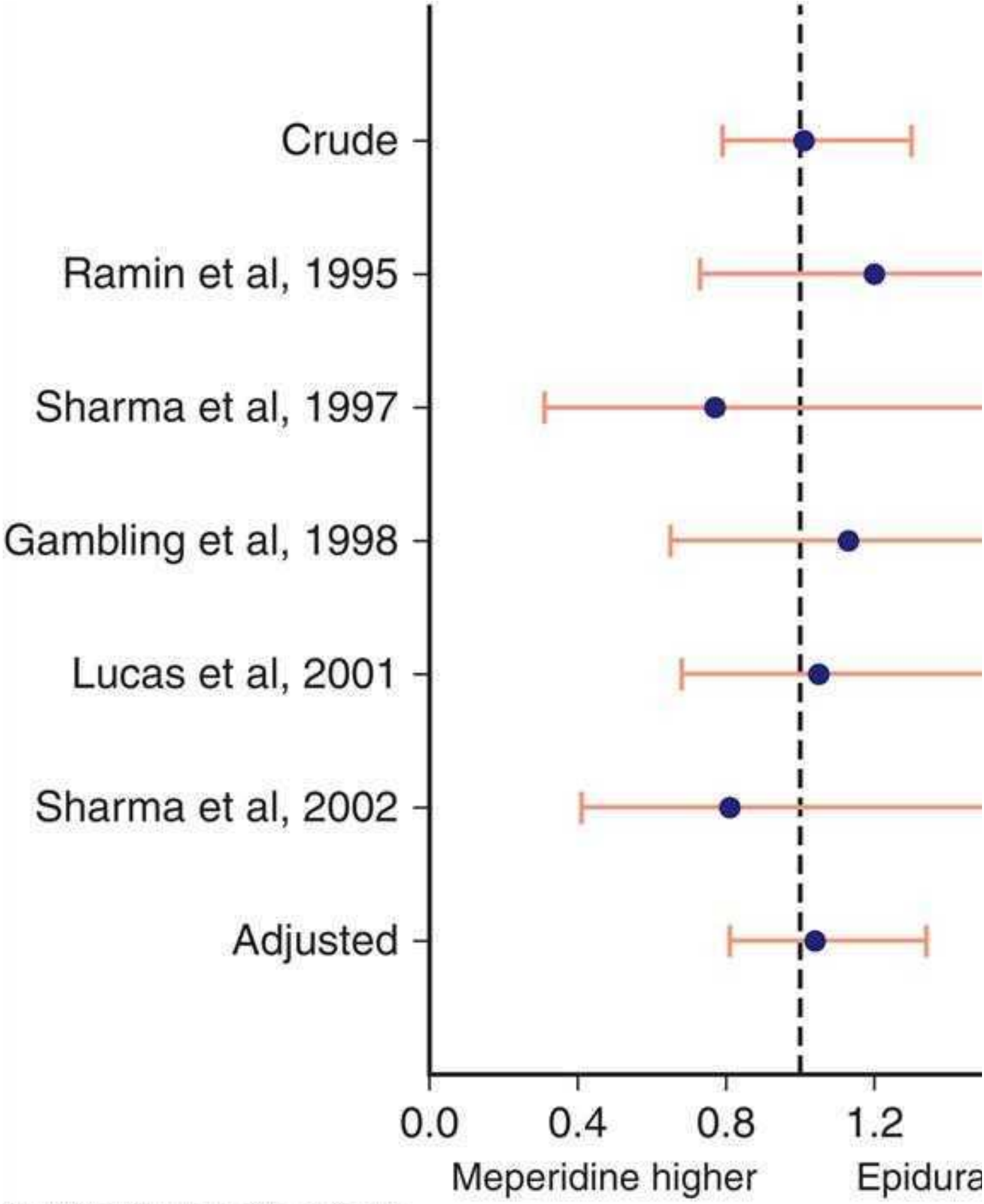
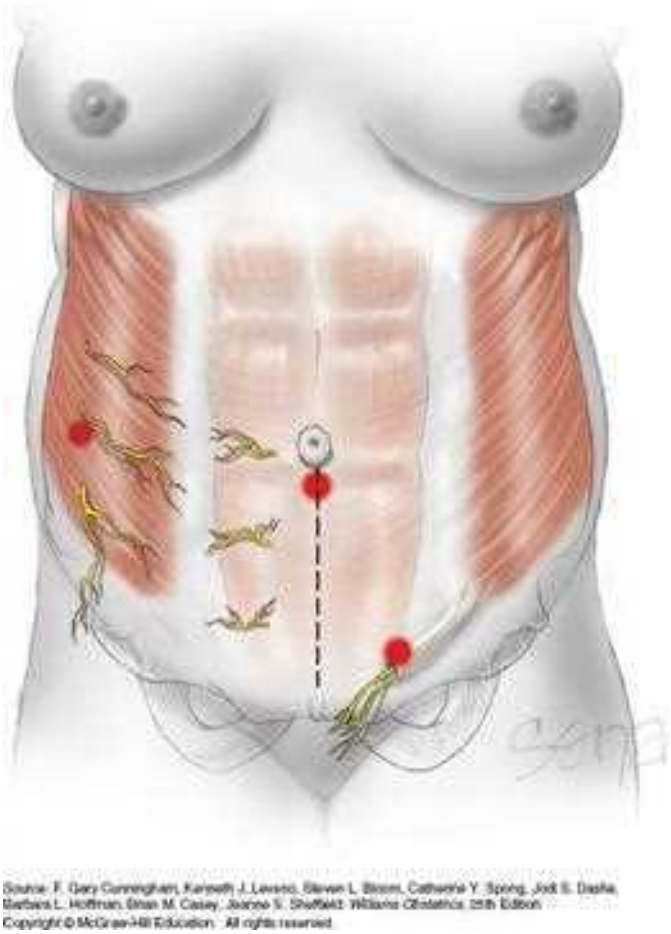


FIGURE 25-5

Local anesthetic block for cesarean delivery. The first injection site is halfway between the costal margin and iliac crest in the midaxillary line to block the 10th, 11th, and 12th intercostal nerves. A second injection at the external inguinal ring blocks branches of the genitofemoral and ilioinguinal nerves. These two sites are

infiltrated bilaterally. The fifth and final site is along the line of proposed skin incision.



Timing of Epidural Placement

In several retrospective studies, epidural placement in early labor was linked to an increased risk of cesarean delivery (Lieberman, 1996; Rogers, 1999; Seyb, 1999). These observations prompted at least five randomized trials, which showed that timing of epidural placement has no effect on the risk of cesarean birth, forceps delivery, or fetal malposition (Chestnut, 1994a,b; Ohel, 2006; Wong, 2005, 2009). Thus, withholding epidural placement until some arbitrary cervical dilation has been attained is unsupportable and serves only to deny women maximal labor pain relief.

Safety

The relative safety of epidural analgesia is reflected by the extraordinary earlier experiences reported by Crawford (1985) from the Birmingham Maternity Hospital in England. Similarly, there were no anesthesia-related maternal deaths among nearly 20,000 women who received epidural analgesia in the MFMU Network study cited earlier (Bloom, 2005). And, Ruppen and associates (2006) reviewed data from 27 studies involving 1.4 million pregnant women who received epidural analgesia. They calculated risks of 1:145,000 for deep epidural infection, 1:168,000 for epidural hematoma, and 1:240,000 for persistent neurological injury.

Contraindications

Thrombocytopenia

For epidural analgesia, contraindications are similar to those with spinal analgesia (see Table 25-6). Although low platelet counts are intuitively worrisome, the level at which epidural bleeding *might* develop is unknown according to the American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016). Epidural hematomas are rare, and incidence of nerve damage from a hematoma is estimated to be 1 in 150,000 (Grant, 2007). The American College of Obstetricians and Gynecologists (2016b) has concluded that selected women with platelet counts of 80,000 to 100,000/μL may be candidates for regional analgesia. Caveats include a stable platelet count, no acquired or congenital coagulopathy, normal platelet function, no antiplatelet-specific drugs, and anticoagulation parameters, described next, that are met. Counts between 50,000 and 80,000 require an individualized decision on risks and benefits (van Veen, 2010). Single-shot spinal anesthesia with a 25-gauge needle is less traumatic than epidural or combined spinal-epidural anesthesia with a 17- or 18-gauge epidural needle and thus may be safer for patients with platelets in this range.

Anticoagulation

Women receiving anticoagulation therapy who are given regional analgesia are at increased risk for spinal cord hematoma and subsequent cord compression (Chap. 52, Labor and Delivery). Our practice pattern includes the following:

1. Women receiving unfractionated heparin therapy should be able to receive regional analgesia if they have a normal activated partial thromboplastin time (aPTT).

2. Women receiving prophylactic doses of unfractionated heparin or low-dose aspirin are not at increased risk and can be offered regional analgesia.
3. For women receiving once-daily, low-dose low-molecular-weight heparin, regional analgesia should not be placed until 12 hours after the last injection.
4. Low-molecular-weight heparin should be withheld for at least 2 hours after epidural catheter removal.
5. The safety of regional analgesia in women receiving twice-daily low-molecular-weight heparin has not been studied sufficiently. It is not known whether delaying regional analgesia for 24 hours after the last injection is adequate.

Severe Preeclampsia-Eclampsia

Potential concerns with epidural analgesia in women with severe preeclampsia include hypotension as well as hypertension from pressor agents given to correct hypotension. Additionally, pulmonary edema following infusion of large volumes of crystalloid is a potential risk. These are outweighed by disadvantages of general anesthesia. Tracheal intubation may be difficult because of upper airway edema. Moreover, general anesthesia can lead to severe, sudden hypertension that can cause pulmonary or cerebral edema or intracranial hemorrhage.

With improved techniques for infusion of dilute local anesthetics into the epidural space, most obstetricians and obstetrical anesthesiologists have come to favor epidural blockade for labor and delivery in women with severe preeclampsia. There seems to be no argument that epidural analgesia for women with severe preeclampsia-eclampsia can be safely used when implemented by trained anesthesiologists and obstetricians (Lucas, 2001).

Women with severe preeclampsia have remarkably diminished intravascular volumes compared with unaffected gravidas (Zeeman, 2009). Conversely, extravascular volume is increased because of the capillary leak caused by endothelial cell activation (Chap. 40, Pathophysiology). This imbalance is manifested as pathological peripheral edema, proteinuria, ascites, and total lung water. For all of these reasons, aggressive volume replacement increases the risk for pulmonary edema, especially in the first 72 hours postpartum. In one study, Hogg and associates (1999) reported that 3.5 percent of women with severe preeclampsia developed pulmonary edema when preloaded without a protocol limitation to volume. Importantly, this risk can be reduced or obviated with judicious prehydration—usually with 500 to 1000 mL of crystalloid solution. Specifically, in the study by Lucas and colleagues (2001), there were no instances of pulmonary edema among the women in whom the crystalloid preload was limited to 500 mL. Moreover, vasodilation produced by epidural blockade is less abrupt if the analgesia level is achieved slowly with dilute solutions of local anesthetic agents. This allows maintenance of blood pressure while simultaneously avoiding infusion of large crystalloid volumes.

Combined Spinal–Epidural Analgesia

The combination of spinal and epidural techniques has increased in popularity and may provide rapid and effective analgesia for labor and for cesarean delivery. An introducer needle is first placed in the epidural space. A small-gauge spinal needle is then introduced through the epidural needle into the subarachnoid space—this is called the *needle-through-needle technique* (see Fig. 25-3). A single bolus of an opioid, sometimes in combination with a local anesthetic, is injected into the subarachnoid space. The spinal needle is withdrawn, and an epidural catheter is then placed through the introducer needle. A subarachnoid opioid bolus results in the rapid onset of profound pain relief with virtually no motor blockade. The epidural catheter permits repeated analgesia dosing. Miro and associates (2008) compared epidural analgesia with combined spinal-epidural analgesia for labor in 6497 women and found the overall outcomes and complications to be similar for the two techniques. In a randomized comparison, however, Abrão and colleagues (2009) reported that combined spinal-epidural analgesia was associated with a greater incidence of fetal heart rate abnormalities related to uterine hypertonus. Beamon and coworkers (2014) reported similar results.

Continuous Spinal Analgesia During Labor

There is emerging interest in continuous spinal analgesia for relief of labor pain. Arkoosh (2008) randomized 429 laboring women to either continuous spinal or conventional epidural analgesia. Complication rates between these two neuraxial techniques did not differ. Tao and colleagues (2015) reported their experiences with 113 women. With a dilute bupivacaine solution for analgesia, they found no cases of peripheral nerve injury and a headache rate of 2.6 percent. The utility of continuous spinal analgesia in labor and delivery remains to be further studied.

LOCAL INFILTRATION FOR CESAREAN DELIVERY

A local block is occasionally useful to augment an inadequate or “patchy” regional block that was given emergently. Rarely, local infiltration may be needed to perform an emergent cesarean delivery to save the life of a fetus in the absence of anesthesia support (Young, 2012).

In one technique, the skin is infiltrated along the proposed incision, and the subcutaneous, muscle, and rectus sheath layers are injected as the abdomen is opened. Up to a total of 70 mL of 0.5-percent lidocaine with 1:200,000 epinephrine is prepared for infiltration. Injection of large volumes into the fatty layers, which are relatively devoid of nerve supply, is avoided to limit the total dose of local anesthetic needed.

A second technique involves a field block of the major branches supplying the abdominal wall, to include the 10th, 11th, and 12th intercostal nerves and the ilioinguinal and genitofemoral nerves (Nandagopal, 2001). As shown in Figure 25-5, the former group of nerves is located at a point midway between the costal margin and iliac crest in the midaxillary line. The latter group is found at the level of the external inguinal ring. Only one skin puncture is made at each of the four sites (right and left sides). At the intercostal block site, the needle is directed medially, and injection is carried down to the fascia, avoiding injection of the subcutaneous fat. Approximately 5 to 8 mL of 0.5-percent lidocaine is injected. The procedure is repeated at a 45-degree angle cephalad and caudad to this line. The other side is then injected. At the ilioinguinal and genitofemoral sites, the injection is started at a site 2 to 3 cm lateral from the pubic tubercle at a 45-degree angle. Finally, the skin overlying the planned incision is injected.

GENERAL ANESTHESIA

Trained personnel and specialized equipment including alternative airways, video laryngoscopes, and fiberoptic intubation scopes are mandatory for the safe use of general anesthesia. A common cause of death cited for general anesthesia is failed intubation. This occurs in approximately 1 of every 400 general anesthetics administered to pregnant women (Kinsella, 2015). There is a growing trend to continue surgery with a supraglottic airway device, such as a laryngeal mask airway, in the event of a failed intubation (Mushambi, 2015). Because of these relatively greater morbidity and mortality rates, neuraxial analgesia is the preferred method of pain control and should be used unless contraindicated (see Table 25-6). Indeed, in two reports from the MFMU Network, 93 percent of more than 54,000 cesarean deliveries were performed using neuraxial analgesia (Bloom, 2005; Brookfield, 2013). A higher incidence of general anesthesia use for nonwhite women has been reported (Butwick, 2014).

Patient Preparation

Before anesthesia induction, several steps are taken to help minimize complication risks:

1. Antacid administration shortly before anesthesia induction has probably lowered mortality rates from general anesthesia more than any other single practice. The American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016) recommends timely administration of a nonparticulate antacid, an H_2-receptor antagonist, or metoclopramide. For many years, we have administered 30 mL of Bicitra—sodium citrate with citric acid—a few minutes before anesthesia induction by either general or major neuraxial block. If more than 1 hour has passed after the first dose was given and anesthesia has not yet been induced, then a second dose is given.

2. Lateral uterine displacement is also provided, as the uterus may compress the inferior vena cava and aorta when the mother is supine. With uterine displacement, the duration of general anesthesia has less effect on neonatal condition than if the woman remains supine.

3. Preoxygenation is done because functional reserve lung capacity is reduced and the pregnant woman becomes hypoxemic more rapidly during periods of apnea. Obesity exacerbates this tendency (McClelland, 2009). To minimize hypoxia between the time of muscle relaxant injection and intubation, oxygen is introduced into the lungs in place of nitrogen. This preoxygenation is accomplished by administering 100-percent oxygen via face mask for 2 to 3 minutes before anesthesia induction. In an emergency, four vital capacity breaths of 100-percent oxygen via a tight breathing circuit will provide similar benefit (Norris, 1985).

Induction and Intubation

Almost all parturients are considered to have a full stomach, which necessitates a rapid-sequence induction. Namely, an intravenous anesthetic and rapid-onset muscle relaxant are simultaneously administered while cricoid pressure is applied by an assistant.

Of anesthetics, intravenous propofol or etomidate is widely used and offers a smooth, rapid induction. Propofol is associated with a quick onset and recovery, and it may lower the incidence of nausea and vomiting. Since thiopental is no longer available, propofol is used as the primary agent for induction of general anesthesia with a reasonable safety record. Etomidate is the induction agent of choice for hemodynamically unstable parturients. Alternatively, ketamine can be used but is avoided in hypertensive women. For muscle relaxation, succinylcholine is an ultrafast-onset, short-acting agent commonly used in obstetrics. It offers intense muscle relaxation to aid endotracheal intubation but also allows for the rapid return of spontaneous respiration in the case of failed intubation. Rocuronium is an alternative muscle relaxant if succinylcholine is contraindicated or unavailable. Its duration is much longer than succinylcholine unless its effect is reversed by sugammadex (Bridion), a specific binding agent recently approved by the FDA. To decrease the incidence of fetal respiratory depression, an intermediate or long-acting opioid is usually avoided upon induction of general anesthesia. The intense stimulation from direct laryngoscopy may worsen hypertension and tachycardia in certain women. Remifentanil, an ultrashort-acting narcotic, has been used during induction for cesarean deliveries with favorable maternal hemodynamics and fetal outcome (Heesen, 2013).

During induction and intubation, cricoid pressure is applied by a trained assistant to occlude the esophagus and thereby minimize regurgitation of the gastric contents—the Sellick maneuver. Positive mask ventilation during rapid sequence induction is typically avoided to lower the risk of increased intragastric pressure, which raises the risk of vomiting. Surgery should begin only after an airway is secured or, depending on the status of the mother and fetus, effective ventilation has been established.

Failed Intubation

Although uncommon, failed intubation is a major cause of anesthesia-related maternal mortality. A history of prior difficult intubation and a careful anatomical assessment of the neck and maxillofacial, pharyngeal, and laryngeal structures may help predict intubation complications. Even in cases in which the initial airway assessment was unremarkable, edema may develop intrapartum and present considerable challenges. Morbid obesity is another major factor for failed or difficult intubation. The American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016) stresses the importance of appropriate preoperative preparation. This includes the immediate availability of specialized equipment such as different-shaped laryngoscopes, laryngeal mask airways, a fiberoptic bronchoscope, and a transtracheal ventilation set, as well as liberal use of awake oral intubation techniques.

Management

Ideally, an operative procedure is initiated only after it has been ascertained that tracheal intubation has been successful and that adequate ventilation can be accomplished. Even with an abnormal fetal heart rate pattern, cesarean delivery initiation will only serve to complicate matters if there is difficult or failed intubation. Frequently, the woman must be allowed to awaken and a different technique used, such as an awake intubation or regional analgesia.

Following failed intubation, the woman is ventilated by mask and cricoid pressure is applied to reduce the aspiration risk. Surgery may proceed with mask ventilation, or the woman may be allowed to awaken. In those cases in which the woman has been paralyzed and ventilation cannot be reestablished by insertion of

an oral airway, by laryngeal mask airway, or by use of a fiberoptic laryngoscope to intubate the trachea, then a life-threatening emergency exists. To restore ventilation, percutaneous or even open cricothyrotomy is performed and jet ventilation begun. Failed intubation drills have been recommended to optimize the response to such an emergency.

Inhalational Anesthetics

With the endotracheal tube secured, anesthesia is maintained with a halogenated agent, typically mixed with air or nitrous oxide. The most commonly used inhalational anesthetics in the United States include desflurane and sevoflurane. Both have low solubility in blood and fat. As a result, they offer faster onset and clearance than more traditional gases such as isoflurane. In addition to providing amnesia, they produce profound uterine relaxation when given in high concentrations. This is advantageous when relaxation is a requisite, such as for internal podalic version of the second twin, for breech decomposition, or for replacement of the acutely inverted uterus. That said, unless the woman is already under general anesthesia, intravenous nitroglycerine is preferred by many in such situations.

Extubation

The endotracheal tube may be safely removed only if the woman is conscious to a degree that enables her to follow commands and is capable of maintaining oxygen saturation with spontaneous respiration. Consideration is given to emptying the stomach via a nasogastric tube before extubation. As induction has become safer, extubation may now be relatively more perilous. Of 15 anesthesia-related deaths of pregnant women from 1985 to 2003 in Michigan, none occurred during induction. Five resulted from hypoventilation or airway obstruction during emergence, extubation, or recovery (Mhyre, 2007).

Aspiration

Massive gastric acidic inhalation may cause pulmonary insufficiency from aspiration pneumonitis. In the past, this was the most common cause of anesthetic deaths in obstetrics and therefore deserves special attention. To minimize this risk, antacids are given routinely, intubation is accompanied by cricoid pressure, and regional analgesia is employed when possible.

Fasting

According to the American Society of Anesthesiologists Task Force on Obstetrical Anesthesia (2016) and the American College of Obstetricians and Gynecologists (2017b), data are insufficient regarding fasting times for clear liquids and the risk of pulmonary aspiration during labor. Recommendations are that modest amounts of clear liquids such as water, clear tea, black coffee, carbonated beverages, and pulp-free fruit juices be allowed in uncomplicated laboring women (Chap 22, Oral Intake). Obvious solid foods are avoided. A fasting period of 6 to 8 hours for solid food is recommended for uncomplicated parturients prior to undergoing elective cesarean delivery or puerperal tubal ligation.

O'Sullivan (2009) randomized 2426 low-risk nulliparas to consume either water and ice chips alone or small amounts of bread, biscuits, vegetables, fruits, yogurt, soup, and fruit juice. Approximately 30 percent of women in each arm of the study underwent cesarean delivery. No cases of aspiration occurred during the study, although approximately a third of women in each study arm vomited during labor or delivery. Epidural analgesia during labor was used in this study, although the authors did not report the type of anesthesia used for cesarean deliveries. Presumably, neuraxial analgesia was used, and this greatly minimized the pulmonary aspiration risk. Given the low prevalence of aspiration, this trial was not powered to measure whether feeding during labor was safe (Sperling, 2016).

Pathophysiology

In 1952, Teabeaut demonstrated experimentally that if the pH of aspirated fluid was <2.5, severe chemical pneumonitis developed. It was later demonstrated that the pH of gastric juice in nearly half of women tested intrapartum was <2.5 (Taylor, 1966). The right mainstem bronchus usually offers the simplest pathway for aspirated material to reach the lung parenchyma, and therefore, the right lower lobe is most often involved. In severe cases, there is bilateral widespread involvement.

The woman who aspirates may develop evidence of respiratory distress immediately or several hours after aspiration, depending in part on the material aspirated and the severity of the response. Aspiration of a large amount of solid material causes obvious airway obstruction. Smaller particles without acidic liquid may lead to patchy atelectasis and later to bronchopneumonia.

When highly acidic liquid is inspired, decreased oxygen saturation along with tachypnea, bronchospasm, rhonchi, rales, atelectasis, cyanosis, tachycardia, and hypotension are likely to develop. At the injury sites, there is pulmonary capillary leakage and exudation of protein-rich fluid containing numerous erythrocytes into the lung interstitium and alveoli. This causes decreased pulmonary compliance, shunting of blood, and severe hypoxemia. Radiographic changes may not appear immediately, and these may be variable, although the right lung most often is affected. Thus, chest radiographs alone should not be used to exclude aspiration.

Treatment

The methods recommended for treatment of aspiration have changed appreciably in recent years, indicating that previous therapy was not very successful. Suspicion of aspiration of gastric contents demands close monitoring for evidence of pulmonary damage. Respiratory rate and oxygen saturation as measured by pulse oximetry are the most sensitive and earliest indicators of injury.

Inhaled fluid should be immediately and thoroughly wiped from the mouth and removed from the pharynx and trachea by suction. Saline lavage may further disseminate the acid throughout the lung and is not recommended. If large particulate matter is inspired, bronchoscopy may be indicated to relieve airway obstruction. No convincing evidence supports that corticosteroid therapy or prophylactic antimicrobial administration is beneficial (Marik, 2001). If infection

develops, however, then vigorous treatment is given. If acute respiratory failure develops, mechanical ventilation with positive end-expiratory pressure may be lifesaving (Chap. 47, Clinical Course).

POSTPARTUM ANALGESIA

Goals for postoperative pain management include maximizing patient satisfaction, minimizing side effects, aiding functional capacity, and preventing prolonged hospital stays (Lavoie, 2013). In a prospective study, 96 percent of women reported pain immediately after delivery (Eisenach, 2008). The incidence of persistent pain 1 and 2 years following cesarean delivery was reported to approximate 20 percent (Hannah, 2004; Kainu, 2010).

The American Society of Anesthesiologists (2016) recommends neuraxial opioids for postoperative analgesia. Although most cesarean deliveries in the United States are performed under neuraxial anesthesia, in certain situations a peripheral nerve block such as a transversus abdominis plane (TAP) block may be considered (McDonnell, 2007). These include cases in which the parturient did not receive neuraxial opioids, underwent general anesthesia, or has persistent pain following neuraxial anesthesia. It is usually performed under ultrasound guidance and involves injection of a local anesthetic into the transversus abdominis plane between the internal oblique and transversus abdominis muscles. The nerves lying in this plane supply the anterior abdominal wall at the T_6 to L_1 dermatomes. A metaanalysis of 31 controlled trials showed that ultrasound-guided TAP block marginally reduced opioid consumption at 6 hours following abdominal surgery (Baeriswyl, 2015).

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CHAPTER 26: Induction and Augmentation of Labor

In other cases, if interference becomes imperative, the introduction of a bougie into the uterus, or the employment of a small Champetier de Ribes rubber bag acts as an effective uterine irritant and brings about complete dilatation.

—J. Whitridge Williams (1903)

INTRODUCTION

No effective means of labor induction were available when Williams wrote the first edition of this book. Labor augmentation methods were largely ineffective, and manual cervical dilation was performed as a last resort. Contrast with today, when several pharmacological agents permit labor induction or augmentation, and ironically the use of a "bougie" has come back into vogue.

Induction implies stimulation of contractions before the spontaneous onset of labor, with or without ruptured membranes. When the cervix is closed and uneffaced, labor induction will often commence with *cervical ripening*, a process that generally employs prostaglandins to soften and open the cervix. *Augmentation* refers to enhancement of spontaneous contractions that are considered inadequate because of failed cervical dilation and fetal descent—*inertia uteri*—as described by Williams (1903).

In the United States, the incidence of labor induction rose 2.5-fold from 9.5 percent in 1991 to 23.8 percent in 2015 (Martin, 2017). The incidence varies between practices. At Parkland Hospital, approximately 35 percent of labors are induced or augmented. By comparison, at the University of Alabama at Birmingham Hospital, labor is induced in approximately 20 percent of women, and another 35 percent are given oxytocin for augmentation—a total of 55 percent. This chapter discusses indications for labor induction and augmentation and various techniques to effect preinduction cervical ripening.

LABOR INDUCTION

Indications

Induction is indicated when the benefits to either mother or fetus outweigh those of pregnancy continuation. The more common indications include membrane rupture without labor, gestational hypertension, oligohydramnios, nonreassuring fetal status, postterm pregnancy, and various maternal medical conditions such as chronic hypertension and diabetes (American College of Obstetricians and Gynecologists, 2016).

Methods to induce or augment labor are contraindicated by most conditions that preclude spontaneous labor or delivery. The few maternal contraindications are related to prior uterine incision type, contracted or distorted pelvic anatomy, abnormally implanted placentas, and uncommon conditions such as active genital herpes infection or cervical cancer. Fetal factors include appreciable macrosomia, severe hydrocephalus, malpresentation, or nonreassuring fetal status.

Techniques

Oxytocin has been used for decades to induce or augment labor. Other effective methods include prostaglandins, such as misoprostol and dinoprostone, and mechanical methods that encompass membrane stripping, artificial rupture of membranes, extraamnionic saline infusion, transcervical balloons, and hygroscopic cervical dilators. Importantly, and as recommended in *Guidelines for Perinatal Care*, each obstetrical department should have its own written protocols that describe administration of these methods for labor induction and augmentation (American Academy of Pediatrics, 2017).

Risks

Maternal complications associated with labor induction are cesarean delivery, chorioamnionitis, uterine rupture, and postpartum hemorrhage from uterine atony. Of these, labor induction carries a two- to threefold greater risk for cesarean delivery (Hoffman, 2003; Maslow, 2000; Smith, 2003). This risk is particularly higher among nulliparas (Luthy, 2004; Wolfe, 2014; Yeast, 1999). More recently, this association has been questioned (Macones, 2009; Melamed, 2016; Miller, 2015; Saccone, 2015). Indeed, Darney and colleagues (2012) reported the cesarean delivery risk was actually lower for women with labor induction at 39 weeks' gestation compared with that in women expectantly managed. In their review, Little and Caughey (2015) found a reduced cesarean delivery rate when women undergoing labor induction were compared with women expectantly managed, as opposed to women spontaneously laboring. Currently, this is the topic of a randomized trial by the Maternal–Fetal Medicine Units (MFMU) Network—A Randomized Trial of Induction Versus Expectant Management—ARRIVE (National Institutes of Health, 2015).

Amniotomy is often selected to augment labor (Amniotomy for Induction and Augmentation). Women whose labor is managed with amniotomy have a higher incidence of chorioamnionitis compared with those in spontaneous labor (American College of Obstetricians and Gynecologists, 2016).

Rupture of a prior uterine incision during labor in women with a history of prior uterine surgery can be catastrophic (Chap. 31, Uterine Scar Rupture). The MFMU Network reported a threefold greater risk of uterine scar rupture with oxytocin, and this was even higher with prostaglandin use (Landon, 2004). The American College of Obstetricians and Gynecologists (2017b) recommends against the use of prostaglandins for preinduction cervical ripening or labor induction in women with a prior uterine incision.

Uterine atony and associated postpartum hemorrhage are more common in women undergoing induction or augmentation (Chap. 41, Risk Factors). And, atony with intractable hemorrhage, especially during cesarean delivery, is a frequent indication for peripartum hysterectomy. In a study from Parkland Hospital, labor induction was associated with 17 percent of 553 emergency peripartum hysterectomies (Hernandez, 2013). In the United States, the postpartum hysterectomy rate rose 15 percent between 1994 and 2007 (Bateman, 2012). This was largely attributed to increased rates of atony associated with more medical labor inductions and more primary and repeat cesarean deliveries. In another analysis, elective induction was also linked with a threefold higher rate of hysterectomy (Bailit, 2010).

Elective Labor Induction

Until recently, elective induction for convenience had become increasingly prevalent. Clark and coworkers (2009) described 14,955 deliveries at ≥37 weeks' gestation. They noted that 32 percent were elective deliveries, and 19 percent were elective labor inductions.

The American College of Obstetricians and Gynecologists (2016) does not endorse this once widespread practice. Occasional exceptions might include logistical and other reasons such as a risk of rapid labor, a woman who lives a long distance from the hospital, or psychosocial indications. Because of the greater risks for adverse maternal outcomes, we are also of the opinion that routine elective induction at term is not justified. Elective delivery before 39 completed weeks is also associated with significant adverse neonatal morbidity (Chiossi, 2013; Clark, 2009; Salemi, 2016; Tita, 2009). If elective induction is considered at term, inherent risks must be discussed, informed consent obtained, and guidelines followed as promulgated by the American College of Obstetricians and Gynecologists (2016), which are detailed in Chapter 31 (Labor and Delivery Considerations).

Guidelines to discourage elective inductions have been described by Fisch (2009) and Oshiro (2013) and their associates. Both groups reported significant declines in elective delivery rates following guideline initiation. In 2011, the Texas Medicaid program began to deny payment for elective induction prior to 39 weeks' gestation. This resulted in a 14-percent drop in such early-term deliveries and a rise in birthweights (Dahlen, 2017). A program in Oregon also reduced early-term deliveries, but maternal and fetal outcomes were not improved (Snowden, 2016).

Factors Affecting Induction Success

Several factors affect the ability of labor induction to achieve vaginal delivery. Favorable factors include younger age, multiparity, body mass index (BMI) <30, favorable cervix, and birthweight <3500 g (Gibson, 2015; Roland, 2017; Sievert, 2017). In many cases, the uterus is simply poorly prepared for labor. One example is an "unripe cervix." Indeed, investigators with the *Consortium on Safe Labor* reported that elective induction resulted in vaginal delivery in 97 percent of multiparas and 76 percent of nulliparas, but that induction was more often successful with a ripe cervix (Laughon, 2012).

The greater cesarean delivery risk associated with induction is likely also strongly influenced by the induction attempt duration, especially with an unfavorable cervix (Spong, 2012). In one study, labor duration to reach the active phase and to complete dilation was adversely affected by a higher BMI (Kominiarek, 2011). Similar findings were reported for women with diabetes (Hawkins, 2017). Simon and Grobman (2005) concluded that a latent phase as long as 18 hours allowed most women undergoing labor induction to achieve a vaginal delivery without a significantly increased risk of maternal or neonatal morbidity. Rouse and associates (2000) recommend a minimum of 12 hours of uterine stimulation with oxytocin after membrane rupture, whereas Kawakita and coworkers (2016) recommend up to 15 hours for multiparas.

PREINDUCTION CERVICAL RIPENING

As discussed, the condition of the cervix—described as cervical "ripeness" or "favorability"—is important to successful labor induction. However, at least some estimates of favorability are highly subjective (Feltovich, 2017). That said, pharmacological and mechanical methods can enhance cervical favorability—also termed *preinduction cervical ripening*.

Some of the techniques described may have benefits when compared with oxytocin induction alone (Table 26-1). Some are also quite successful for initiating labor. However, few data support the premise that any of these techniques lower cesarean delivery rates or lessen maternal or neonatal morbidity compared with women in whom these methods are not used.

TABLE 26-1

Some Commonly Used Regimens for Preinduction Cervical Ripening and/or Labor Induction

Techniques	Agent	Route/Dose	Comments
Pharmacological			
Prostaglandin E_2	Dinoprostone gel, 0.5 mg (Prepidil) Dinoprostone insert, 10 mg (Cervidil)	Cervical 0.5 mg; repeat in 6 hr; permit 3 doses total Posterior fornix, 10 mg	1. Shorter I-D times with oxytocin infusion than oxytocin alone 2. Insert has shorter I-D times than gel 3. 6–12 hr interval from last insert to oxytocin infusion
Prostaglandin E_1[a]	Misoprostol tablet, 100 or 200 µg (Cytotec)[b]	Vaginal, 25 µg; repeat 3–6 hr prn Oral, 50–100 µg; repeat 3–6 hr prn	1. Contractions within 30–60 min 2. Success comparable to oxytocin for ruptured membranes at term and/or favorable cervix 3. Tachysystole common with vaginal doses >25 µg
Mechanical			
Transcervical 36F Foley catheter	30-mL balloon		1. Improves Bishop scores rapidly 2. 80-mL balloon more effective 3. Combined with oxytocin infusion is superior to PGE_1 vaginally 4. With EASI, results improved and possible decreased infection rate
Hygroscopic dilators		Laminaria, hydrogel	1. Rapidly improves Bishop score 2. May not shorten I-D times with oxytocin 3. Uncomfortable, requires speculum and placement on an examination table

[a]Off-label use.

[b]Tablets must be divided for 25- and 50-µg dose, but drug is evenly dispersed.

EASI = extraamnionic saline infusion at 30–40 mL/hr; I-D = induction-to-delivery.

Cervical "Favorability"

One quantifiable method used to predict labor induction outcomes is the score described by Bishop (1964) and presented in Table 26-2. As favorability or Bishop score declines, the rate of induction to effect vaginal delivery also decreases. A *Bishop score* of 9 conveys a high likelihood for a successful induction. For research purposes, a Bishop score of 4 or less identifies an unfavorable cervix and may be an indication for cervical ripening.

TABLE 26-2

Bishop Scoring System Used for Assessment of Inducibility

	Cervical Factor				
Score	**Dilatation (cm)**	**Effacement (%)**	**Station (–3 to +2)**	**Consistency**	**Position**
0	Closed	0–30	–3	Firm	Posterior
1	1–2	40–50	–2	Medium	Midposition
2	3–4	60–70	–1	Soft	Anterior
3	≥5	≥80	+1, +2	—	—

From Bishop, 1964.

Laughon and coworkers (2011) attempted to simplify the Bishop score by performing a regression analysis on 5610 singleton, uncomplicated deliveries between $37^{0/7}$ and $41^{6/7}$ weeks' gestation in nulliparas. Only cervical dilation, station, and effacement were significantly associated with successful vaginal delivery. Thus, a simplified Bishop score, which incorporated only these three parameters, had a similar or improved positive- or negative-predictive value compared with that of the original Bishop score. Other investigators have reported similar findings when consistency and position are omitted (Ivars, 2016; Raghuraman, 2016).

Transvaginal sonographic measurement of cervical length is the only biophysical marker that has been evaluated as a Bishop score alternative (Feltovich, 2017). In one metaanalysis of trials in which cervical length was used to predict successful induction, study criteria heterogeneity precluded the authors from reaching a summary answer (Hatfield, 2007). A subsequent metaanalysis of 31 trials found overall low sensitivity and specificity and limited predictive utility for sonographic cervical length and "wedging" to predict successful labor induction (Verhoeven, 2013).

Pharmacological Techniques

Unfortunately, women frequently have an indication for induction but also have an unfavorable cervix. Several techniques are available, and these can also stimulate contractions and thereby aid subsequent labor induction or augmentation. Methods most commonly used for preinduction cervical ripening and induction include several prostaglandin analogues.

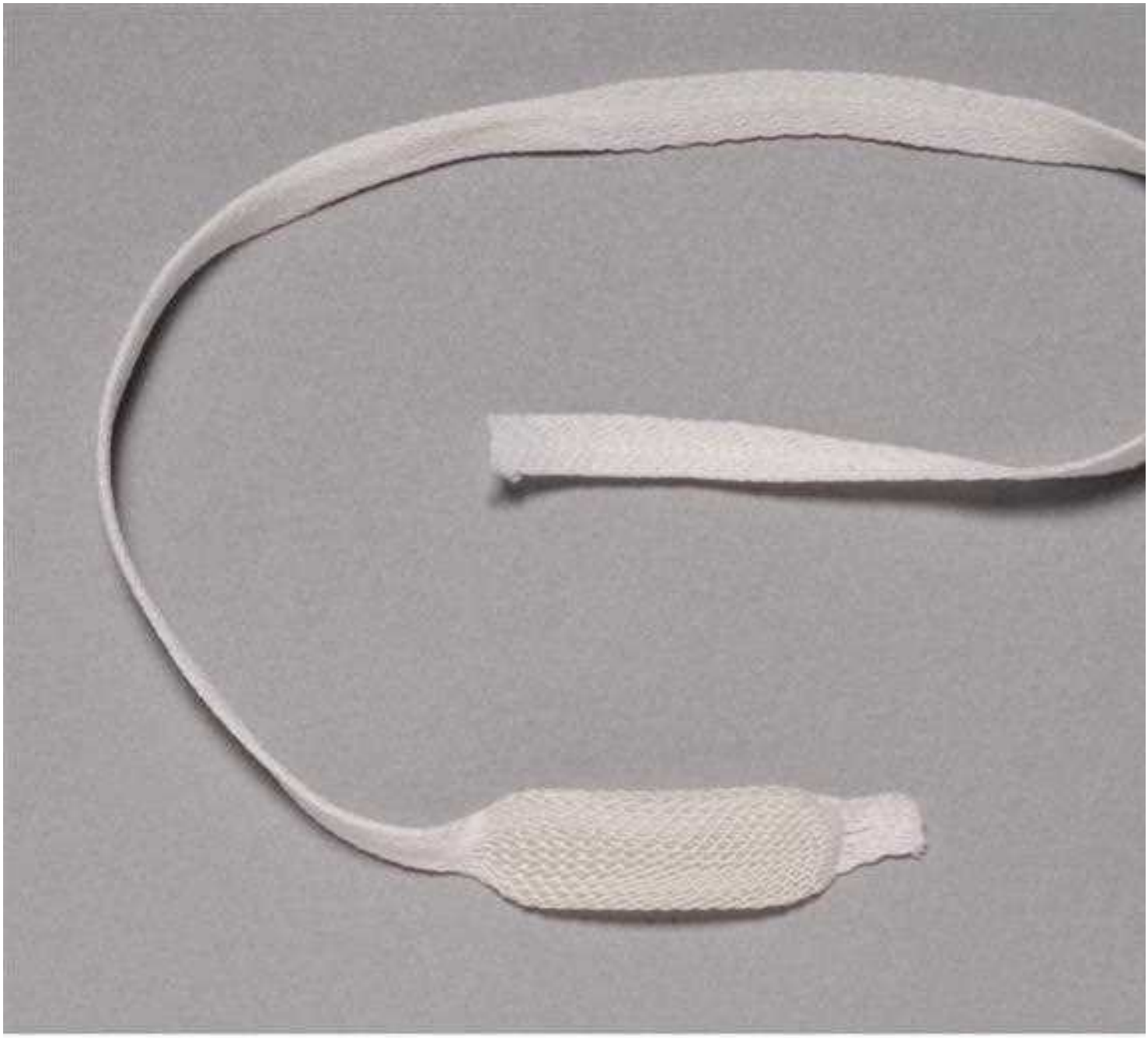
Prostaglandin E_2

Dinoprostone is a synthetic analogue of prostaglandin E_2 (PGE_2). It is commercially available in three forms: a gel, a time-release vaginal insert, and a 20-mg suppository (Table 26-1). The gel and time-release vaginal insert formulations are indicated only for cervical ripening before labor induction. However, the 20-mg suppository is not indicated for cervical ripening. It instead is used for pregnancy termination between 12 and 20 weeks' gestation and for evacuation of the uterus after fetal demise up to 28 weeks.

Local application of its gel form—*Prepidil*—is available in a 2.5-mL syringe for an intracervical application of 0.5 mg of dinoprostone. With the woman supine, the tip of a prefilled syringe is placed intracervically, and the gel is deposited just below the internal cervical os. After application, the woman remains reclined for at least 30 minutes. Doses may be repeated every 6 hours, with a maximum of three doses recommended in 24 hours.

A 10-mg dinoprostone vaginal insert—*Cervidil*—is also approved for cervical ripening. This is a thin, flat, rectangular polymeric wafer held within a small, white, mesh polyester sac (Fig. 26-1). The sac has a long attached tail to allow easy removal from the vagina. The insert provides slower release of medication—0.3 mg/hr—than the gel form. Cervidil is used as a single dose placed transversely in the posterior vaginal fornix. Lubricant is used sparingly, if at all, because it can coat the device and hinder dinoprostone release. Following insertion, the woman remains recumbent for at least 2 hours. The insert is removed after 12 hours or with labor onset and at least 30 minutes before the administration of oxytocin.

FIGURE 26-1
Cervidil vaginal insert contains 10 mg of dinoprostone designed to release approximately 0.3 mg/hr during a 10-hour period.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Most metaanalyses of dinoprostone efficacy report a reduced time-to-delivery within 24 hours, however, they do not consistently show a reduction in the cesarean delivery rate. Thomas and colleagues (2014) provided a Cochrane review of 70 trials and 11,487 women given vaginal prostaglandins or either placebo or no treatment. They noted a higher vaginal delivery rate within 24 hours when prostaglandins were used. They also reported a threefold greater risk of tachysystole accompanied by fetal heart rate changes, but cesarean delivery rates were not significantly decreased. Similar results were noted in another Cochrane review of intracervical dinoprostone gel (Boulvain, 2008). Compared with placebo or no treatment, a reduced risk of cesarean delivery was found only in a subgroup of women with an unfavorable cervix and intact membranes. Finally, the Foley catheter versus vaginal PGE_2 gel for induction of labor at term—PROBAAT-P and -M trials—were unblinded, randomized trials comparing these two options (Jozwiak, 2011, 2013, 2014). The cesarean delivery rate did not differ, a finding consistent with accompanying metaanalyses.

Side Effects

Uterine tachysystole follows vaginally administered PGE_2 in 1 to 5 percent of women (Hawkins, 2012). Although definitions of abnormal uterine activity vary among studies, most use the definition recommended by the American College of Obstetricians and Gynecologists (2017a):

1. *Uterine tachysystole* is defined as >5 contractions in a 10-minute period. It should always be qualified by the presence or absence of fetal heart rate abnormalities.
2. *Uterine hypertonus, hyperstimulation,* and *hypercontractility* are terms no longer defined, and their use is not recommended.

Because uterine tachysystole associated with fetal compromise may develop when prostaglandins are used with preexisting spontaneous labor, such use is not recommended. If tachysystole follows the 10-mg insert, its removal by pulling on the tail of the surrounding net sac will usually reverse this effect. Irrigation to remove the gel preparation has not been shown to be helpful.

The manufacturers recommend caution when these preparations are used in women with ruptured membranes. This concern is also extended to women with glaucoma or asthma. However, in a review of 189 women with asthma, dinoprostone was not associated with asthma worsening or exacerbation (Towers, 2004). Other contraindications listed by the manufacturers include a history of dinoprostone hypersensitivity, suspicion of fetal compromise or cephalopelvic disproportion, unexplained vaginal bleeding, women already receiving oxytocin, those with six or more previous term pregnancies, those with a contraindication to vaginal delivery, or women with a contraindication to oxytocin or who may be endangered by prolonged uterine contractions, for example, those with a history of cesarean delivery or uterine surgery.

Administration

PGE_2 preparations should only be administered in or near the delivery suite. Moreover, uterine activity and fetal heart rate should be monitored (American College of Obstetricians and Gynecologists, 2016). These guidelines stem from the risk of uterine tachysystole. When contractions begin, they are usually apparent in the first hour and show peak activity in the first 4 hours. According to manufacturer guidelines, oxytocin induction that follows prostaglandin use for cervical ripening should be delayed for 6 to 12 hours following PGE_2 gel administration or for at least 30 minutes after removal of the vaginal insert.

Prostaglandin E_1

Misoprostol—*Cytotec*—is a synthetic prostaglandin E_1 (PGE_1) that is approved as a 100- or 200-µg tablet for peptic ulcer prevention. It has been used "off label" for preinduction cervical ripening and may be administered orally or vaginally. The tablets are stable at room temperature. Although widespread, the off-label use of misoprostol has been controversial (Wagner, 2005; Weeks, 2005). Specifically, G. D. Searle & Company notified physicians that misoprostol is not approved for labor induction or abortion (Cullen, 2000). Still, the American College of Obstetricians and Gynecologists (2016) reaffirmed its recommendation for use of the drug because of proven safety and efficacy. It currently is the preferred prostaglandin for cervical ripening at Parkland Hospital. In one review of 234 women administered misoprostol, no instances of asthma exacerbation were associated with its use, and the risk of this was calculated to be <2 percent (Rooney Thompson, 2015).

Vaginal Administration

Compared with intracervical or intravaginal PGE_2, vaginally administered misoprostol tablets offer equivalent or superior efficacy for cervical ripening or labor induction. A metaanalysis of 121 trials also confirmed these findings (Hofmeyr, 2010). Compared with oxytocin or with intravaginal or intracervical dinoprostone, vaginal misoprostol increased the vaginal delivery rate within 24 hours. In this review, although the uterine tachysystole rate rose, this did not affect cesarean delivery rates. Moreover, compared with dinoprostone, misoprostol lowered the need for oxytocin induction, but it increased the frequency of meconium-stained amnionic fluid. Higher doses of misoprostol are associated with a decreased need for oxytocin but with more uterine tachysystole, with and without fetal heart rate changes. The American College of Obstetricians and Gynecologists (2016) recommends a 25-µg vaginal dose—a fourth of a 100-µg tablet. The drug is evenly distributed among these quartered tablets.

Wing and colleagues (2013) described use of a vaginal polymer insert containing 200 µg of PGE_1. They compared its efficacy with 10-mg dinoprostone inserts, and preliminary observations are favorable.

Oral Administration

PGE_1 tablets are also effective when given orally. One Cochrane metaanalysis of 76 trials reported that oral misoprostol compared with placebo significantly raised the rate of vaginal birth within 24 hours, while decreasing the need for oxytocin and lowering the cesarean delivery rate. Comparisons of oral misoprostol and oxytocin and of oral misoprostol and dinoprostone also found significantly reduced rates of cesarean delivery with misoprostol. Similar efficacy was noted between oral misoprostol and vaginal administration, although oral administration was associated with significantly higher Apgar scores and less postpartum hemorrhage (Alfirevic, 2014). Thorbiörnson and associates (2017) also reported lower rates of cesarean delivery for oral misoprostol compared with vaginal dinoprostone.

Nitric Oxide Donors

Several findings have prompted a search for clinical agents that stimulate nitric oxide (NO) production locally (Chanrachakul, 2000). First, NO is likely a mediator of cervical ripening. Also, cervical NO metabolite concentrations are increased at the beginning of uterine contractions. And, cervical NO production is very low in postterm pregnancy (Väisänen-Tommiska, 2003, 2004).

Bullarbo and colleagues (2007) reviewed rationale and use of two NO donors, *isosorbide mononitrate* and *glyceryl trinitrate*. Isosorbide mononitrate induces cervical cyclooxygenase 2 (COX-2), and it also initiates cervical ultrastructure rearrangement similar to that seen with spontaneous cervical ripening (Ekerhovd, 2002, 2003). Despite this, NO donors are less effective clinically than prostaglandins, either PGE_2 or misoprostol, for cervical ripening. In one large metaanalysis, the rate of cesarean delivery was not reduced in those given NO donors compared with those given placebo, intravaginal or intracervical prostaglandins, intravaginal misoprostol, or intracervical catheter (Ghosh, 2016). However, NO donors were associated with significantly more headaches, nausea, and vomiting.

Mechanical Techniques

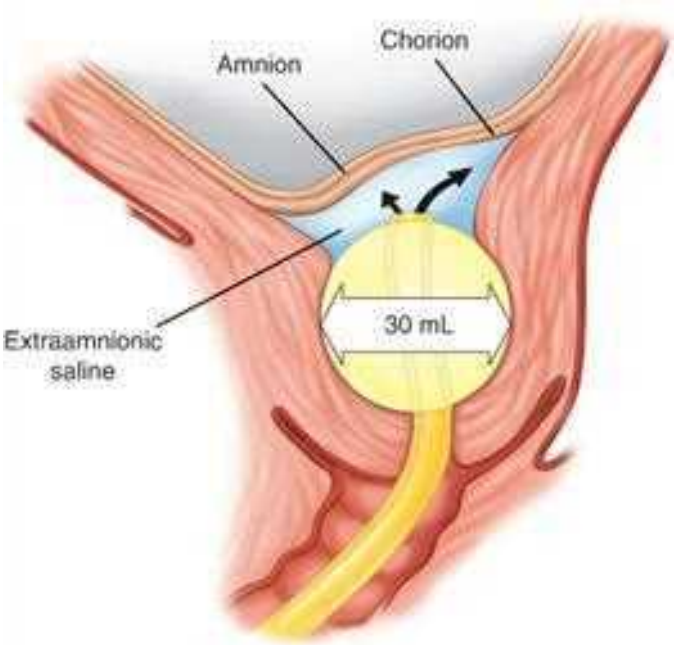
These include transcervical placement of a Foley catheter, with or without extraamnionic saline infusion; hygroscopic cervical dilators; and membrane stripping. In their metaanalysis, Jozwiak and associates (2012) reported that mechanical techniques reduced the risk of uterine tachysystole compared with prostaglandins, although cesarean delivery rates were unchanged. Trials comparing mechanical techniques with oxytocin found a lower rate of cesarean delivery with mechanical methods. Trials comparing mechanical techniques with dinoprostone found a higher rate of multiparas undelivered at 24 hours with mechanical techniques. In

another metaanalysis comparing Foley catheter placement with intravaginal dinoprostone inserts, rates of cesarean delivery were similar, but uterine tachysystole was less frequent with catheter use (Jozwiak, 2013).

Transcervical Catheter

Generally, these techniques are only used when the cervix is unfavorable because the catheter tends to come out as the cervix opens. It is suitable for women with intact or ruptured membranes. In most cases, a Foley catheter is placed through the internal cervical os, and downward tension is created by taping the catheter to the thigh (Mei-Dan, 2014). A modification of this—*extraamnionic saline infusion (EASI)*—adds a constant saline infusion through the catheter into the space between the internal os and placental membranes (Fig. 26-2). Karjane and coworkers (2006) reported that chorioamnionitis was significantly less frequent when infusion was done compared with no infusion—6 versus 16 percent. Similarly, in a large metaanalysis, transcervical catheters were not associated with higher rates of maternal or fetal infection (McMaster, 2015).

FIGURE 26-2
Extraamnionic saline infusion (EASI) through a 26F Foley catheter that is placed through the cervix. The 30-mL balloon is inflated with saline and pulled snugly against the internal os, and the catheter is taped to the thigh. Room-temperature normal saline is infused through the catheter port of the Foley at 30 or 40 mL/hour by intravenous infusion pump.



As discussed above, transcervical catheters do not reduce the cesarean delivery rate compared with prostaglandins. The PROBAAT trials (-I, -P, -M, and II), in which cervical ripening with a Foley catheter was compared with vaginal dinoprostone gel, dinoprostone vaginal inserts, and vaginal or oral misoprostol, reported similar outcomes between the mechanical technique and the prostaglandin agents. Also, fewer overall cases of cardiotocographic changes were seen in the mechanical technique group (Jozwiak, 2011, 2013, 2014; Ten Eikelder, 2016).

Similar cesarean delivery rate results are found in other comparison studies. Schoen and coworkers (2017) observed that concurrent oxytocin with a transcervical Foley catheter shortened the median time-to-delivery compared with a Foley catheter followed by oxytocin. However, rates of cesarean delivery were unchanged. Connolly and associates (2016) reported similar findings for women within intact membranes undergoing labor induction. Amorosa and colleagues (2017) found no benefit for transcervical catheter coupled with oxytocin compared against oxytocin alone for women with ruptured membranes. Other studies of concurrent misoprostol reported reduced time-to-delivery without affecting cesarean delivery rates (Carbone, 2013; Levine, 2016). Finally, the concurrent addition of tension does not appear to enhance catheter efficacy. Fruhman and coworkers (2017) randomized 140 women to transcervical Foley catheter with and without tension, and reported similar vaginal delivery rates within 24 hours or overall.

Hygroscopic Cervical Dilators

Cervical dilation can be accomplished using hygroscopic osmotic cervical dilators, as described for early pregnancy termination (Chap. 18, First-Trimester Abortion Methods). Intuitive concerns of ascending infection have not been verified, and their use appears to be safe. Placement generally requires a speculum and positioning of the woman on an examination table. Several studies performed in the 1990s compared hygroscopic cervical dilators and prostaglandins and found few benefits of this mechanical technique. And, more recent studies verified these conclusions (Maier, 2017).

METHODS OF INDUCTION AND AUGMENTATION

Labor induction has primarily been effected with the use of amniotomy, prostaglandins, and oxytocin, alone or in combination. Because preinduction cervical ripening frequently eventuates in labor, studies to determine induction efficacy for some of these agents have produced sometimes confusing results. The use of

prostaglandins for labor augmentation has generally been considered experimental due to their high rates of uterine tachysystole.

Prostaglandin E_1

Both vaginal and oral misoprostol are used for either cervical ripening or labor induction. For labor induction in women at or near term with either prematurely ruptured membranes or a favorable cervix, 100 µg of oral or 25 µg of vaginal misoprostol has similar efficacy compared with intravenous oxytocin. From these studies, evidence supports that oral misoprostol may be superior (Alfirevic, 2014; Hofmeyr, 2010; Lo, 2003). Misoprostol may be associated with a greater rate of uterine tachysystole, particularly at higher doses. Also, induction with PGE_1 may prove ineffective and require subsequent induction or augmentation with oxytocin.

Thus, although there are trade-offs regarding the risks, costs, and ease of administration of each drug, either is suitable for labor induction. At Parkland Hospital, we administer an initial oral 100-µg dose, which may be repeated after 6 hours for inadequate labor. Six hours after the second dose or in those with tachysystole, an oxytocin infusion is begun, if needed, for hypotonic labor. Döbert and colleagues (2017) have described preliminary use of a misoprostol vaginal insert.

For *labor augmentation*, results of a randomized controlled trial showed oral misoprostol, 75 µg given at 4-hour intervals for a maximum of two doses, to be safe and effective (Bleich, 2011). The 75-µg dose was based on a previous dose-finding study (Villano, 2011). Although there was more uterine tachysystole among women with labor augmented with misoprostol, the frequency of nonreassuring fetal status or cesarean delivery did not differ between oxytocin and misoprostol.

Oxytocin

In many instances, preinduction cervical ripening and labor induction are simply a continuum. Thus, “ripening” can also stimulate labor. If not, induction or augmentation may be continued with solutions of oxytocin given by infusion pump. Its use in augmentation is a key component in the *active management of labor,* described in Chapter 22 (Labor Management Protocols). With oxytocin use, the American College of Obstetricians and Gynecologists (2016) recommends fetal heart rate and uterine contraction monitoring. Contractions can be monitored either by palpation or by electronic means.

Intravenous Oxytocin Administration

The goal of induction or augmentation is to effect uterine activity sufficient to produce cervical change and fetal descent, while avoiding development of a nonreassuring fetal status. In general, oxytocin is discontinued if the number of contractions persists with a frequency of more than five in a 10-minute period or more than seven in a 15-minute period or with a persistent nonreassuring fetal heart rate pattern. Oxytocin discontinuation nearly always rapidly lowers contraction frequency. When oxytocin is stopped, its concentration in plasma rapidly falls because the half-life is approximately 3 to 5 minutes. Seitchik and associates (1984) found that the uterus contracts within 3 to 5 minutes of beginning an oxytocin infusion and that a plasma steady state is reached in 40 minutes. Response is highly variable and depends on preexisting uterine activity, cervical status, pregnancy duration, and individual biological differences. Caldeyro-Barcia and Poseiro (1960) reported that the uterine response to oxytocin increases from 20 to 30 weeks’ gestation and rises rapidly at term (Chap. 24, Intrapartum Surveillance of Uterine Activity).

Oxytocin Dosage

A 1-mL ampule containing 10 units of oxytocin usually is diluted into 1000 mL of a crystalloid solution and administered by infusion pump. A typical infusate consists of 10 or 20 units, which is 10,000 or 20,000 mU or one or two 1-mL vials, respectively, mixed into 1000 mL of lactated Ringer solution. This mixture results in an oxytocin concentration of 10 or 20 mU/mL, respectively. To avoid bolus administration, the infusion should be inserted into the main intravenous line close to the venipuncture site.

Oxytocin is generally very successful when used to stimulate labor. In one large Cochrane metaanalysis, oxytocin was compared with expectant management, and fewer women—8 versus 54 percent—failed to deliver vaginally within 24 hours with oxytocin (Alfirevic, 2009). This analysis studied different oxytocin dosing regimens.

Oxytocin Regimens

Several evidence-based regimens for labor stimulation are now recommended by the American College of Obstetricians and Gynecologists (2016). These and others are shown in Table 26-3. Initially, only variations of low-dose protocols were used in the United States. Subsequently, O’Driscoll and colleagues (1984) described their Dublin protocol for the active management of labor that called for oxytocin at a starting dosage of 6 mU/min and advanced in 6-mU/min increments. Subsequent comparative trials during the 1990s studied high-dose (4 to 6 mU/min) versus conventional low-dose (0.5 to 1.5 mU/min) regimens, both for labor induction and for augmentation.

TABLE 26-3

Various Low- and High-Dose Oxytocin Regimens Used for Labor Induction

Regimen	Starting Dose (mU/min)	Interval (min)	Incremental Increase (mU/min)
Low-dose	0.5–1.5	15–40	1
	2	15	4, 8, 12, 16, 20, 25, 30
High-dose	4	15	4
	4.5	15–30	4.5
	6	20–40[a]	6[b]

[a]Uterine tachysystole is more common with shorter intervals.

[b]With uterine tachysystole and after oxytocin infusion is discontinued, it is restarted at one half the previous dose and then increased at 3 mU/min incremental doses.

Data from Merrill, 1999; Satin, 1992, 1994; Xenakis, 1995.

From Parkland Hospital, Satin and associates (1992) evaluated an oxytocin regimen using an initial and incremental dosage of 6 mU/min compared with one using 1 mU/min. Increases at 20-minute intervals were provided as needed. Among 1112 women undergoing induction, the 6-mU/min regimen resulted in a shorter mean admission-to-delivery time, fewer failed inductions, and no cases of neonatal sepsis. Among 1676 women who had labor augmentation, those who received the 6-mU/min regimen had a shorter duration-to-delivery time, fewer forceps deliveries, fewer cesarean deliveries for dystocia, and lower rates of intrapartum chorioamnionitis or neonatal sepsis. With this protocol, uterine tachysystole was managed by oxytocin discontinuation followed by resumption when indicated and at half the stopping dosage. Thereafter, the dosage was increased at 3 mU/min when appropriate, instead of the usual 6-mU/min increase used for women without tachysystole. No adverse neonatal effects were observed.

Xenakis and coworkers (1995) reported benefits using an incremental oxytocin regimen starting at 4 mU/min. In another study, 816 women were randomly assigned for labor induction and 816 for augmentation with incremental oxytocin given at either 1.5 or 4.5 mU/min (Merrill, 1999). Women randomized to the 4.5 mU/min dosage had significantly shorter mean durations of induction-to-second-stage labor and induction-to-delivery times. Nulliparas randomized to the 4.5 mU/min dosage had a significantly lower cesarean delivery rate for dystocia compared with those given 1.5 mU/min dosage—6 versus 12 percent. Thus, benefits favor higher-dose regimens of 4.5 to 6 mU/min compared with lower dosages of 0.5 to 1.5 mU/min.

In 1990 at Parkland Hospital, routine use of the 6-mU/min oxytocin beginning and incremental dosage was incorporated and continues through today. In other labor units, a 2-mU/min beginning and incremental oxytocin regimen is preferred and administered. With either regimen, dosages are employed for either labor induction or augmentation. Although a Cochrane metaanalysis of randomized and quasi-randomized trials comparing high-dose versus low-dose regimens for labor induction at term reported no benefit of higher dosing, the metaanalysis included studies judged to have high potential bias. The authors concluded that the results might be confounded by these poor-quality studies (Budden, 2014).

Interval between Incremental Dosing

Intervals to increase oxytocin doses vary from 15 to 40 minutes (see Table 26-3). Satin and associates (1994) addressed this aspect with a 6-mU/min regimen providing increases at either 20- or 40-minute intervals. Women assigned to the 20-minute interval regimen for labor augmentation had a significantly reduced cesarean delivery rate for dystocia compared with that for the 40-minute interval regimen—8 versus 12 percent. As perhaps expected, uterine tachysystole was significantly more frequent with the 20-minute escalation regimen.

Other investigators reported even more frequent incremental increases. Frigoletto (1995) and Xenakis (1995) and their coworkers gave oxytocin at 4 mU/min with increases as needed every 15 minutes. Merrill and Zlatnik (1999) started with 4.5 mU/min doses and increased this every 30 minutes. López-Zeno and associates (1992) used 6 mU/min doses and 15-minute intervals. Thus, there are several acceptable oxytocin protocols that at least appear dissimilar. But, a comparison of protocols from two institutions indicates that this is not so:

1. The Parkland Hospital protocol uses a starting dose of oxytocin at 6 mU/min, which is increased by 6-mU/min every 40 minutes, and employs flexible dosing based on uterine tachysystole.

2. The University of Alabama at Birmingham Hospital protocol begins oxytocin at 2 mU/min and increases it as needed every 15 minutes to 4, 8, 12, 16, 20, 25, and 30 mU/min.

Thus, although the regimens at first appear disparate, if there is no uterine activity, either regimen is delivering 12 mU/min by 45 minutes into the infusion.

Maximal Oxytocin Dosage

The *maximal* effective dose of oxytocin to achieve adequate contractions in all women is different. Wen and colleagues (2001) studied 1151 consecutive nulliparas and found that the likelihood of progression to vaginal delivery decreased at and beyond an oxytocin dosage of 36 mU/min. Still, at a dosage of 72 mU/min, half of

the nulliparas were delivered vaginally. Thus, if contractions are not adequate—less than 200 Montevideo units—and if the fetal status is reassuring and labor has arrested, an oxytocin infusion dose greater than 48 mU/min has no apparent risks.

Risks versus Benefits

Unless the uterus is scarred, uterine rupture associated with oxytocin infusion is rare, even in parous women. Flannelly and associates (1993) reported no cases of uterine ruptures, with or without oxytocin, in 27,829 nulliparas. There were eight instances of overt uterine rupture during labor in 48,718 parous women. Only one of these was associated with oxytocin use. A population-based retrospective review from Denmark reported a rupture rate of 3.3 per 100,000 women without prior cesarean, with the highest risk among multiparas (Thisted, 2015). Our experiences from Parkland Hospital are that oxytocin induction and augmentation are associated with uterine rupture (Happe, 2017). During an 8-year period in which there were about 95,000 births, 15 women suffered a primary uterine rupture, and 14 of these cases were associated with oxytocin use. In half of these women, prostaglandins were also given before augmentation with oxytocin.

Oxytocin has amino-acid homology similar to arginine vasopressin and has significant antidiuretic action. When infused at doses of 20 mU/min or more, renal free water clearance drops markedly. If aqueous fluids are infused in appreciable amounts along with oxytocin, *water intoxication* can lead to convulsions, coma, and even death. In general, if oxytocin is to be administered in high doses for a considerable period of time, its concentration should be increased rather than raising the flow rate of a more dilute solution. Consideration also should be given to use of crystalloids—either normal saline or lactated Ringer solution.

Uterine Contraction Pressures

Contraction forces in spontaneously laboring women range from 90 to 390 Montevideo units (Chap. 24, Intrapartum Surveillance of Uterine Activity). Caldeyro-Barcia (1950) and Seitchik (1984) with their coworkers found that the mean or median spontaneous uterine contraction pattern between 140 and 150 Montevideo units resulted in progression to vaginal delivery.

In the management of active-phase arrest, and with no contraindication to intravenous oxytocin, decisions must be made with knowledge of the safe upper range of uterine activity. Hauth and colleagues (1986) described an effective and safe protocol for oxytocin augmentation for active-phase arrest. With it, more than 90 percent of women achieved an average of at least 200 to 225 Montevideo units. They later reported that nearly all women in whom active-phase arrest persisted despite oxytocin generated more than 200 Montevideo units (Hauth, 1991). Importantly, despite no labor progression, no adverse maternal or perinatal effects were noted in those ultimately requiring cesarean delivery. There are no data regarding safety and efficacy of contraction patterns in women with a prior cesarean delivery, with twins, or with an overdistended uterus.

Active-Phase Arrest

First-stage arrest of labor is defined as a completed latent phase and contractions exceeding 200 Montevideo units for more than 2 hours without cervical change. Some have attempted to define a more accurate duration for active-phase arrest (Spong, 2012). Arulkumaran and coworkers (1987) extended the 2-hour limit to 4 hours and reported a 1.3-percent cesarean delivery rate in women who continued to have adequate contractions and progressive cervical dilation of at least 1 cm/hr. In women without progressive cervical dilation who were allowed another 4 hours of labor, half required cesarean delivery.

Rouse and colleagues (1999) prospectively managed 542 women at term with active-phase arrest and no other complications. Their protocol was to achieve a sustained pattern of at least 200 Montevideo units for a *minimum* of 4 hours. This time frame was extended to 6 hours if activity of 200 Montevideo units or greater could not be sustained. Almost 92 percent of these women were delivered vaginally. As discussed in Chapter 23 (Active-Phase Protraction), these and other studies support the practice of allowing an active-phase arrest of 4 hours (Rouse, 2001).

Zhang and coworkers (2002) analyzed labor duration from 4 cm to complete dilatation in 1329 nulliparas at term. They found that before dilation of 7 cm was reached, lack of progress for more than 2 hours was not uncommon in those who delivered vaginally. Alexander and associates (2002) reported that epidural analgesia prolonged active labor by 1 hour compared with duration of the active phase as defined by Friedman (1955). Consideration of these changes in the management of labor, especially in nulliparas, may safely reduce the cesarean delivery rate.

As data have accrued, investigators have increasingly questioned the thresholds for labor arrest disorders established by Friedman and others in the 1960s. In particular, investigators with the *Consortium on Safe Labor* reported that half of cases of dystocia after labor induction occurred before 6 cm of cervical dilation (Boyle, 2013; Zhang, 2010c). Even for women with spontaneous labor, these researchers found that active-phase labor was more likely to occur at 6 cm, and after slow progress between 4 and 6 cm (Zhang, 2010a). Additionally, they reported that a 2-hour threshold for diagnosing arrest disorders may be too brief when cervical dilation is <6 cm (Zhang, 2010b). This is discussed in detail in Chapter 23 (Obstetric Care Consensus Committee). Importantly, however, these studies of data from the Collaborative Perinatal Project included only singleton term gestation with spontaneous onset of labor, vaginal delivery, and a normal perinatal outcome. By excluding abnormal outcomes, cesarean deliveries, and those who were more than 6 cm dilated upon arrival, the above studies that sought to redefine the labor curve have been faulted for introducing biases that limit general use of these findings (Cohen, 2015a,b).

Amniotomy for Induction and Augmentation

Elective amniotomy with the intention of accelerating labor is often performed. Shown in Table 26-4, amniotomy at approximately 5-cm dilation accelerated spontaneous labor by 1 to 1½ hours. Importantly, neither the need for oxytocin stimulation nor the overall cesarean delivery rate was increased. Although the incidences of mild and moderate cord compression patterns were raised following amniotomy, cesarean delivery rates for fetal distress were not higher. Most importantly, there were no adverse perinatal effects.

TABLE 26-4

Randomized Clinical Trials of Elective Amniotomy in Early Spontaneous Labor at Term

		Effects of Amniotomy					
Study	**Number**	**Mean Dilation at Amniotomy**	**Mean Shortening of Labor**	**Need for Oxytocin**	**Cesarean Delivery Rate**	**Abnormal Tracing**	**Neonatal Effects**
Fraser (1993)	925	<5 cm	125 min	None	None[a]	None	None
Garite (1993)	459	5.5 cm	81 min	Decreased	None	Increased[b]	None
UK Amniotomy Group (1994)	1463	5.1 cm	60 min	None	None	NA	None

[a]No effect on overall rate; cesarean delivery for fetal distress significantly increased.

[b]Increased mild and moderate umbilical cord compression patterns.

NA = not assessed.

For labor induction, artificial rupture of the membranes—sometimes called *surgical induction*—can be used and always implies a commitment to delivery. The main disadvantage of amniotomy used alone for labor induction is the unpredictable and occasionally long interval until labor onset. That said, in a randomized trial, Bakos and Bäckström (1987) found that amniotomy alone or combined with oxytocin was superior to oxytocin alone. Mercer and colleagues (1995) randomly assigned 209 women undergoing oxytocin induction to either early amniotomy at 1 to 2 cm or late amniotomy at 5 cm. Early amniotomy was associated with a 4-hour reduction in labor duration. With early amniotomy, however, the incidence of chorioamnionitis was elevated.

For labor augmentation, amniotomy is commonly performed when labor is abnormally slow. Rouse and associates (1994) found that amniotomy with oxytocin augmentation for arrested active-phase labor shortened the time to delivery by 44 minutes compared with that of oxytocin alone. Although amniotomy did not alter the delivery route, one drawback was that it significantly increased the incidence of chorioamnionitis.

Regardless of the indication, amniotomy is associated with a risk of cord prolapse. To minimize this risk, disengagement of the fetal head during amniotomy is avoided. Toward this goal, fundal or suprapubic pressure or both may be helpful. Some clinicians prefer to rupture membranes during a contraction. If the vertex is not well applied to the lower uterine segment, a gradual egress of amnionic fluid can sometimes be accomplished by several membrane punctures with a 26-gauge needle held with a ring forceps and with direct visualization using a vaginal speculum. In many of these, however, membranes tear and fluid is lost rapidly. Because of the risk of cord prolapse or rarely abruption, the fetal heart rate is assessed before and immediately after amniotomy.

Membrane Stripping for Labor Induction

Labor induction by membrane "stripping" is a frequent practice. Several studies have suggested that membrane stripping is safe and lowers the incidence of postterm pregnancy without consistently raising the incidence of ruptured membranes, infection, or bleeding. Authors of one large metaanalysis found that membrane stripping reduced the number of women remaining undelivered after 41 weeks without elevating the infection risk. They concluded that eight women would need to undergo membrane stripping to avoid one labor induction. Downsides are discomfort and associated bleeding (Boulvain, 2005).

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CHAPTER 27: Vaginal Delivery

As soon as the head appears at the vulva the physician should be ready to restrain its progress. He should hold his hand in such a manner as to be able to bring it immediately into action, for in many instances the resistance of the vulva is unexpectedly overcome, and a single pain may be sufficient to push the head suddenly through it with a resulting perineal tear.

—J. Whitridge Williams (1903)

INTRODUCTION

As described by Williams, the natural culmination of second-stage labor is controlled vaginal delivery of a healthy neonate with minimal trauma to the mother. Vaginal delivery is the preferred route of delivery for most fetuses, although various clinical settings may favor cesarean delivery. Of delivery routes, spontaneous vaginal vertex delivery poses the lowest risk of most maternal comorbidity, and comparisons with cesarean delivery are found in Chapter 30 (Cesarean Delivery Risks). Delivery is usually spontaneous, although some maternal or fetal complications may warrant operative vaginal delivery, described in Chapter 29 (Indications). Last, a malpresenting fetus or multifetal gestation in many cases may be delivered vaginally but requires special techniques. These are described in Chapters 28 (Labor and Delivery Management) and 45 (Evaluation of Fetal Presentation).

PREPARATION FOR DELIVERY

The end of second-stage labor is heralded as the perineum begins to distend, the overlying skin becomes stretched, and the fetal scalp is seen through the separating labia. Increased perineal pressure from the fetal head creates reflexive bearing-down efforts, which are encouraged when appropriate. At this time, preparations are made for delivery. If the bladder is distended, catheterization may be necessary. Continued attention is also given to fetal heart rate monitoring. As one example, a nuchal cord often tightens with descent and may lead to deepening variable decelerations.

During second-stage labor, pushing positions may vary. But for delivery, the dorsal lithotomy position is most common and often the most satisfactory. For better exposure, leg holders or stirrups are used. Corton and associates (2012) found no increased rates of perineal lacerations with or without their use. With positioning, legs are not separated too widely or placed one higher than the other. Within the leg holder, the popliteal region should rest comfortably in the proximal portion and the heel in the distal portion. The legs are not strapped into the stirrups, thereby allowing quick flexion of the thighs backward onto the abdomen should shoulder dystocia develop. Legs may cramp during second-stage pushing, and cramping is relieved by repositioning the affected leg or by brief massage.

Preparation for delivery includes vulvar and perineal cleansing. If desired, sterile drapes may be placed in such a way that only the immediate area around the vulva is exposed. Scrubbing, gowning, gloving, and donning protective mask and eyewear protect both the laboring woman and accoucheur from infectious agents.

OCCIPUT ANTERIOR POSITION

Delivery of the Head

By the time of perineal distention, the position of the occiput is usually known. In some cases, however, molding and caput formation may have precluded early accurate identification. At this time, careful assessment is again performed as described in Chapter 22 (Vaginal Examination). In most cases, position is directly occiput anterior (OA) or is rotated slightly oblique. But, in perhaps 5 percent, occiput posterior (OP) positioning persists.

With each contraction, the vulvovaginal opening is dilated by the fetal head to gradually form an ovoid and finally, an almost circular opening (Fig. 27-1). This encirclement of the largest head diameter by the vulvar ring is termed *crowning*. The perineum thins and may spontaneously lacerate. The anus becomes greatly stretched, and the anterior wall of the rectum can easily be seen through it.

Routine episiotomy is no longer recommended, and selective use aims to enlarge the vaginal opening for specific indications (Episiotomy). To limit spontaneous vaginal laceration, some perform antenatal massage of the perineal body to increase perineal distensibility or intrapartum perineal massage to widen the introitus for head passage. During massage with a lubricant, the perineum is grasped in the midline by both hands using the thumb and opposing fingers. Outward and lateral stretching to thin the perineum is repeatedly performed. But in randomized studies, this technique did not significantly prevent perineal laceration (Beckmann, 2013; Mei-dan, 2008; Stamp, 2001). Antepartum use of the *Epi-No* intravaginal pump balloon has a similar aim, but it also fails to prevent perineal trauma or levator injury (Brito, 2015; Kamisan Atan, 2016).

When the head distends the vulva and perineum enough to open the vaginal introitus to a diameter of 5 cm or more, a gloved hand may be used to support the perineum (Fig. 27-2). The other hand is used to guide and control the fetal head to deliver the smallest head diameter through the introitus and to avoid expulsive delivery. Slow delivery of the head may decrease lacerations (Laine, 2008). Overall, bracing the perineum lowers rates of anal sphincter injury compared with a "hands off" approach to delivery (Bulchandani, 2015; McCandlish, 1998).

FIGURE 27-1
Perineum is supported as the head crowns.

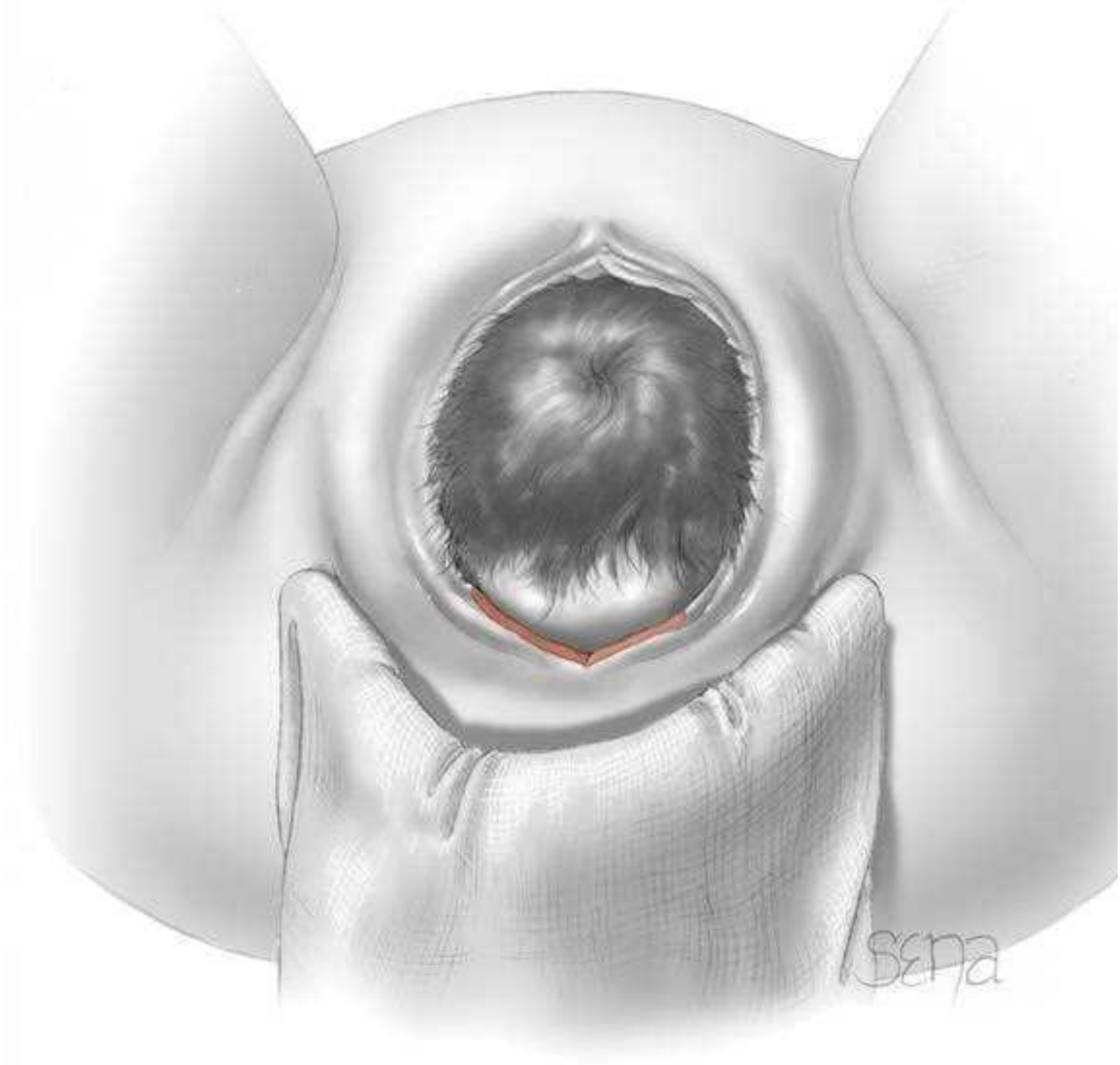


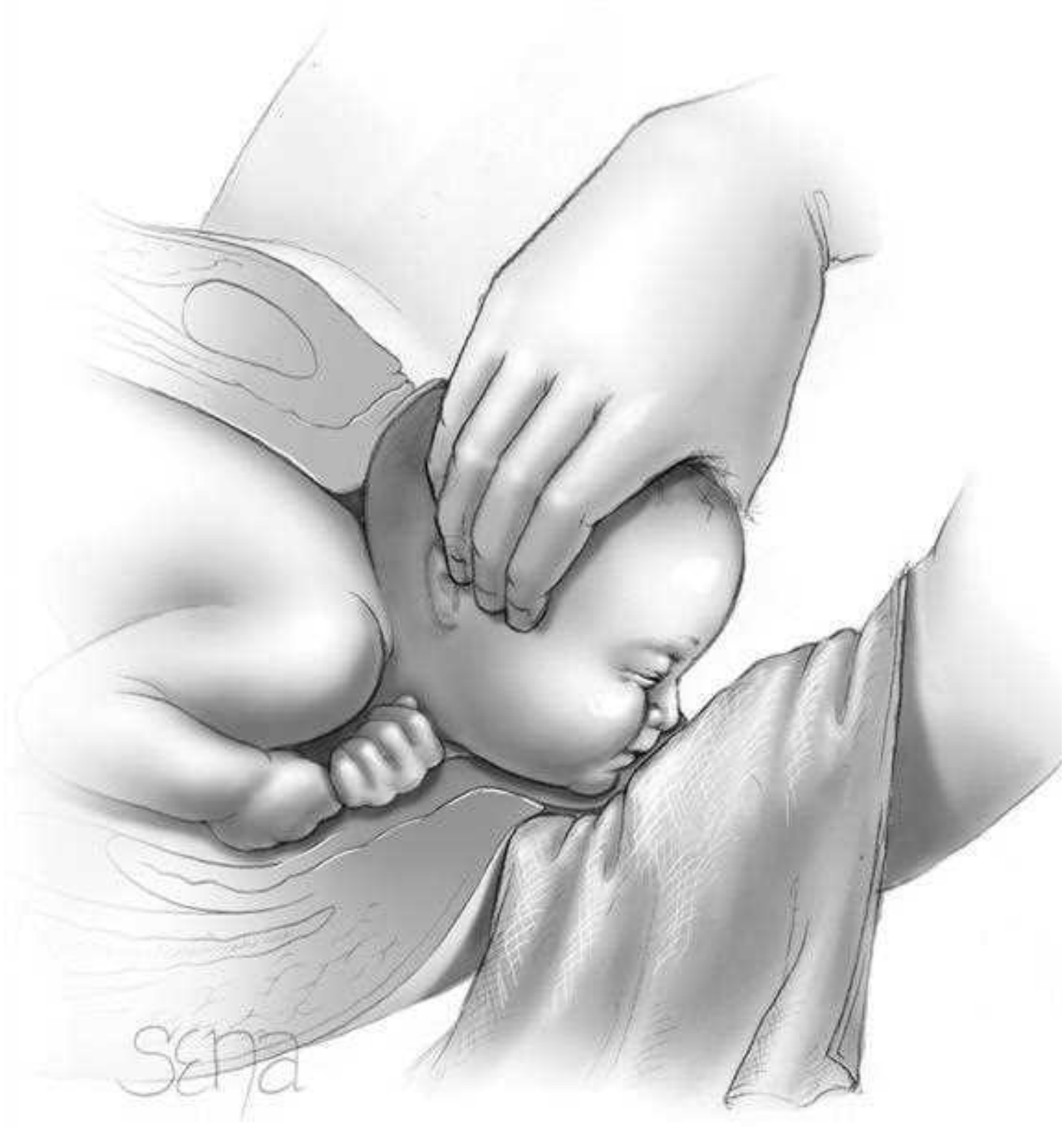
FIGURE 27-2

Delivery of the head. The mouth appears over the perineum.

Alternatively, if expulsive efforts are inadequate or expeditious delivery is needed, the *modified Ritgen maneuver* may be employed or an episiotomy cut. With the modified maneuver, gloved fingers beneath a draped towel exert forward pressure on the fetal chin through the perineum just in front of the coccyx. Concurrently, the other hand presses against the occiput (Fig. 27-3). Originally described in 1855, the maneuver allows controlled fetal head delivery (Cunningham, 2008). It also favors neck extension so that the head passes through the introitus and over the perineum with its smallest diameters. Comparing the Ritgen maneuver with simple perineal support in 1623 women, Jönsson and colleagues (2008) found a similar incidence of third- and fourth-degree tears, defined later (Immediate Postpartum Care).

FIGURE 27-3

Modified Ritgen maneuver. Moderate upward pressure is applied to the fetal chin by the posterior hand covered by a sterile towel. The other hand applies occipital pressure.



Delivery of the Shoulders

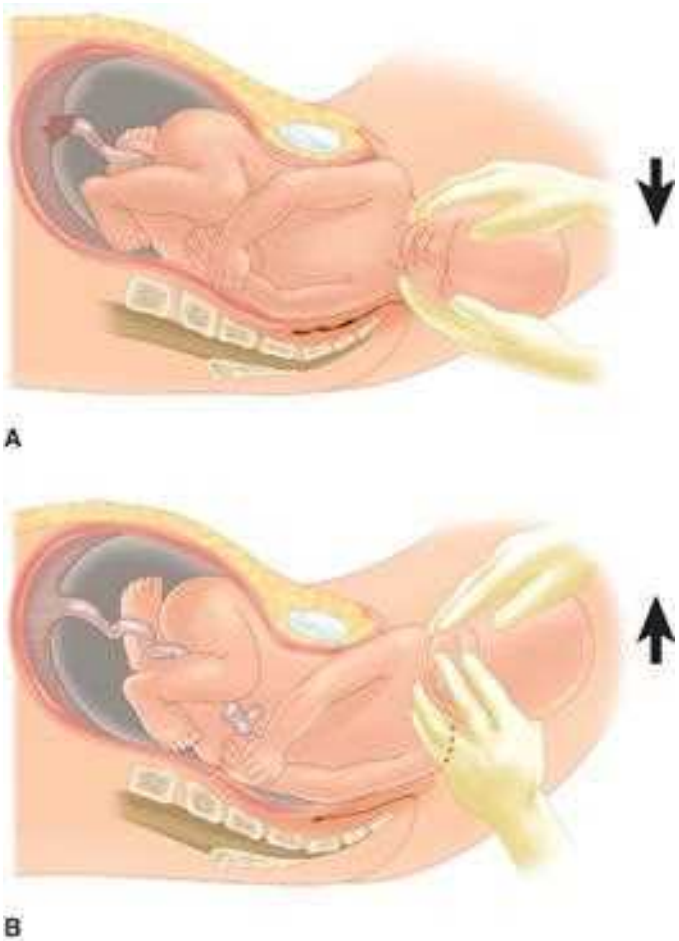
Following delivery of the fetal head, a finger is passed across the fetal neck to determine whether it is encircled by one or more umbilical cord loops. The nuchal cord incidence increases with gestational age and is found in nearly 25 percent of deliveries at term (Larson, 1997; Ogueh, 2006). If an umbilical cord coil is felt, it is slipped over the head if loose enough. If applied too tightly, the loop is cut between two clamps. Tight nuchal cords complicate approximately 6 percent of all deliveries but are not associated with worse neonatal outcome than those without a cord loop (Henry, 2013).

Following its delivery, the fetal head falls posteriorly, bringing the face almost into contact with the maternal anus. The occiput promptly turns toward one of the maternal thighs, and the head assumes a transverse position. This external rotation indicates that the bisacromial diameter, which is the distance between the shoulders, has rotated into the anteroposterior diameter of the pelvis.

Most often, the shoulders appear at the vulva just after external rotation and are born spontaneously. If delayed, extraction aids controlled delivery. The sides of the head are grasped with two hands, and *gentle* downward traction is applied until the anterior shoulder appears under the pubic arch (Fig. 27-4). Next, by an upward movement, the posterior shoulder is delivered. During delivery, abrupt or powerful force is avoided to avert fetal brachial plexus injury.

FIGURE 27-4

Delivery of the shoulders. **A.** Gentle downward traction to effect descent of the anterior shoulder. **B.** Delivery of the anterior shoulder completed. Gentle upward traction to deliver the posterior shoulder.



The rest of the body almost always follows the shoulders without difficulty. With prolonged delay, however, its birth may be hastened by moderate outward traction on the head and moderate pressure on the uterine fundus. Hooking the fingers in the axillae is avoided. This can injure upper extremity nerves and produce a transient or possibly permanent paralysis. Immediately after delivery of the newborn, a gush of amnionic fluid that is often blood-tinged but not grossly bloody usually follows.

Previously, immediate nasopharyngeal bulb suctioning of the newborn was routine to remove secretions. It was found, however, that suctioning of the nasopharynx may lead to neonatal bradycardia (Gungor, 2006). The current American Heart Association neonatal resuscitation recommendations eschew most suctioning immediately following birth—even with meconium present (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy). And with meconium-stained fluid, routine intubation for tracheal suction is not recommended for vigorous or for nonvigorous neonates. Suctioning is reserved for neonates who have obvious obstruction to spontaneous breathing or who require positive-pressure ventilation (Wyckoff, 2015). For suctioning, options are bulb syringe or suction catheter aspiration and may include intubation and suctioning if the airway is obstructed.

Cord Clamping

The umbilical cord is cut between two clamps placed 6 to 8 cm from the fetal abdomen, and later an umbilical cord clamp is applied 2 to 3 cm from its insertion into the fetal abdomen.

For term neonates, the timing of umbilical cord clamping remains debatable. Delayed umbilical cord clamping transfers a greater volume of blood to the newborn. A delay for up to 60 seconds may increase total body iron stores, expand blood volume, and decrease anemia incidence in the neonate (Andersson, 2011; Yao, 1974). This practice may be particularly valuable in populations in which iron deficiency is prevalent (Kc, 2017; World Health Organization, 2014).

Conversely, a higher hemoglobin concentration increases risks for hyperbilirubinemia and extended hospitalization for neonatal phototherapy (McDonald, 2013). Delayed cord clamping may also hinder timely and needed neonatal resuscitation. That said, early pilot studies are assessing the value of resuscitating newborns at the bedside to permit delayed clamping (Katheria, 2017; Winter 2017). Fortunately, in general, delayed umbilical cord clamping compared with early clamping does

not worsen Apgar scores, umbilical cord pH, or respiratory distress caused by polycythemia. Regarding maternal outcomes, rates of postpartum hemorrhage are similar between early and delayed clamping groups (Andersson, 2013). Fewer data are available regarding cord "milking," in which the operator pushes blood through the cord toward the newborn. This maneuver appears safe and may be advantageous if rapid cord clamping is clinically indicated (Upadhyay, 2013).

For the preterm neonate, delayed cord clamping has several benefits. These include higher red cell volume, decreased need for blood transfusion, and lower rates of intraventricular hemorrhage and of necrotizing enterocolitis (Backes, 2014; Rabe, 2012). For neonates who require expedited resuscitation, cord milking may have benefits to quickly transfer volume (Al-Wassia, 2015; Katheria, 2015; Patel, 2014). Still, because of rapid blood volume changes, the American Heart Association currently suggests against the routine use of cord milking for neonates born <29 weeks' gestation (Wyckoff, 2015).

The American College of Obstetricians and Gynecologists (2017a) notes sufficient evidence to support delayed umbilical cord clamping for term and preterm neonates for at least 30 to 60 seconds after birth. This opinion is also endorsed by the American Academy of Pediatrics (2017a). The American Heart Association guidelines advise that the practice may have benefits for term or preterm neonates not needing immediate resuscitation at birth (Wyckoff, 2015).

Occiput Transverse Position

In the absence of a pelvic architecture abnormality or asynclitism, the occiput transverse (OT) position is usually transitory. Thus, unless contractions are hypotonic, the head usually spontaneously rotates to an OA position. If rotation ceases because of poor expulsive forces, vaginal delivery usually can be accomplished readily in several ways. The easiest is manual rotation of the occiput either anteriorly to OA or less commonly, posteriorly to occiput posterior. If either is successful, Le Ray and coworkers (2007) reported a 4-percent cesarean delivery rate compared with a 60-percent rate in women in whom manual rotation was not successful. Some recommend rotation with Kielland forceps for the persistent OT position as outlined in Chapter 29 (Occiput Transverse Positions). These forceps are used to rotate the occiput to the anterior position, and delivery is accomplished with the same forceps or by substitution with Simpson, Tucker–McLane, or similar forceps.

In some cases, pelvic shape leads to a persistent OT position that is not easily overcome. For example, a platypelloid pelvis is flattened anteroposteriorly and an android pelvis is heart shaped. With these, space may be inadequate for occipital rotation to either an anterior or posterior position (Fig. 2-17). Because of these concerns, undue force is avoided if forceps delivery is attempted.

PERSISTENT OCCIPUT POSTERIOR POSITION

Approximately 2 to 10 percent of singleton term cephalic fetuses deliver in an occiput posterior (OP) position (Cheng, 2010). Many fetuses delivering OP are OA in early labor and reflect malrotation during labor. Predisposing risks include epidural analgesia, nulliparity, greater fetal weight, and prior delivery with OP positioning (Cheng, 2006a; Gardberg, 2004; Lieberman, 2005). Regarding pelvic shape, an anthropoid pelvis and narrow subpubic angle can predispose (Barth, 2015; Ghi, 2016).

Morbidity

Women with a persistent OP position have higher associated rates of prolonged second-stage labor, cesarean delivery, and operative vaginal delivery. For women who deliver vaginally, rates of blood loss and of third- and fourth-degree lacerations are increased (Senécal, 2005).

Newborns delivered from an OP position have higher complication rates then those born positioned OA. Cheng and coworkers (2006b) compared outcomes of 2591 women undergoing delivery with a persistent OP position with those of 28,801 women whose newborns were delivered OA. Virtually every possible delivery complication was found more frequently with persistent OP position. Only 46 percent of these women delivered spontaneously, and the remainder accounted for 9 percent of cesarean deliveries performed. These investigators also found that an OP position at delivery was associated with more adverse short-term neonatal outcomes that included acidemic umbilical cord gases, birth trauma, Apgar scores <7, and intensive care nursery admission, among others. Similar results were reported by Ponkey (2003) and Fitzpatrick (2001) and their associates.

Methods to prevent persistent OP position and its associated morbidity have been investigated. First, digital examination for identification of fetal head position can be inaccurate, and transabdominal sonography can be used to increase accuracy (Dupuis, 2005; Zahalka, 2005). The transducer is placed transversely just cephalad to the maternal mons pubis. In the sonogram, fetal orbits and nasal bridge lie ventrally, whereas the occiput apposes the lower sacrum. Such information may provide an explanation for prolonged second-stage labor or may identify suitable candidates for rotation. Of other possible interventions, varying maternal position either antepartum or during labor does not appear to lower rates of persistent OP position (Desbriere, 2013; Kariminia, 2004; Le Ray, 2016).

Delivery

The fetus in an OP position may be delivered either spontaneously or by operative vaginal delivery. First, if the bony pelvic outlet is roomy and the perineum is somewhat relaxed from prior deliveries, rapid spontaneous OP delivery will often take place. Conversely, if the perineum is resistant to stretch, second- stage labor may be appreciably prolonged. During each expulsive effort, the head is driven against the perineum to a much greater degree than when the head position is OA. This leads to greater rates of third- and fourth-degree lacerations (Groutz, 2011; Melamed, 2013).

In some cases, spontaneous vaginal delivery from an OP position does not appear feasible or expedited delivery is needed. Here, manual rotation with spontaneous delivery from an OA position may be preferred. This technique is described fully in Chapter 29 (Occiput Posterior Positions). Successful rotation rates range from 47 to 90 percent. And, as would be expected, lower rates of cesarean delivery, vaginal laceration, and maternal blood loss follow rotation to OA position and vaginal delivery (Le Ray, 2005; Sen, 2013; Shaffer, 2006, 2011). Disadvantageously, manual rotation is linked with higher cervical laceration rates. Thus, careful inspection of the cervix following rotation is mandatory.

For exigent delivery, forceps or vacuum device can be applied to a persistent OP position. This is often performed in conjunction with an episiotomy. Also, if the head is engaged, the cervix fully dilated, and the pelvis adequate, forceps rotation may be attempted for those with suitable skills. These operative vaginal techniques are detailed in Chapter 29 (Occiput Transverse Positions).

Infrequently, protrusion of fetal scalp through the introitus is the consequence of marked elongation of the fetal head from molding combined with formation of a large caput succedaneum. In some cases, the head may not even be engaged—that is, the biparietal diameter may not have passed through the pelvic inlet. In these, labor is characteristically long and descent of the head is slow. Careful palpation above the symphysis may disclose the fetal head to be above the pelvic inlet. Prompt cesarean delivery is appropriate.

At Parkland Hospital, spontaneous delivery or manual rotation is preferred for management of persistent OP position. When needed, either manual rotation to OA position followed by forceps delivery or forceps delivery from the OP position is used. If neither can be completed with ease and safety, cesarean delivery is performed.

SHOULDER DYSTOCIA

Following complete emergence of the fetal head during vaginal delivery, the remainder of the body may not rapidly follow. The anterior fetal shoulder can become wedged behind the symphysis pubis and fail to deliver using normally exerted downward traction and maternal pushing. Because the umbilical cord is compressed within the birth canal, this dystocia is an emergency. Several maneuvers, in addition to downward traction on the fetal head and neck, may be performed to free the shoulder. This requires a team approach, in which effective communication and leadership are critical.

Consensus regarding a specific definition of shoulder dystocia is lacking. Some focus on whether maneuvers to free the shoulder are needed, whereas others use the head-to-body delivery time interval as defining (Beall, 1998). Spong and coworkers (1995) reported that the mean head-to-body delivery time in normal births was 24 seconds compared with 79 seconds in those with shoulder dystocia. These investigators proposed that a head-to-body delivery time >60 seconds be used to define shoulder dystocia. Currently, however, the diagnosis continues to rely on the clinical perception that the normal downward traction needed for fetal shoulder delivery is ineffective.

Because of these differing definitions, the incidence of shoulder dystocia varies. One recent review cites a clinically useful average of 1 percent of all deliveries (Ouzounian, 2016). The incidence has increased in recent decades, likely due to increasing fetal birthweight (MacKenzie, 2007; Øverland, 2014). Increased identification and documentation may also raise the incidence (Kim, 2016).

Maternal and Neonatal Consequences

In general, shoulder dystocia poses greater risk to the fetus than to the mother. The main maternal risks are serious perineal tears and postpartum hemorrhage, usually from uterine atony but also from lacerations (Gauthaman, 2016; Rahman, 2009). In contrast, significant neonatal neuromusculoskeletal injury and asphyxia are concerns. These specific injuries are described in Chapter 33 (Spinal Cord Injury). In one review of 1177 shoulder dystocia cases, brachial plexus injury was diagnosed in 11 percent and clavicular or humeral fracture in 2 percent (Chauhan, 2014). MacKenzie and associates (2007) reviewed 514 cases. Of the neonates, 7 percent showed evidence of acidosis at delivery, and 1.5 percent required cardiac resuscitation or developed hypoxic ischemic encephalopathy (HIE). In another review of 200 cases, rates of severe fetal acidosis and HIE were each 0.5 percent if delivery was completed within 5 minutes. These rates rose to 6 and 24 percent, respectively, with delivery delays ≥5 minutes (Leung, 2011a).

Prediction and Prevention

Fetal macrosomia, maternal obesity, prolonged second-stage labor, and a prior event raise risks for shoulder dystocia (Mehta, 2004; Overland, 2009; Schummers, 2015). Although these factors are clearly associated with this complication, identification of individual instances before the fact has proved to be impossible. The American College of Obstetricians and Gynecologists (2017c) reviewed studies and concluded that:

1. Most cases of shoulder dystocia cannot be accurately predicted or prevented.
2. Elective induction of labor or elective cesarean delivery for all women suspected of having a macrosomic fetus is not appropriate.
3. Planned cesarean delivery may be considered for the nondiabetic woman with a fetus whose estimated fetal weight is >5000 g or for the diabetic woman whose fetus is estimated to weigh >4500 g.

Birthweight

There is a corresponding rise in the incidence of shoulder dystocia with increasing birthweight (Acker, 1985; Øverland, 2012; Stotland, 2004). Commonly cited maternal characteristics associated with increased fetal birthweight are obesity, postterm pregnancy, multiparity, and diabetes (Jolly, 2003; Koyanagi, 2013). The combination of fetal macrosomia and maternal diabetes mellitus escalates the frequency of shoulder dystocia (Langer, 1991; Nesbitt, 1998). This predisposition may stem from the fact that fetuses of diabetic women have larger shoulder and extremity circumferences and greater shoulder-to-head and chest-to-head size differences relative to comparable-weight fetuses of nondiabetic mothers (McFarland, 1998; Modanlou, 1982). That said, translating these specific measurements into stand-alone sonographic clinical thresholds has shown poor predictive sensitivity (Burkhardt, 2014).

Preventively, early labor induction has yielded conflicting results. In one study, approximately 800 women with suspected macrosomic fetuses were randomized either to early induction between 37 and 39 weeks or to expectant care (Boulvain, 2015). Dystocia rates were lowered by two thirds in the intervention group, and neither group suffered brachial plexus injury. Although not measured, this practice is balanced against morbidity of early delivery. Moreover, the poor accuracy of

antepartum fetal weight prediction should be considered as well (Hoopmann, 2010; Malin, 2016; Noumi, 2005). In contrast, an earlier randomized study of 284 women showed that rates of shoulder dystocia were not lowered by early induction at 38 weeks (Gonen, 1997).

As previously discussed, cesarean delivery may be considered to prevent shoulder dystocia. That said, Rouse and Owen (1999) concluded that a prophylactic cesarean delivery policy for macrosomic fetuses would require more than 1000 cesarean deliveries with attendant morbidity to avert a single permanent brachial plexus injury.

Prior Shoulder Dystocia

The risk of recurrent shoulder dystocia ranges from 1 to 13 percent (Bingham, 2010; Moore, 2008; Ouzounian, 2013). For many women with prior shoulder dystocia, a trial of labor may be reasonable. The American College of Obstetricians and Gynecologists (2017c) recommends that estimated fetal weight, gestational age, maternal glucose intolerance, and severity of prior neonatal injury be evaluated and risks and benefits of cesarean delivery discussed with any woman with a history of shoulder dystocia. After discussion, either mode of delivery may be appropriate.

Management

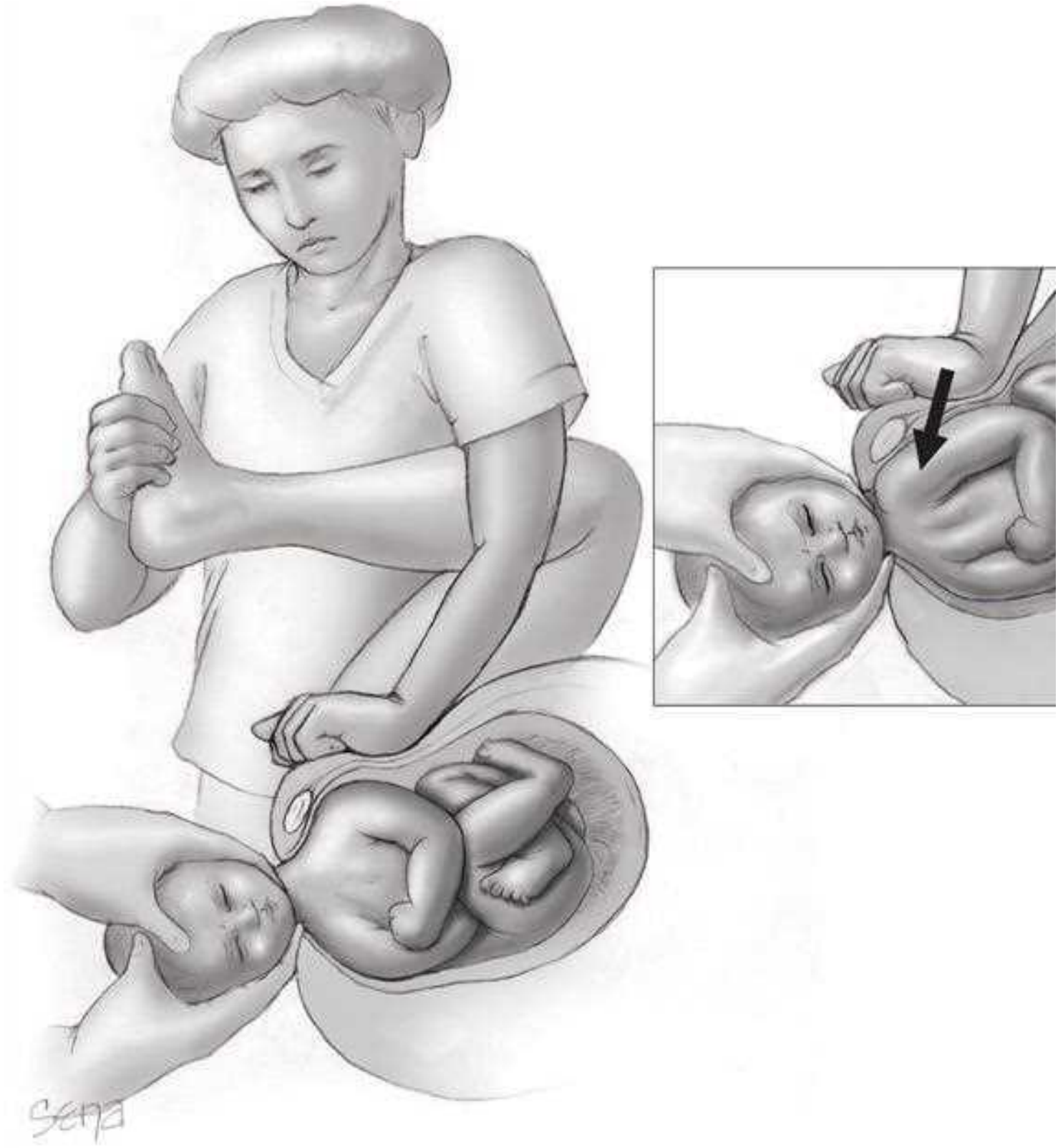
Because shoulder dystocia cannot be accurately predicted, clinicians should be well versed in its management principles. Because of ongoing cord compression with this dystocia, one goal is to reduce the head-to-body delivery time. This is balanced against the second goal, which is avoiding fetal and maternal injury from aggressive manipulations. Accordingly, an initial gentle attempt at traction, assisted by maternal expulsive efforts, is recommended. Adequate analgesia is certainly ideal. Some clinicians advocate performing a large episiotomy to provide room for manipulations. Episiotomy itself does not lower brachial plexus injury rates but raises third- and fourth-degree laceration rates (Gurewitsch, 2004; Paris, 2011; Sagi-Dain, 2015). Episiotomy may be elected to complete needed maneuvers.

After gentle traction, various techniques can be used to free the anterior shoulder from its impacted position behind the symphysis pubis. A more detailed discussion of these and the topic is found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Cunningham, 2017). Of these, moderate *suprapubic pressure* can be applied by an assistant, while downward traction is applied to the fetal head. Pressure is applied with the heel of the hand to the anterior shoulder wedged above and behind the symphysis. The anterior shoulder is thus either depressed or rotated, or both, so the shoulders occupy the oblique plane of the pelvis. Here, the anterior shoulder can be freed.

The *McRoberts maneuver* is often selected next if additional steps are needed. The maneuver consists of removing the legs from the stirrups and sharply flexing them up toward the abdomen. Suprapubic pressure is often concurrently applied (Fig. 27-5). Gherman and associates (2000) analyzed the McRoberts maneuver using x-ray pelvimetry. They found that the procedure caused straightening of the sacrum relative to the lumbar vertebrae, rotation of the symphysis pubis toward the maternal head, and a decrease in the angle of pelvic inclination. Although this does not increase pelvic dimensions, pelvic rotation cephalad tends to free the impacted anterior shoulder. Gonik and coworkers (1989) tested the McRoberts position objectively with laboratory models and found that the maneuver reduced the forces needed to free the fetal shoulder. If unsuccessful, most move next either to free the posterior shoulder or to rotate the bisacromial diameter into one of the oblique diameters of the maternal pelvis.

FIGURE 27-5

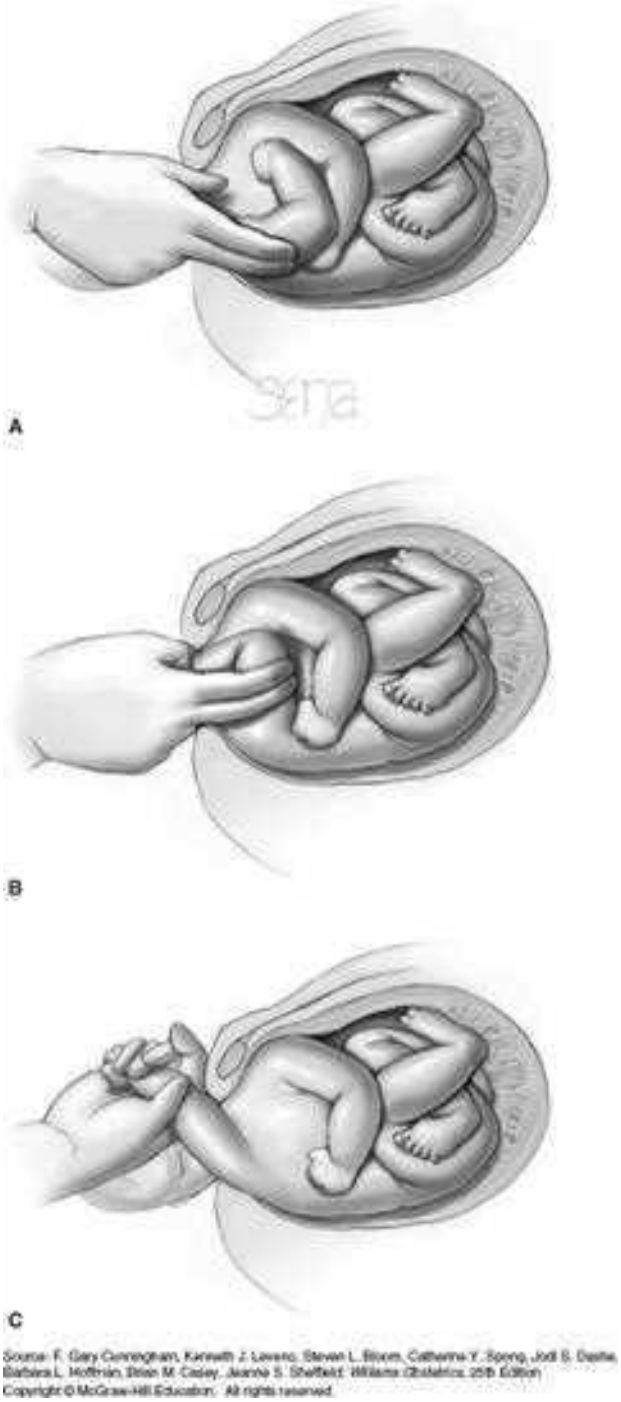
The McRoberts maneuver. The maneuver consists of removing the legs from the stirrups and sharply flexing the thighs up toward the abdomen. The assistant is also providing suprapubic pressure simultaneously (*arrow*).



With *delivery of the posterior shoulder,* the accoucheur carefully sweeps the posterior arm of the fetus across its chest, followed by delivery of the arm (Fig. 27-6). If possible, the operator's fingers are aligned parallel to the long axis of the fetal humerus to lower bone fracture risks. The shoulder girdle is then rotated into one of the oblique diameters of the pelvis with subsequent delivery of the anterior shoulder.

FIGURE 27-6

Delivery of the posterior shoulder for relief of shoulder dystocia. **A.** The operator's hand is introduced into the vagina along the fetal posterior humerus. **B.** The arm is splinted and swept across the chest, keeping the arm flexed at the elbow. **C.** The fetal hand is grasped and the arm extended along the side of the face. The posterior arm is delivered from the vagina.



Of rotational maneuvers, Woods (1943) reported that by progressively rotating the posterior shoulder 180 degrees in a corkscrew fashion, the impacted anterior shoulder could be released. This is frequently referred to as the *Woods corkscrew maneuver* (Fig. 27-7). Rubin (1964) recommended two maneuvers. First, the fetal shoulders are rocked from side to side by applying force to the maternal abdomen. If this is not successful, the pelvic hand reaches the most easily accessible fetal shoulder, which is then pushed toward the anterior surface of the chest. This maneuver most often abducts both shoulders, which in turn produces a smaller bisacromial diameter. This permits displacement of the anterior shoulder from behind the symphysis (Fig. 27-8).

FIGURE 27-7

Woods maneuver. The hand is placed behind the posterior shoulder of the fetus. The shoulder is then rotated in a corkscrew manner so that the impacted anterior shoulder is released.

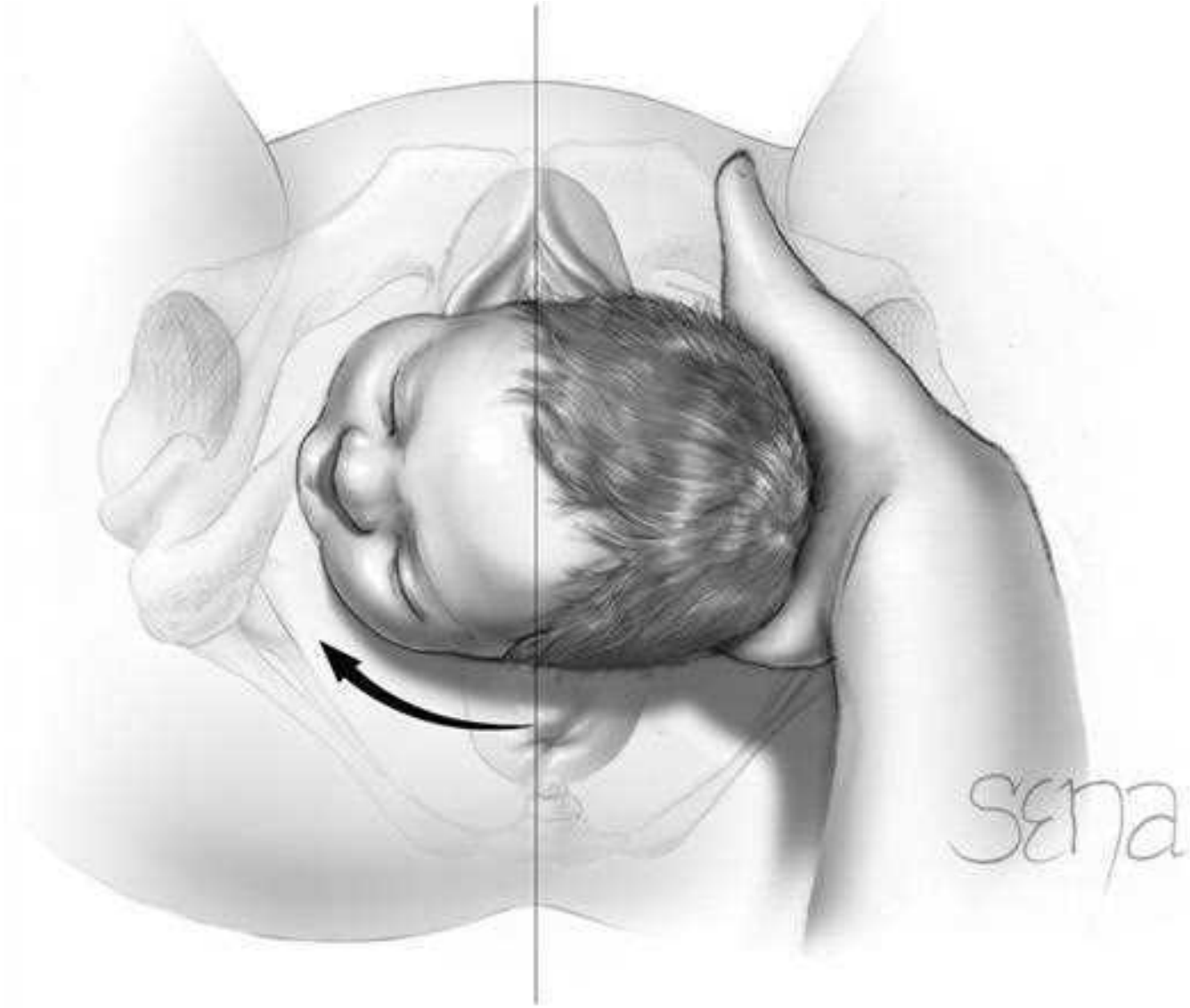
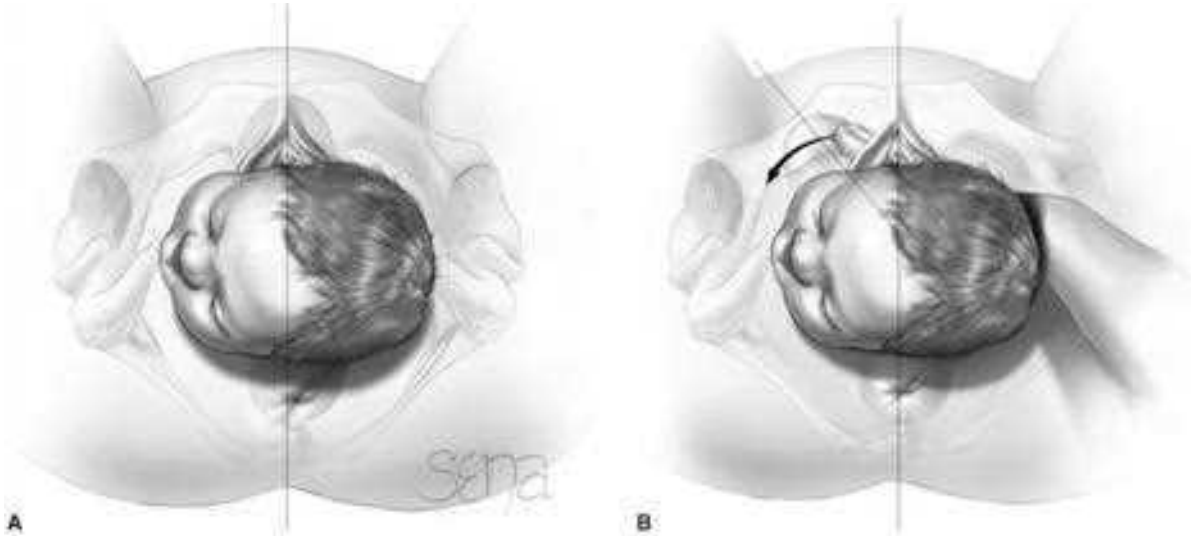


FIGURE 27-8

The second Rubin maneuver. **A.** The bisacromial diameter is aligned vertically. **B.** The more easily accessible fetal shoulder (the anterior is shown here) is pushed toward the anterior chest wall of the fetus (*arrow*). Most often, this results in abduction of both shoulders, which reduces the bisacromial diameter and frees the impacted anterior shoulder.



If the above are initially unsuccessful, they may be repeated, and finally other methods may be elected. With an *all-fours maneuver*, also called the Gaskin maneuver, the parturient rolls onto her knees and hands. Here, downward traction against the head and neck attempts to free the posterior shoulder (Bruner, 1998). Challenges with this include immobility from regional analgesia and time lost in patient repositioning.

In some, the posterior arm is inaccessible for delivery. Cluver and Hofmeyr (2009) described *posterior axilla sling traction* to deliver the posterior arm. With this alternative method, a suction catheter is threaded under the axilla and both ends are brought together above the shoulder. Upward and outward traction on the catheter loop delivers the shoulder. In a small series of 19 cases, this maneuver was successful in 18 cases. However, neonatal injury included three cases of humeral fracture and one permanent and four transient cases of Erb palsy (Cluver, 2015).

Deliberate *fracture of the anterior clavicle* using the thumb to press it toward and against the pubic ramus can be attempted to free the shoulder impaction. In practice, however, deliberate fracture of a large neonate's clavicle is difficult. If successful, the fracture will heal rapidly and is usually trivial compared with brachial nerve injury, asphyxia, or death.

The *Zavanelli maneuver* involves replacement of the fetal head into the pelvis followed by cesarean delivery (Sandberg, 1985). Terbutaline, 0.25 mg, is given subcutaneously to produce uterine relaxation. The first part of the maneuver consists of returning the head to an OA or OP position. The operator flexes the head and slowly pushes it back into the vagina. Cesarean delivery is then performed. Sandberg (1999) reviewed 103 reported cases. It was successful in 91 percent of cephalic cases and in all cases of breech head entrapments. Despite successful replacement, fetal injuries were common but may have resulted from the multiple manipulations used before the Zavanelli maneuver (Sandberg, 2007).

Symphysiotomy, in which the intervening symphyseal cartilage and much of its ligamentous support is cut to widen the symphysis pubis, is described in Chapter 28 (Total Breech Extraction). It has been used successfully for shoulder dystocia (Goodwin, 1997; Hartfield, 1986). Maternal morbidity can be significant due to urinary tract injury. *Cleidotomy* consists of cutting the clavicle with scissors or other sharp instruments and is usually done for a dead fetus (Schramm, 1983).

Shoulder Dystocia Drill

Hernandez and Wendel (1990) suggest use of a shoulder dystocia drill to better organize emergency management:

1. Call for help—mobilize assistants and anesthesia and pediatric personnel. Initially, a gentle attempt at traction is made. Drain the bladder if it is distended.
2. A generous episiotomy may be desired at this time to afford room posteriorly.
3. Suprapubic pressure is used initially by most practitioners because it has the advantage of simplicity. Only one assistant is needed to provide suprapubic pressure, while normal downward traction is applied to the fetal head.
4. The McRoberts maneuver requires two assistants. Each assistant grasps a leg and sharply flexes the maternal thigh toward the abdomen.

   These maneuvers will resolve most cases of shoulder dystocia.

   If the above listed steps fail, the following steps may be attempted, and any of the maneuvers may be repeated:
5. Delivery of the posterior arm is attempted. With a fully extended arm, however, this is usually difficult to accomplish.
6. Woods screw maneuver is applied.
7. Rubin maneuver is attempted.

The American College of Obstetricians and Gynecologists (2017c) has concluded that no one maneuver is superior to another in releasing an impacted shoulder or reducing the chance of injury. Performance of the McRoberts maneuver, however, is deemed a reasonable initial approach. In one review of more than 2000 cases, Hoffman and colleagues (2011) noted an 84-percent success rate with posterior shoulder delivery and comparable rates of neonatal injury compared with other standard methods. This contrasts with a review of 205 cases, in which posterior shoulder delivery yielded greater neonatal injury rates than rotational methods (Leung, 2011b). Spain and associates (2015) found that duration rather than a specific maneuver increased neonatal injury.

Importantly, progression from one maneuver to the next should be organized and methodical. As noted, the urgency to relieve the dystocia should be balanced against potentially injurious traction forces and manipulations. Lerner and coworkers (2011) in their evaluation of 127 shoulder dystocia cases reported that all neonates without sequelae from shoulder dystocia were born by 4 minutes. Conversely, most depressed neonates–57 percent–had head-to-body delivery intervals >4 minutes. The percentage of depressed neonates rose sharply after 3 minutes.

Shoulder dystocia training and protocols using simulation-based education and drills has evidence-based support. These tools improve performance and retention of drill steps (Buerkle, 2012; Crofts, 2008; Grobman, 2011). Their use has translated into improved neonatal outcome in some, but not all, investigations (Crofts, 2016; Fransen, 2017; Kim, 2016; Walsh, 2011). The American College of Obstetricians and Gynecologists (2012) also has created a Patient Safety Checklist to guide the documentation process with shoulder dystocia.

SPECIAL POPULATIONS

Home Birth

In 2014, 0.7 percent of deliveries in the United States were planned home births and 0.2 percent were unplanned (MacDorman, 2016). Of *unplanned* births in a 15-year epoch in Norway, 69 of 6027 or 1.1 percent resulted in fetal or neonatal death. This high rate was attributable to infection, prematurity, and placental abruption

(Gunnarsson, 2017). Multiparity and distance from the hospital were ascribed risks (Gunnarsson, 2014). In the United States, youth, lack of prenatal care, minority race, and lower educational attainment were associated risks for unplanned home birth (Declercq, 2010).

In contrast, the demographics of women choosing *planned* home birth in the United States favor those who are white, nonsmoking, self-pay, college-educated, and multiparous (MacDorman, 2016). As perceived benefits, planned delivery at home for those with low-risk pregnancies results in fewer medical interventions that include labor augmentation, episiotomy, operative vaginal delivery, and cesarean delivery (Bolten, 2016; Cheyney, 2014). Regarding the safety of planned home birth, data from randomized trial are lacking, and large observational studies derive from heterogeneous care systems, whose results may not be generalizable. For example, several developed countries deliver at home a large volume of carefully screened women, delivered by midwives with substantial training and in a setting closely integrated with the local health-care system (Birthplace in England Collaborative Group, 2011; de Jonge, 2015; Hutton, 2016). The level of such coordination in the United States is less uniform.

Overall, risks of home births in the United States are small but greater than those of hospital delivery. Midwife-attended home births carry a neonatal mortality risk of 1.3 per 1000 births. This is a nearly fourfold greater rate compared with midwife-attended hospital births. The most common underlying causes of death are those attributed to labor and delivery events, to congenital anomalies, and to infection. Of neonatal injuries, rates of neonatal seizure and serious neurological dysfunction are similarly elevated in home-birth groups (Grünebaum, 2013, 2014, 2017; Snowden, 2015; Wasden, 2016). Importantly, substantial risks attend home birth for those with prior cesarean delivery, with breech presentation, and with multifetal gestation (Cheyney, 2014; Cox, 2015). The American College of Obstetricians and Gynecologists (2017b) considers these to be absolute contraindications. Further, the College considers accredited hospitals and birthing centers to be the safest site for birth but recognizes the autonomy of the well-counseled patient.

Water Birth

As one option for pain relief, some women choose to spend part of first-stage labor in a large water tub. With this practice, one Cochrane review found lower rates of anesthesia block use and no greater adverse neonatal or maternal effects compared with traditional labor (Cluett, 2009).

For delivery, however, water birth carries greater concern for neonatal harm and without proven benefits. Case reports describe aspiration leading to fresh-water drowning (Pinette, 2004). The risk of cord avulsion during water birth approximates 3 per 1000 births, and stems primary from abruptly bringing the newborn out of the water (Schafer, 2014). Last, case reports also enumerate serious infections, which emphasize the need for rigorous sanitizing protocols. That said, in most large studies comparing land and water births, overall maternal or neonatal infection rates are not increased (Bovbjerg, 2016; Burns, 2012; Thoeni, 2005). In sum, several reviews comment on study shortcomings and isolated complications but do not identify definitive evidence for overall greater rates of neonatal harm from water birth in low-risk populations (Davies, 2015; Taylor, 2016). However, given the paucity of robust data and potential for serious complications, the American College of Obstetricians and Gynecologists (2016a) currently recommend that “birth occur on land, not in water.”

Female Genital Mutilation

This practice refers to medically unnecessary vulvar and perineal modification. In the United States, it is a federal crime to perform unnecessary genital surgery on a girl younger than 18 years. That said, forms of female genital mutilation are practiced in countries throughout Africa, the Middle East, and Asia. As many as 200 million women worldwide have undergone one of these procedures, and approximately 513,000 girls in the United States were at risk for this practice in 2012 (Goldberg, 2016; UNICEF, 2016). Cultural sensitivity is imperative, because many women may be offended by the suggestion that they have been assaulted or mutilated (American College of Obstetricians and Gynecologists, 2014).

The World Health Organization (2008) classifies genital mutilations into four types (Table 27-1). Long-term complications from surgery and its associated scarring include infertility, genital pain, diminished sexual quality of life, and propensity for urogenital infection (Almroth, 2005; Andersson, 2012; Nour, 2015). In general, women with significant symptoms following type III procedures are candidates for corrective surgery. Specifically, division of midline scar tissue to reopen the vulva is termed *deinfibulation*.

TABLE 27-1

World Health Organization Classification of Female Genital Mutilation

Type I	Partial or total removal of the clitoris and/or prepuce
Type II	Partial or total removal of the clitoris and the labia minora, with or without labia majora excision
Type III	Partial or total labial minora and/or majora excision, followed by fusion of the wound, termed infibulation, to cover and narrow the vagina. With or without clitoridectomy
Type IV	Pricking, piercing, incising, scraping, cautery, or other injury to female genitalia

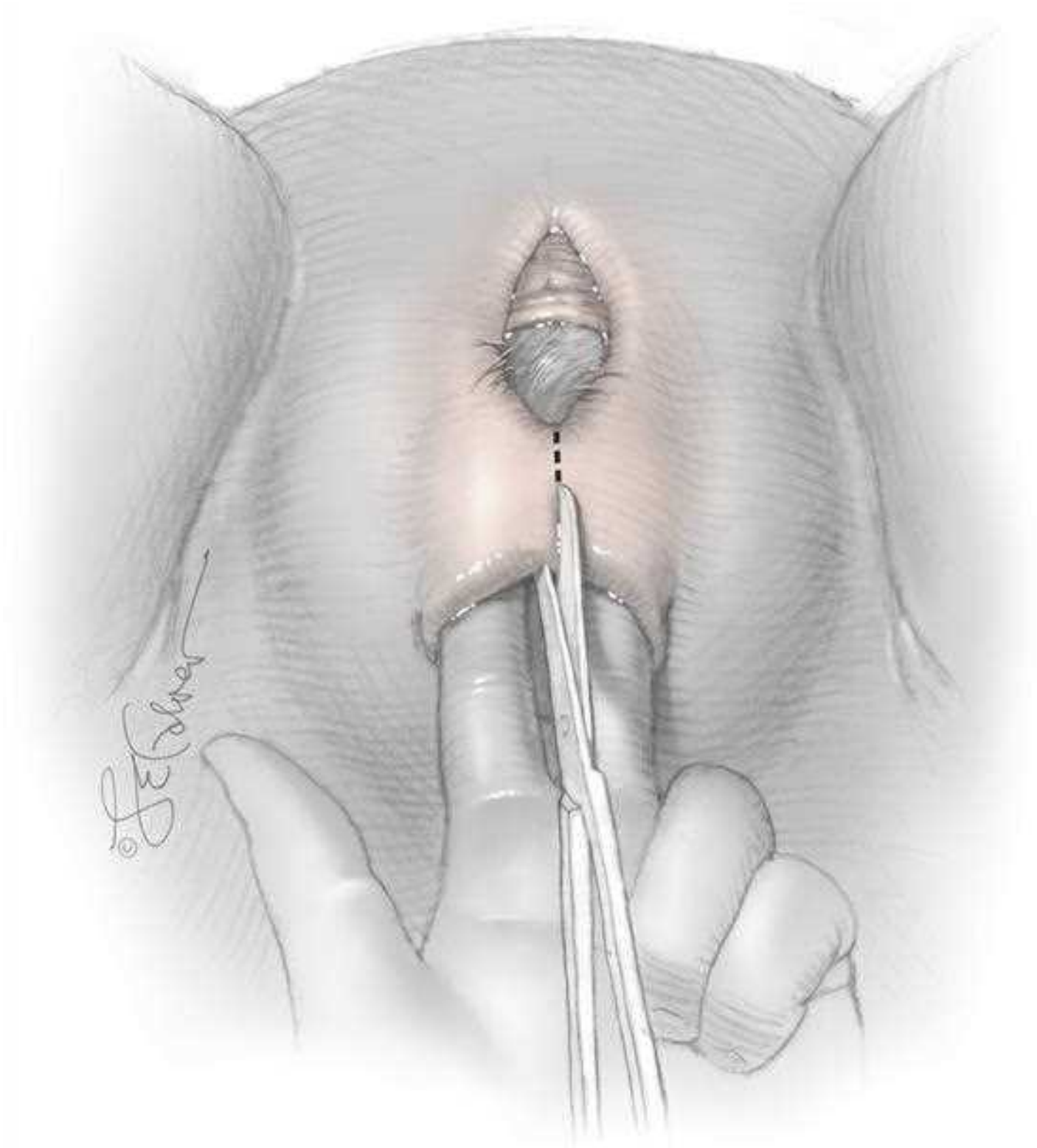
Adapted from the World Health Organization, 2008.

Female genital mutilation has been associated with some adverse maternal and neonatal complications. The World Health Organization (2006, 2008) estimated that these procedures increased perinatal morbidity rates by 10 to 20 per 1000. Small increased risks for prolonged labor, cesarean delivery, and postpartum hemorrhage are also found (Berg, 2014; Chibber, 2011; Wuest, 2009). Importantly, the psychiatric consequences can be profound.

To prevent obstetrical complications, deinfibulation can be performed either antepartum or intrapartum (Fig. 27-9) (Esu, 2017). In women not undergoing deinfibulation, anal sphincter tear rates with vaginal delivery may be increased (Berggren, 2013; Rodriguez, 2016). In our experiences, intrapartum deinfibulation in many cases allows successful vaginal delivery without major complications.

FIGURE 27-9

Deinfibulation. Although not shown here, lidocaine is first infiltrated along the planned incision if regional analgesia is not in place already. As protection, two fingers of one hand are insinuated behind the shelf created by fused labia but in front of the urethra and crowning head. The shelf is then incised in the midline. After delivery, the raw edges are sutured with rapidly absorbable material to secure hemostasis. (Reproduced with permission from Hawkins JS: Lower genital tract procedures. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Prior Pelvic Reconstructive Surgery

These surgeries are performed with increasing frequency in reproductive-aged women, and thus pregnancy following these procedures is not uncommon. Logically, there are concerns for symptom recurrence following vaginal delivery, and high-quality data to aid evidenced-based decisions are limited. For women with prior stress urinary incontinence surgery, slightly greater protection against postpartum incontinence is gained by elective cesarean delivery (Pollard, 2012; Pradhan, 2013). Stated another way, most women with prior corrective surgery for incontinence can be delivered vaginally without symptom recurrence. Also, cesarean delivery is not always protective. Obviously, symptom recurrence and the need for additional vaginal surgery should be weighed against the surgical risk of cesarean delivery (Groenen, 2008). In those with prior surgeries for anal incontinence or pelvic organ prolapse, only scant information regarding outcomes is available. Such cases require individualization.

Anomalous Fetuses

Rarely, delivery can be obstructed by extreme hydrocephaly, by body stalk anomaly, or by massive fetal abdominal enlargement from a greatly distended bladder, ascites, or organomegaly (Costa, 2012; Sikka, 2011). With milder forms of hydrocephaly, if the biparietal diameter is <10 cm or if the head circumference is <36 cm, then vaginal delivery may be permitted (Anteby, 2003).

In rare cases in which neonatal death has occurred or is certain due to associated anomalies, vaginal delivery may be reasonable, but the head or abdomen must be reduced in size for delivery. Removal of fluid by cephalocentesis or paracentesis with sonographic guidance can be performed intrapartum. As described in Shoulder Dystocia Drill, cleidotomy can shorten the bisacromial diameter. For hydrocephalic fetuses that are breech, cephalocentesis can be accomplished suprapubically when the aftercoming head enters the pelvis. Currently, these practices are more germane in developing countries.

THIRD STAGE OF LABOR

Delivery of the Placenta

Third-stage labor begins immediately after fetal birth and ends with placental delivery. Goals include delivery of an intact placenta and avoidance of uterine inversion or postpartum hemorrhage. The latter two are grave intrapartum complications and constitute emergencies, as described in Chapter 41 (General Considerations).

Immediately after newborn birth, uterine fundal size and consistency are examined. If the uterus remains firm and there is no unusual bleeding, watchful waiting until the placenta separates is the usual practice. Neither massage nor downward fundal pressure is employed, but the fundus is frequently palpated to ensure that it does not become atonic and filled with blood from placental separation. *To prevent uterine inversion, umbilical cord traction must not be used to pull the placenta from the uterus.* Signs of separation include a sudden gush of blood into the vagina, a globular and firmer fundus, a lengthening of the umbilical cord as the placenta descends into the vagina, and elevation of the uterus into the abdomen. With the last, the placenta, having separated, passes down into the lower uterine segment and vagina. Here, its bulk pushes the uterine body upward.

These signs appear within minutes after newborn delivery, and the median time ranges from 4 to 12 minutes (Combs, 1991; Frolova, 2016; Shinar, 2016b). Once the placenta has detached from the uterine wall, the mother may be asked to bear down, and the intraabdominal pressure often expels the placenta into the vagina. These efforts may fail or may not be possible because of analgesia. After ensuring that the uterus is contracted firmly, the umbilical cord is kept slightly taut but is not pulled. Pressure is exerted by a hand wrapped around the fundus to propel the detached placenta into the vagina (Fig. 27-10). Concurrently, the heel of the hand exerts downward pressure between the symphysis pubis and the uterine fundus. This also aids inversion prevention. Once the placenta passes through the introitus, pressure on the uterus is relieved. The placenta is then gently lifted away. Care is taken to prevent placental membranes from being torn off and left behind. If the membranes begin to tear, they are grasped with a clamp and removed by gentle teasing (Fig. 27-11).

FIGURE 27-10
Expression of placenta. Note that the hand is *not* trying to push the fundus of the uterus through the birth canal! As the placenta leaves the uterus and enters the vagina, the uterus is elevated by the hand on the abdomen while the cord is held in position. The mother can aid in the delivery of the placenta by bearing down. As the placenta reaches the perineum, the cord is lifted, which in turn lifts the placenta out of the vagina.

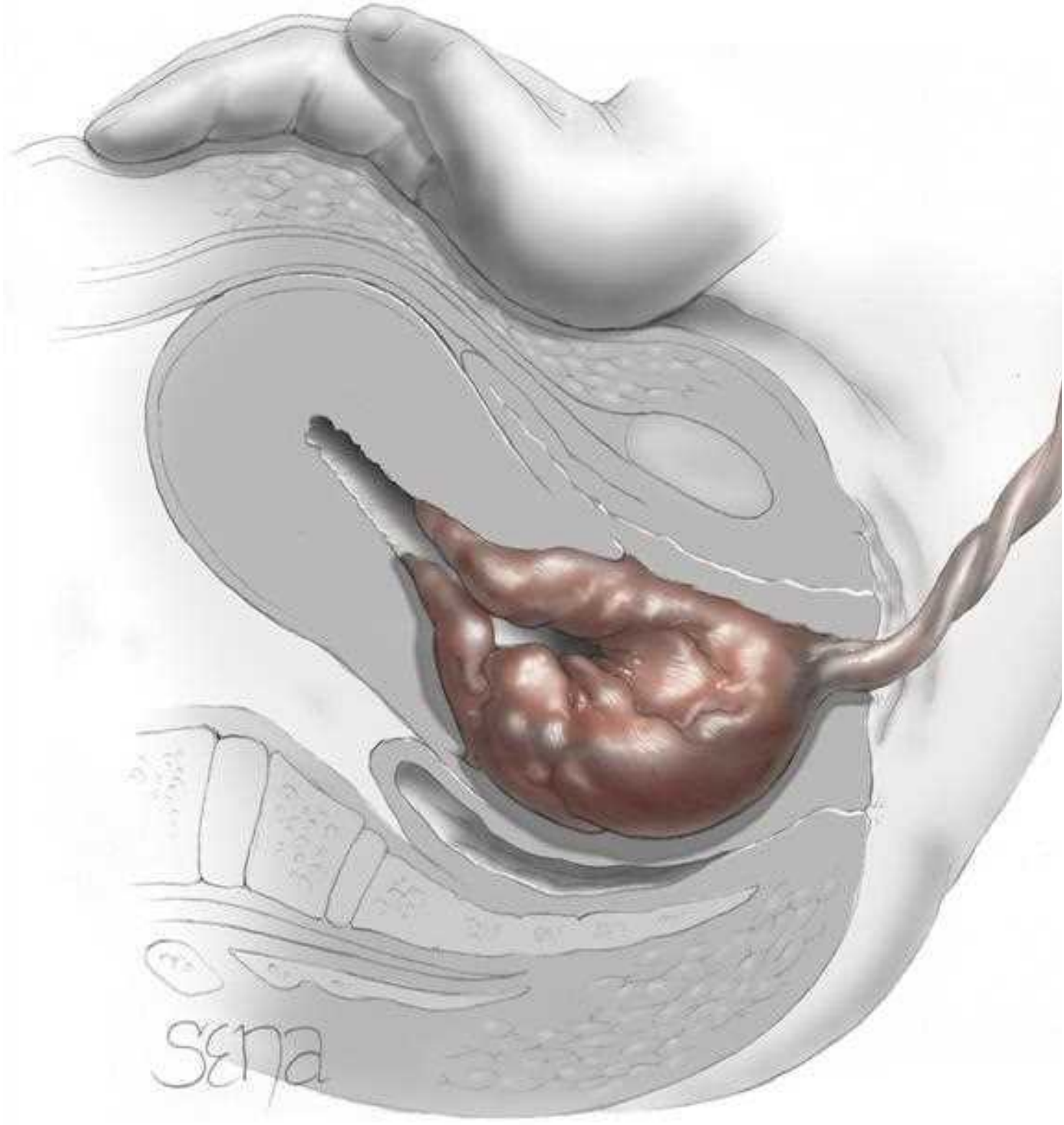
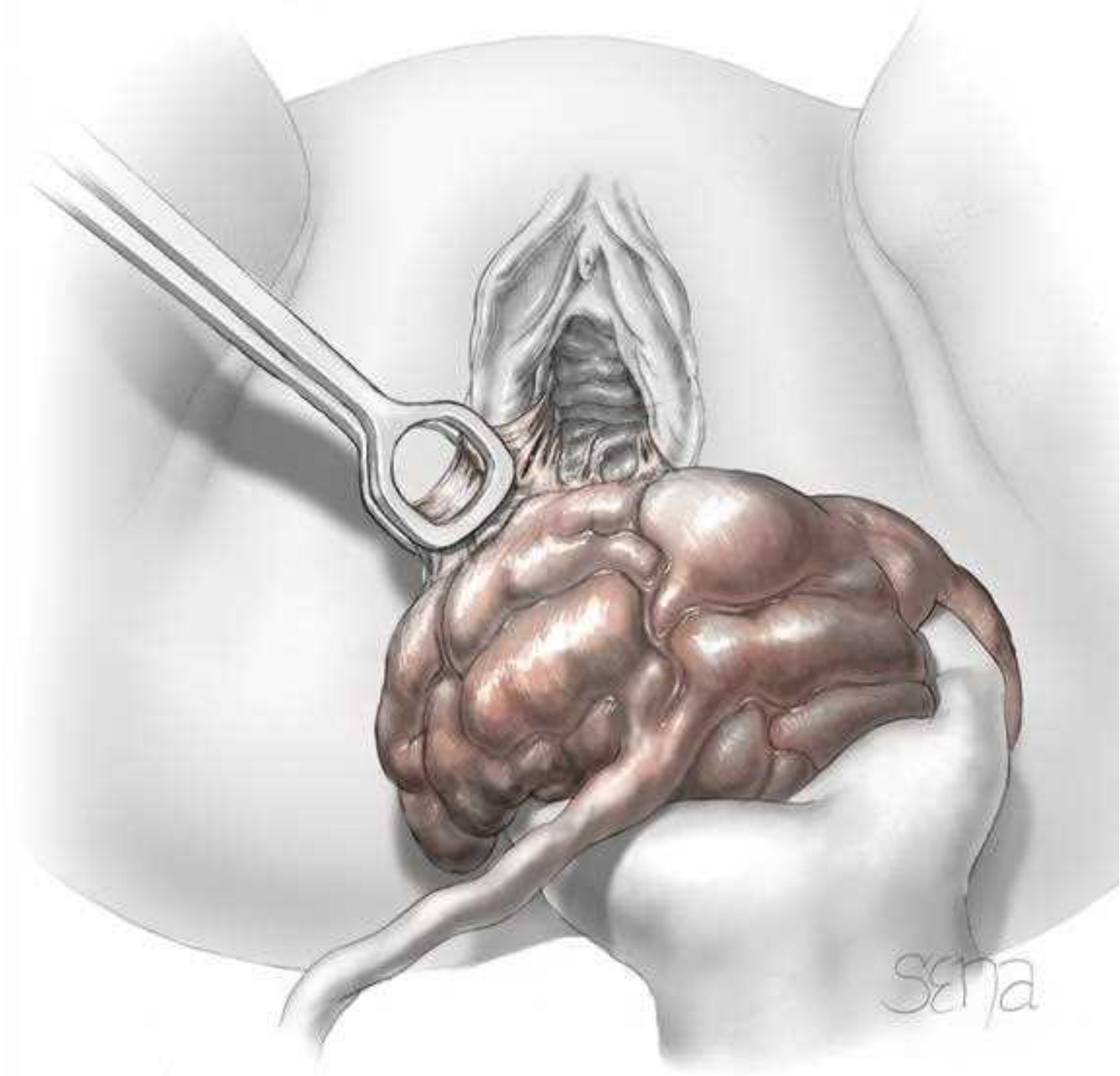


FIGURE 27-11

Membranes that were somewhat adhered to the uterine lining are separated by gentle traction with ring forceps.



Management of the Third Stage

Practices within the third stage of labor may be broadly considered as either expectant or active management. Expectant management involves waiting for placental separation signs and allowing the placenta to deliver either spontaneously or aided by nipple stimulation or gravity (World Health Organization, 2012). In contrast, active management of third-stage labor consists of early cord clamping, controlled cord traction during placental delivery, and immediate administration of prophylactic oxytocin. The goal of this triad is to limit postpartum hemorrhage (Begley, 2015; Jangsten, 2011; Westhoff, 2013).

As noted earlier, delayed cord clamping does not increase postpartum hemorrhage rates, and thus early clamping is a less important component of this trio. Similarly, cord traction may also be less critical (Deneux-Tharaux, 2013; Du, 2014; Gülmezoglu, 2012). Uterine massage following placental delivery is recommended by many, but not all, to prevent postpartum hemorrhage. We support this with the caveat that evidence for this practice is not strong (Abdel-Aleem, 2010).

Therefore, uterotonics play an essential role to decrease postpartum blood loss. Choices include oxytocin (Pitocin), misoprostol (Cytotec), carboprost (Hemabate), and the ergots, namely ergonovine (Ergotrate) and methylergonovine (Methergine). In addition, a combination agent of oxytocin and ergonovine (Syntometrine) is used outside the United States. Also in other countries, carbetocin (Duratocin), a long-acting oxytocin analogue, is available and effective for hemorrhage prevention

during cesarean delivery (Attilakos, 2010; Su, 2012). Of these, the World Health Organization (2012) recommends oxytocin as a first-line agent. Ergot-based drugs and misoprostol are alternatives in settings that lack oxytocin.

Uterotonics may be given before or after placental expulsion without affecting rates of postpartum hemorrhage, placental retention, or third-stage labor length (Soltani, 2010). If they are given before delivery of the placenta, however, they may entrap an undiagnosed, undelivered second twin. Thus, abdominal palpation should confirm no additional fetuses. Notably, this concern is less relevant with current widespread sonography use.

High-Dose Oxytocin

Synthetic oxytocin is identical to that produced by the posterior pituitary. Its action is noted at approximately 1 minute, and it has a mean half-life of 3 to 5 minutes. When given as a bolus, oxytocin can cause profound hypotension. Secher and coworkers (1978) reported that an intravenous bolus of 10 units of oxytocin caused a marked transient fall in blood pressure with an abrupt increase in cardiac output. Svanström and associates (2008) confirmed those findings. These hemodynamic changes could be dangerous for women hypovolemic from hemorrhage or those with certain types of cardiac disease. Thus, oxytocin should be given as a dilute solution by continuous intravenous infusion or as an intramuscular injection.

Water intoxication can result from the antidiuretic action of high-dose oxytocin if administered in a large volume of electrolyte-free dextrose solution (Whalley, 1963). Thus, if oxytocin is to be administered in high doses for a considerable period of time, its concentration should be increased rather than increasing the infusion flow rate.

Despite the routine use of oxytocin, no standard prophylactic dose has been established for its use following either vaginal or cesarean delivery. Our practice is to add 20 units (2 mL) of oxytocin per liter of infusate. This solution is administered after delivery of the placenta at a rate of 10 to 20 mL/min—200 to 400 mU/min—for a few minutes until the uterus remains firmly contracted and bleeding is controlled. The infusion rate then is reduced to 1 to 2 mL/min until the mother is ready for transfer from the recovery suite to the postpartum unit. The infusion is usually then discontinued. For women without intravenous access, 10 units of intramuscular oxytocin are injected.

Other Uterotonics

Ergonovine and methylergonovine have similar activity levels in myometrium, and only methylergonovine is currently manufactured in the United States. These ergot alkaloid agents do not provide superior protection against postpartum hemorrhage compared with oxytocin. Moreover, safety and tolerability are greater with oxytocin (Liabsuetrakul, 2011). For these reasons, ergot alkaloid agents are considered second-line for prevention of postpartum hemorrhage. If selected, a 0.2-mg dose of methylergonovine is slowly given intravenously in a period not less than 60 seconds to avoid sudden hypertension (Novartis, 2012). Methylergonovine is relatively contraindicated in the hypertensive woman.

Misoprostol is a prostaglandin E_1 analogue, which has proved inferior to oxytocin for postpartum hemorrhage prevention (Tunçalp, 2012). However, in resource-poor settings that lack oxytocin, misoprostol is suitable for hemorrhage prophylaxis and is given as a single oral 600-µg dose (Mobeen, 2011; World Health Organization, 2012). Notably, although oxytocin is preferred for prevention of hemorrhage, ergot alkaloids and prostaglandins play a greater role in postpartum hemorrhage treatment, discussed in Chapter 41 (Risk Factors).

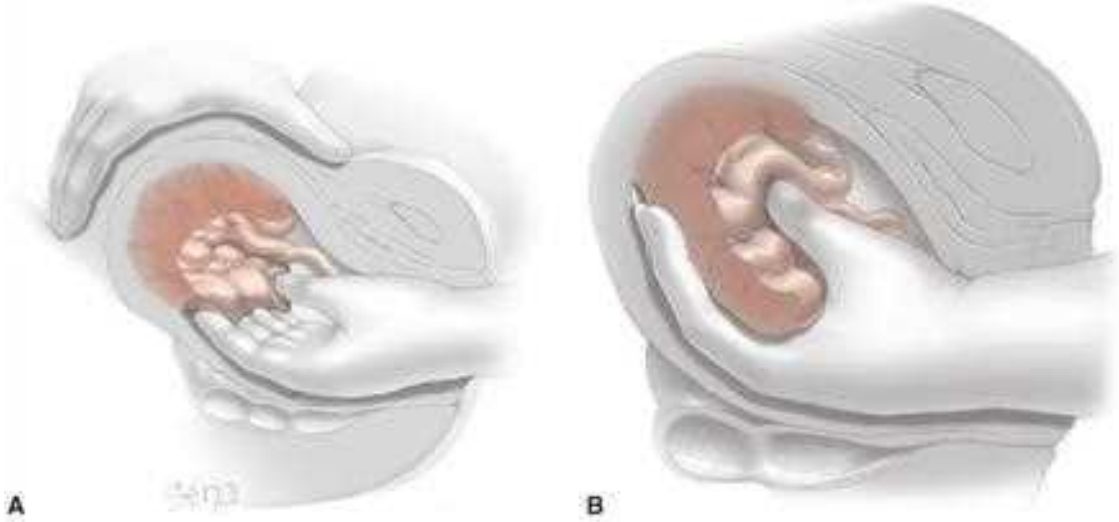
Manual Removal of Placenta

In approximately 2 percent of singleton births, the placenta may not deliver promptly (Cheung, 2011). Three possibilities include *placenta adherens*, in which uterine contractions are insufficient to detach the placenta; lower uterine segment constriction and a detached but trapped placenta; or a morbidly adherent placenta. Consistent risks for retained placenta include stillbirth, prior cesarean delivery, prior retention, and preterm delivery (Belachew, 2014; Coviello, 2015; Endler, 2014; Nikolajsen, 2013). For the last, in one study with nearly 46,000 deliveries, analysis predicted that 90 percent of placentas would spontaneously deliver by 180 minutes for gestations at 20 weeks; 21 minutes at 30 weeks; and 14 minutes at 40 weeks (Dombrowski, 1995).

Postpartum hemorrhage can complicate a retained placenta, and bleeding risk accrues with third-stage length. Thus, in the absence of bleeding, some recommend expectant management for 30 minutes, whereas others use a 15-minute threshold (Cummings, 2016; Deneux-Tharaux, 2009; Shinar, 2016a). The World Health Organization (2012) cites a 60-minute threshold. Notably, if brisk bleeding ensues and the placenta cannot be delivered by standard technique, manual removal of the placenta is indicated (Fig. 27-12). When performed, some administer a single dose of intravenous antibiotics, however, one systematic review of observational studies found no benefits (Chibueze, 2015). Although the American College of Obstetricians and Gynecologists (2016c) concludes that data neither support nor refute this practice, the World Health Organization (2012) recommends prophylaxis. At our institution, we administer a single dose to women not already receiving antibiotics.

FIGURE 27-12

Manual removal of placenta. **A.** One hand grasps the fundus and the other hand is inserted into the uterine cavity and the fingers are swept from side to side as they are advanced. **B.** When the placenta detaches, it is grasped and removed.



IMMEDIATE POSTPARTUM CARE

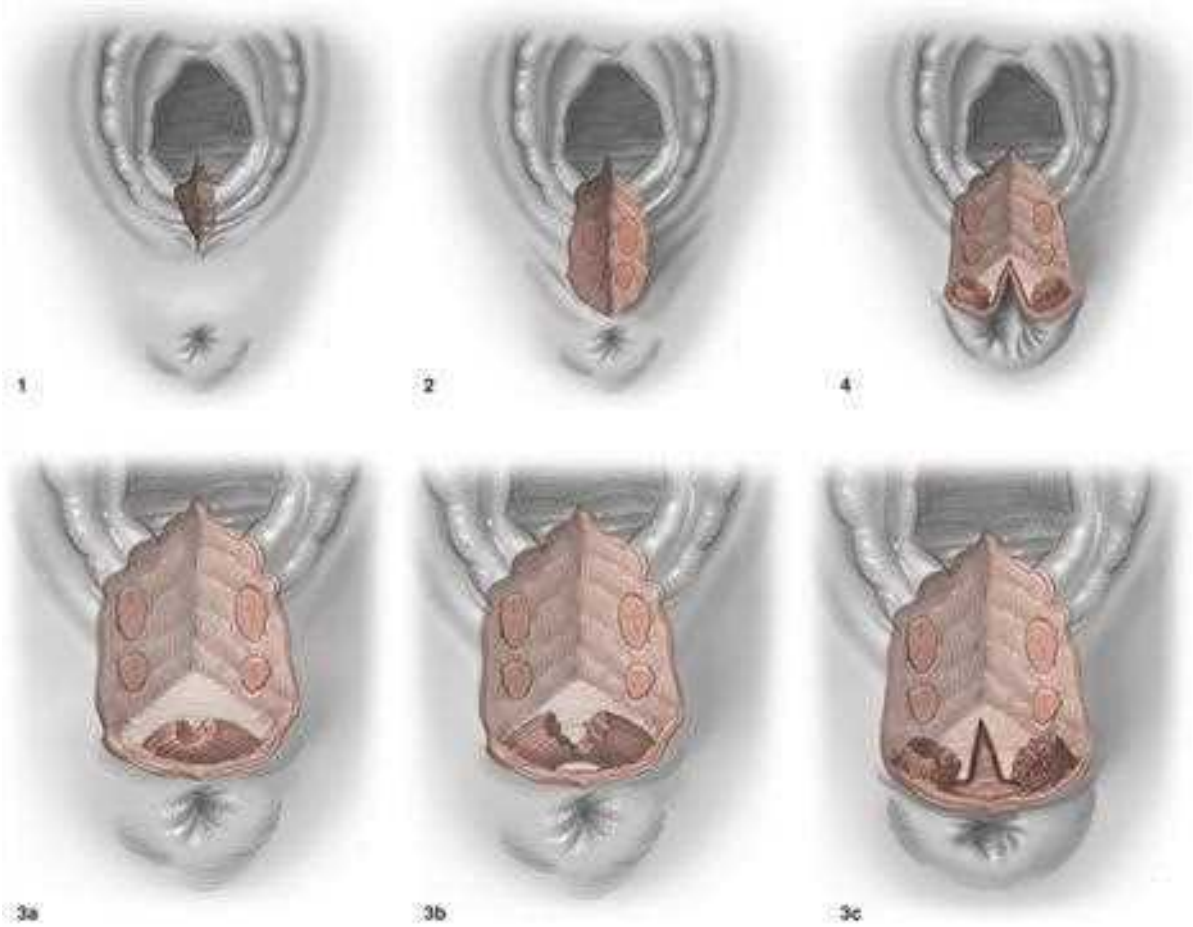
The hour immediately following delivery of the placenta is critical. During this time, lacerations are repaired. Although uterotonics are administered, postpartum hemorrhage as the result of uterine atony is most likely at this time. Hematomas may expand. Consequently, uterine tone and the perineum are frequently evaluated. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017b) recommend that maternal blood pressure and pulse be recorded immediately after delivery and every 15 minutes for the first 2 hours. The placenta, membranes, and umbilical cord are examined for completeness and for anomalies, as described in Chapter 6 (Normal Placenta).

Birth Canal Lacerations

Lower genital tract lacerations may involve the cervix, vagina, or perineum. Those of the cervix and vagina are described in Chapter 41 (Injuries to the Birth Canal). Those of the perineum often follow vaginal delivery, and most are first- and second-degree lacerations. Lacerations are classified by their depth, and complete definitions and visual examples are given in Figure 27-13. Of these, third-degree lacerations reflect anal sphincter injury and are now subcategorized as:

FIGURE 27-13

1. First-degree perineal laceration: injury to only the vaginal epithelium or perineal skin. **2.** Second-degree laceration: injury to perineum that spares the anal sphincter complex but involves the perineal muscles, which are the bulbospongiosus and superficial transverse perineal muscles. **3a.** Third-degree laceration: <50 percent of the external anal sphincter (EAS) is torn. **3b.** Third-degree laceration: >50 percent of the EAS is torn, but the internal anal sphincter (IAS) remains intact. **3c.** Third-degree laceration: EAS and IAS are torn. **4.** Fourth-degree laceration: the perineal body, entire anal sphincter complex, and anorectal mucosa are lacerated. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



(3a) <50 percent external anal sphincter (EAS) tear;

(3b) >50 percent EAS tear; and

(3c) EAS plus internal anal sphincter (IAS) tears.

Third- and fourth-degree lacerations are considered obstetrical anal sphincter injuries (OASIS), and their combined incidence varies from 0.5 to 5 percent (Blondel, 2016; Friedman, 2015). Risk factors for these more complex lacerations include nulliparity, midline episiotomy, persistent OP position, operative vaginal delivery, Asian race, short perineal length, and increasing fetal birthweight (Ampt, 2013; Dua, 2009; Gurol-Urganci, 2013; Landy, 2011). Mediolateral episiotomy is protective in most, but not all, studies (Jangö, 2014; Räisänen, 2011; Shmueli, 2016).

Morbidity rates rise as laceration severity increases. Compared with simpler lacerations, anal sphincter injuries are associated with greater blood loss and puerperal pain. Wound disruption and infection rates are other risks (Goldaber, 1993; Lewicky-Gaupp, 2015). Stock and coworkers (2013) reported that approximately 7 percent of 909 OASIS lacerations had complications. Long term, anal sphincter injuries are linked with approximately doubled rates of fecal incontinence compared with vaginal delivery without OASIS (Evers, 2012; Gyhagen, 2014). Data on long-term dyspareunia are limited, and rates are increased in some but not all studies (Mous, 2008; Otero, 2006; Salim, 2014; Sundquist, 2012).

To ensure appropriate repair, identification and correct categorization is essential. Diagnosis rates of OASIS improve with clinical experience (Andrews, 2006). Intrapartum endoanal ultrasound, performed in research studies, also boosts detection, and rates of clinically occult tears in primiparas range from 6 to 12 percent (Corton, 2013; Faltin, 2005; Ozyurt, 2015). That said, few data currently support routine intrapartum endoanal sonography, and the American College of Obstetricians and Gynecologists (2016b) does not recommended it (Walsh, 2015).

Women with a prior OASIS have a higher recurrence rate compared with multiparas without prior OASIS (Baghestan, 2012; Edozien, 2014; Elfaghi, 2004). That said, the risk mirrors that of primiparas in the general population and is low (Basham, 2013; Boggs, 2014; Priddis, 2013). Fetal macrosomia and operative vaginal delivery are notable risks in this cohort of parturients and can influence counseling in future pregnancies. Specifically, patients may choose to deliver by cesarean to avoid repeat OASIS. This consideration may be most pertinent for those with prior postpartum anal incontinence, with OASIS complications requiring corrective surgery, or with psychological trauma (American College of Obstetricians and Gynecologists, 2016b). However, planned cesarean delivery is balanced against its associated operative risks discussed in Chapter 30 (Cesarean Delivery Risks).

Episiotomy

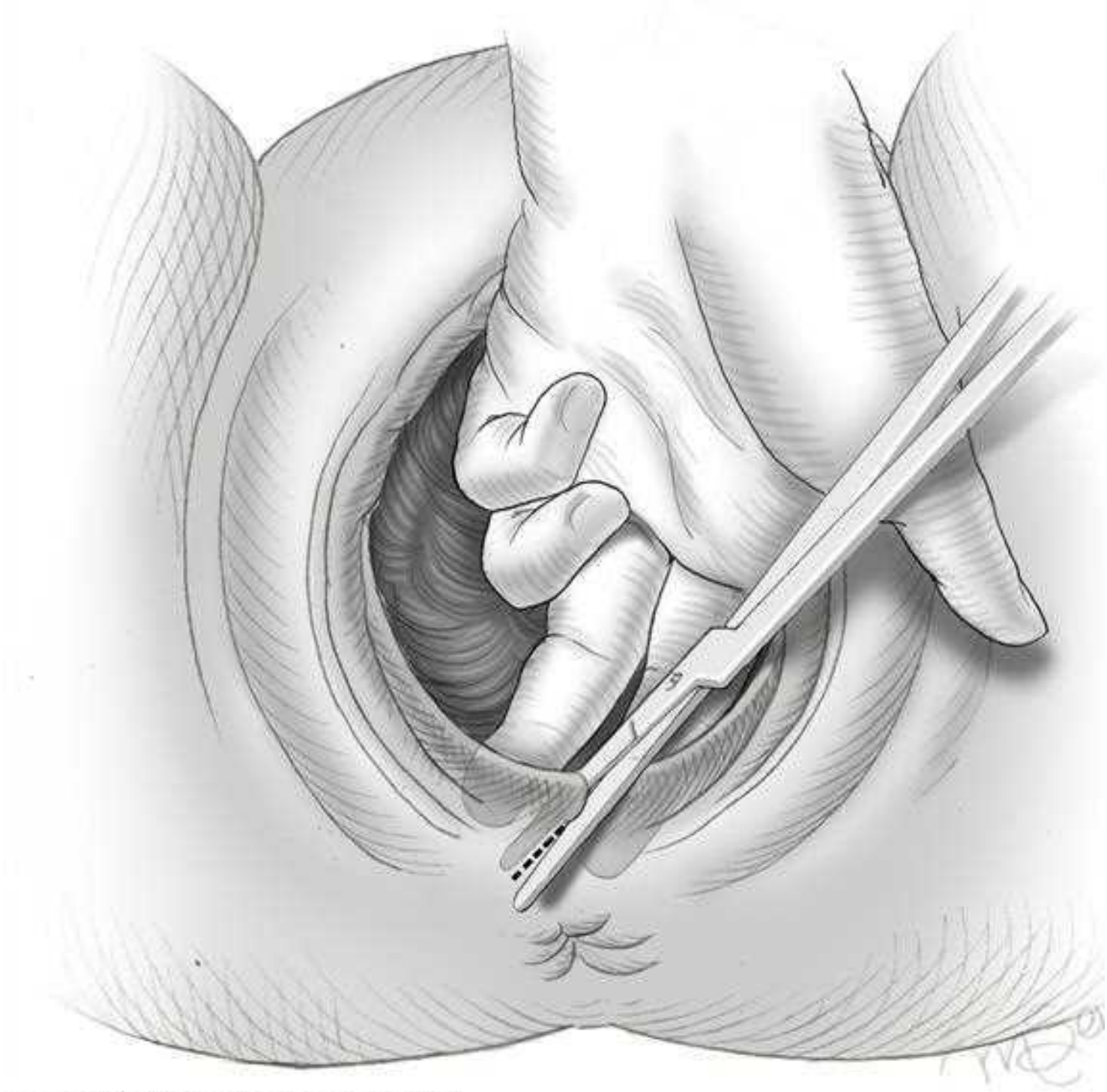
Types

In contrast to spontaneous lacerations, *perineotomy* is intended incision of the perineum. *Episiotomy* is incision of the pudendum–the external genital organs. In common parlance, however, the term episiotomy often is used synonymously with perineotomy, a practice that we follow here. Obstetrical textbooks and organizational guidelines differ considerably in their description of episiotomy techniques. Kalis and associates (2012) have presented a classification, and we agree with the need for terminology standardization.

Midline and mediolateral episiotomies are the two main types and vary by the angle of perineal incision. Involved structures mirror those found with second-degree laceration, and their repairs are analogous. The *midline episiotomy* begins at the fourchette, incises the perineal body in the midline, and ends well before the external anal sphincter is reached. The incision length varies from 2 to 3 cm depending on perineal length and degree of tissue thinning. The *mediolateral episiotomy* begins at the midline of the fourchette and is directed to the right or left at an angle 60 degrees off the midline (Fig. 27-14). This angle accounts for perineal anatomy distortion during crowning and ultimately yields an incision 45 degrees off the midline for suturing (El-Din, 2014; Kalis, 2011). The *lateral episiotomy* begins at point 1 to 2 cm lateral from the midline. It too is angled toward either the right or the left ischial tuberosity.

FIGURE 27-14

A mediolateral episiotomy is cut as the baby's head crowns. Fingers are insinuated between the perineum and head. The incision begins in the midline and is directed toward the ipsilateral ischial tuberosity at an angle 60 degrees off the midline. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Before episiotomy, analgesia may be provided by existing labor regional analgesia, by bilateral pudendal nerve blockade, or by local infiltration of 1-percent lidocaine. Some instead advocate 2.5-percent lidocaine-prilocaine cream (EMLA cream), but this requires application an hour before expected delivery, which may be logistically difficult (Franchi, 2009; Kargar, 2016).

If episiotomy is performed unnecessarily early, incisional bleeding may be considerable before delivery. If it is performed too late, lacerations will not be prevented. Typically, episiotomy is completed when the head is visible during a contraction to a diameter of approximately 4 cm, that is, crowning. When used in conjunction with forceps delivery, most perform an episiotomy after application of the blades.

Few data directly compare midline and mediolateral types. As noted, midline episiotomy has a greater likelihood of associated anal sphincter lacerations (Coats, 1980; de Leeuw, 2001). Short-term rates of self-perceived pain and dyspareunia are similar or increased with mediolateral episiotomy (Fodstad, 2013, 2014; Sartore, 2004).

Even fewer studies compare lateral episiotomy to either mediolateral or midline. One randomized trial compared lateral and mediolateral types in nulliparas. Groups did not differ in pain scores, in sexual quality of life, or in vaginal or perineal trauma, including OASIS (Karbanova, 2014a,b; Necesalova, 2016). The authors also

reported that mediolateral episiotomies required less time and suture for the repair. Thus, among the three, mediolateral episiotomy may be the preferred incision to reduce OASIS rates.

Indications

In the past, routine episiotomy was practiced to avoid a ragged laceration and to limit postoperative pain and anal sphincter injury rates. But, a Cochrane review of randomized trials showed lower rates of severe perineal/vaginal trauma in women managed with a restrictive, that is, selective use of episiotomy for spontaneous delivery rather than with routine episiotomy (Jiang, 2017). Importantly, this review did not discern between midline and mediolateral episiotomies.

The American College of Obstetricians and Gynecologists (2016b) has concluded that restricted use of episiotomy is preferred to routine use. We are of the view that the procedure should be applied selectively for appropriate indications. Thus, episiotomy can be *considered* for indications such as shoulder dystocia, breech delivery, fetal macrosomia, operative vaginal deliveries, persistent OP positions, markedly short perineal length, and other instances in which failure to perform an episiotomy will result in significant perineal rupture. The final rule is that there is no substitute for surgical judgment and common sense.

With this new approach, episiotomy rates have dropped. Oliphant and coworkers (2010) used the National Hospital Discharge Survey to analyze episiotomy rates between 1979 and 2006 in the United States. They noted a 75-percent decline in the age-adjusted episiotomy rate. In the United States in 2012 episiotomy was performed in approximately 12 percent of vaginal births (Friedman, 2015).

Laceration and Episiotomy Repairs

Typically, perineal repairs are deferred until the placenta has been delivered. This policy permits undivided attention to the signs of placental separation and delivery. A further advantage is that the repair is not interrupted or disrupted by placenta delivery. This is especially true if manual removal must be performed. The major disadvantage is continuing blood loss until the repair is completed. Direct pressure from an applied gauze sponge will help to limit this volume.

For suitable repair, an understanding of perineal support and anatomy is necessary and is discussed in Chapter 2 (Perineum). Adequate analgesia is imperative, and women without regional analgesia can experience high levels of pain during perineal suturing. Again, locally injected lidocaine can be used solely or as a supplement to bilateral pudendal nerve blockade. In those with epidural analgesia, additional dosing may be necessary.

First-degree lacerations do not always require repair, and sutures are placed to control bleeding or restore anatomy. Here, few data guide suture selection, and fine-gauge absorbable or delayed-absorbable suture or adhesive glue is suitable.

Second-degree laceration correction as well as midline and mediolateral episiotomy repairs include similar steps. Namely, these close the vaginal epithelium and reapproximate the bulbospongiosus and superficial transverse perineal muscles during restoration of the perineal body (Figs. 27-15 and 27-16). For this, most studies support a continuous suturing method, which is faster than placing interrupted sutures and, with few exceptions, yields less pain (Grant, 2001; Kettle, 2012; Kindberg, 2008; Valenzuela, 2009). Blunt needles are suitable and likely decrease the incidence of needle-stick injuries (El-Refaie, 2012; Mornar, 2008). Commonly used suture materials are 2–0 polyglactin 910 (Vicryl) or chromic catgut. With the former, a decrease in postsurgical pain and lower risk of wound dehiscence are cited as major advantages (Jallad, 2016; Kettle, 2010). Closures with traditional polyglactin 910, however, occasionally require removal of residual suture from the repair site because of pain or dyspareunia. This disadvantage may be reduced by using a rapidly absorbed polyglactin 910 (Vicryl Rapide) (Bharathi, 2013; Kettle, 2002; Leroux, 2006).

FIGURE 27-15

Mediolateral episiotomy repair. **A.** The vaginal epithelium and deeper tissues are closed with a single, continuous, locking suture. The angle seems less acute now (approximately 45°) since the perineum is no longer distended. **B.** After the vaginal component of the laceration is repaired, deeper perineal tissues are reapproximated by a single, continuous, nonlocking suture. Small episiotomies may not require this deeper layer. **C.** With a similar continuous, nonlocking technique, the superficial transverse perineal and bulbospongiosus muscles are reapproximated. **D.** Last, the perineal skin is closed using a subcuticular stitch. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)

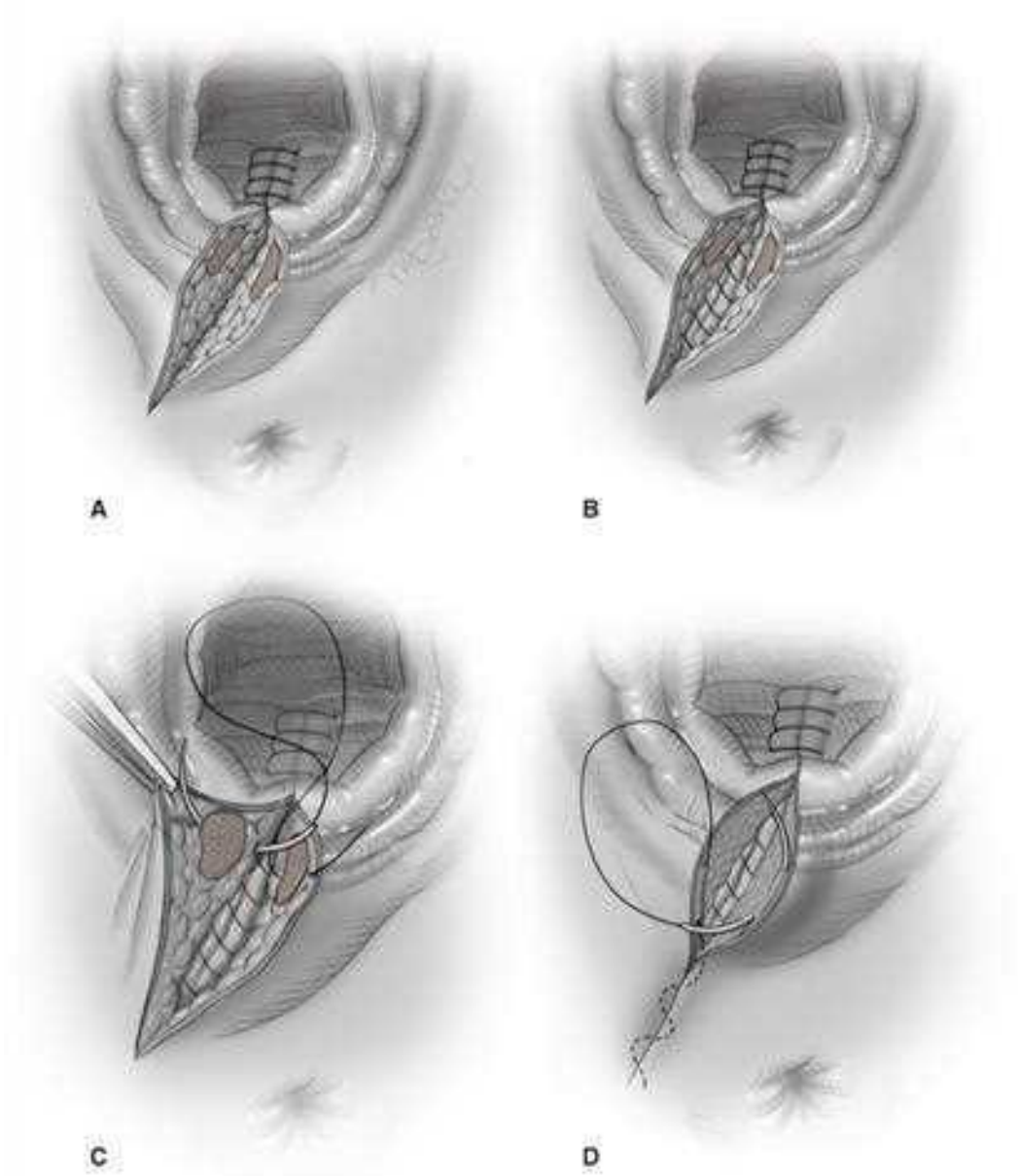
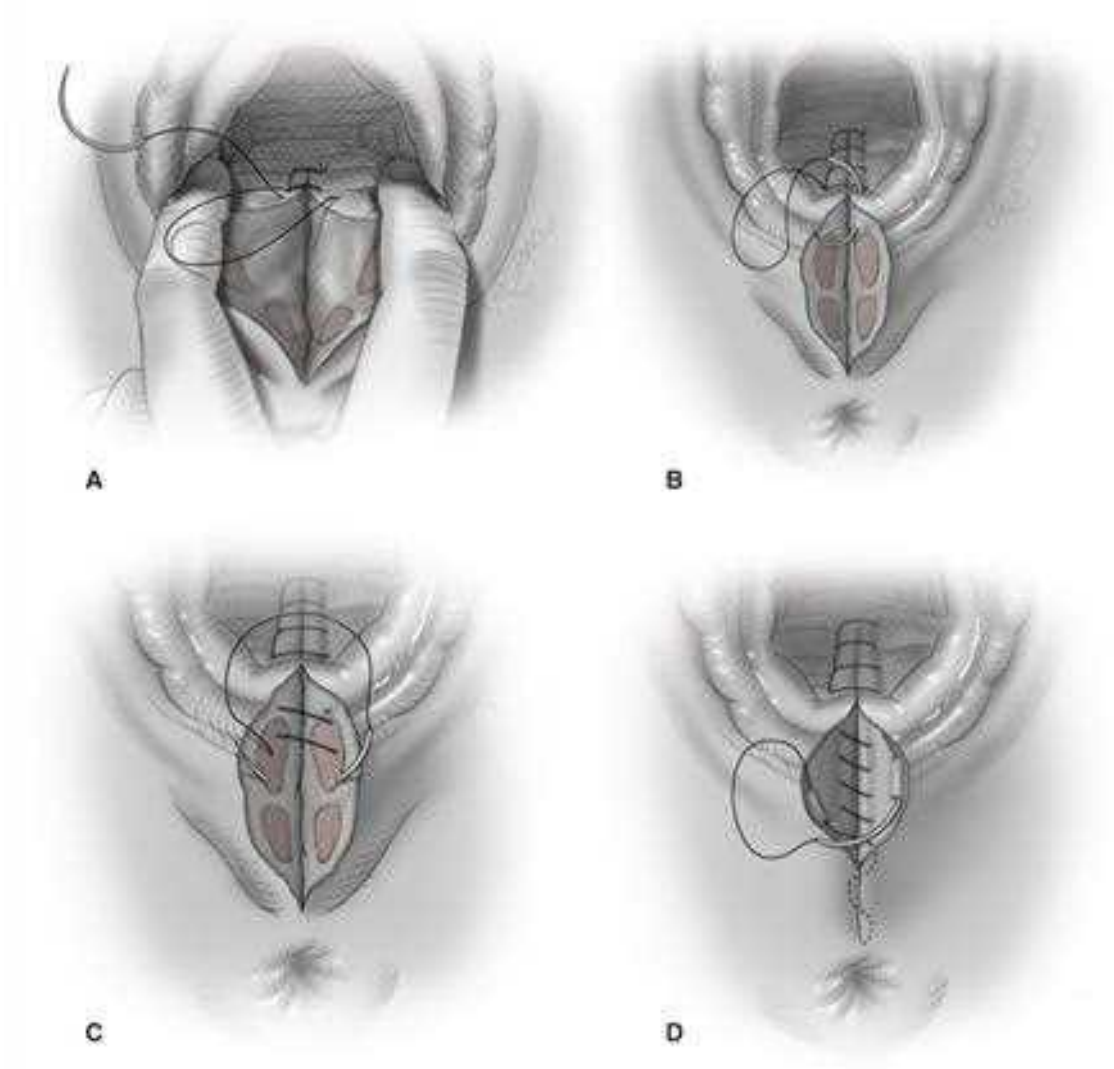


FIGURE 27-16

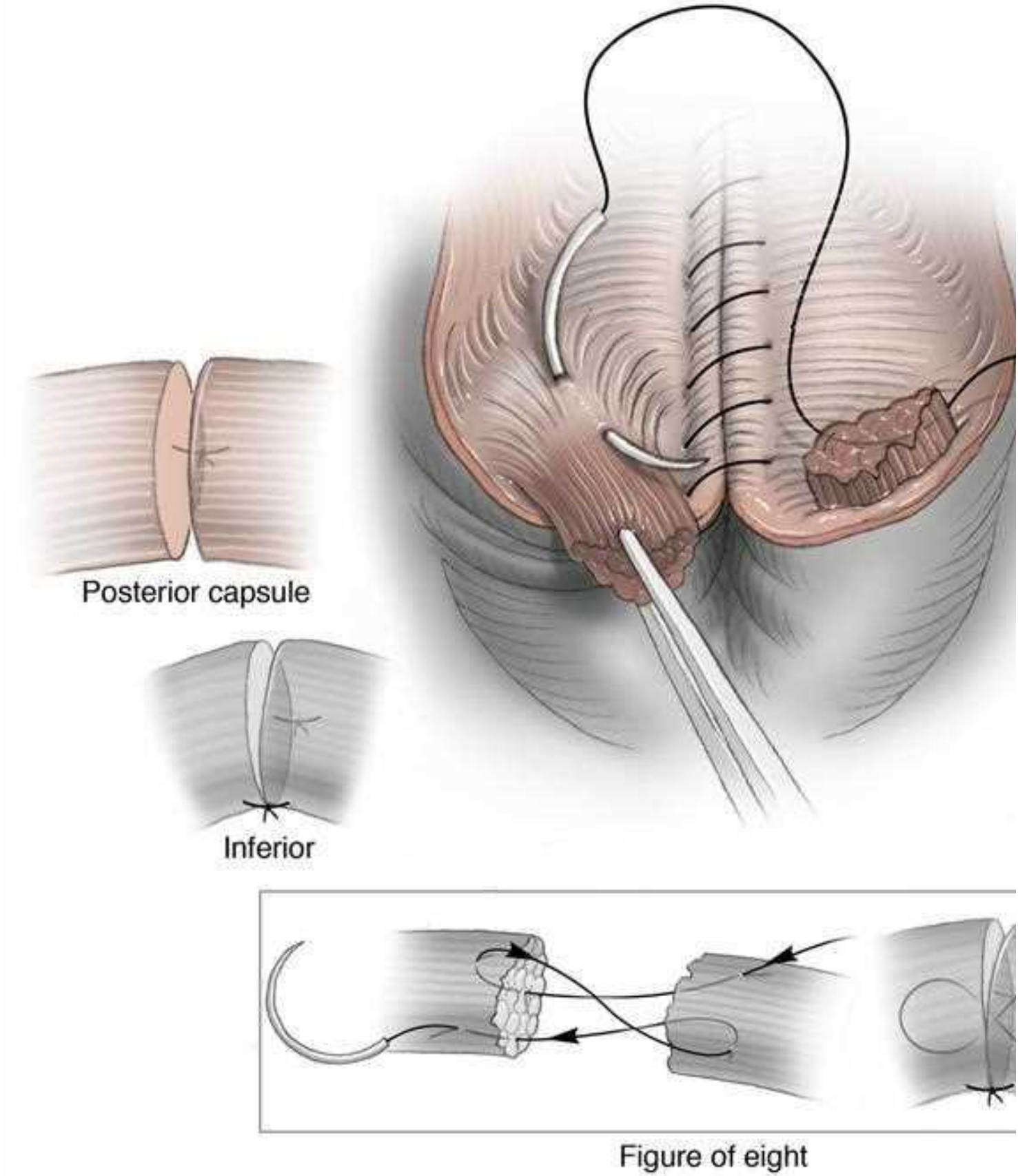
Midline episiotomy repair. **A.** An anchor stitch is placed above the wound apex to begin a running, locking closure with 2–0 suture to close the vaginal epithelium and deeper tissues and reapproximate the hymeneal ring. **B.** A transition stitch redirects suturing from the vagina to the perineum. **C.** The superficial transverse perineal and bulbospongiosus muscles are reapproximated using a continuous, nonlocking technique with the same length of suture. This aids restoration of the perineal body for long-term support. **D.** The continuous suture is then carried upward as a subcuticular stitch. The final knot is tied proximal to the hymeneal ring. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



For third-degree laceration repair, two methods are available to repair the external anal sphincter. The first is an *end-to-end technique*, which we prefer, and is shown in Figure 27-17. Initially, the cut ends of the external anal sphincter, which often retract, are isolated and brought to the midline. Importantly, the strength of this closure is derived from the connective tissue surrounding the sphincter—often called the *capsule*—and not the striated muscle. Thus, serial interrupted sutures incorporate sphincter fibers and perisphincter connective tissue, to bring sphincter ends together. There are few evidence-based data to guide suture selection for sphincter repair, but delayed-absorbable material can provide sustained tensile strength during healing. This theory is supported by the above study by Jallad and coworkers (2016), which showed higher perineal breakdown rate following OASIS repair with chromic gut.

FIGURE 27-17

In overview, with end-to-end approximation of the external anal sphincter (EAS), a suture is placed through the EAS muscle, and four to six simple interrupted 2–0 or 3–0 sutures of polyglactin 910 are placed at the 3, 6, 9, and 12 o'clock positions through the perisphincter connective tissue. To begin, disrupted ends of the striated EAS muscle and capsule are identified and grasped. The first suture is placed posteriorly to maintain clear exposure. Another suture is then placed inferiorly at the 6 o'clock position. The sphincter muscle fibers are next reapposed by a figure-of-eight stitch. Last, the remainder of the fascia is closed with a stitch placed anterior to the sphincter cylinder and again with once placed superior to it. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)

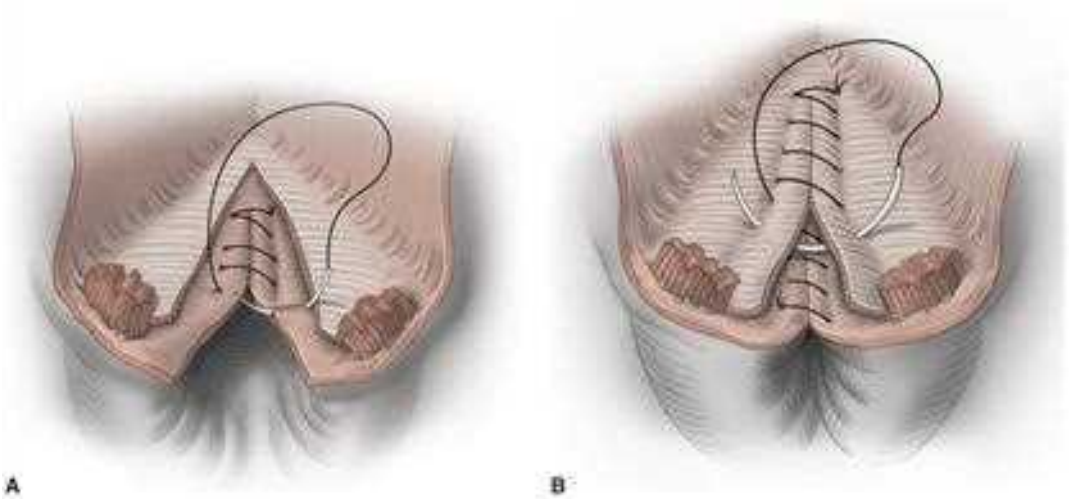


With the *overlapping technique,* the ends of the external anal sphincter are brought to the midline and lie atop one another. This method is only suitable for type 3c lacerations—those involving the external and internal anal sphincter. Two rows of mattress sutures travel through both sphincter ends to recreate the anal ring. In comparing the two methods, neither yields superior long-term anatomical or functional results (Farrell, 2012; Fernando, 2013; Fitzpatrick, 2000). Also with type 3c lacerations, the IAS is repaired before the EAS and is described next.

With fourth-degree laceration repairs, the torn edges of the rectal mucosa are reapproximated (Fig. 27-18). At a point 1 cm proximal to the wound apex, sutures are placed approximately 0.5 cm apart in the rectal muscularis and do not enter the anorectal lumen. Clinicians often use 4–0 polyglactin 910 or chromic gut for this running suture line. Some recommend a second reinforcing layer above this (Hale, 2007). If this is not done, then the next layer to cover the anorectal mucosa is formed by reapproximation of the internal anal sphincter. This running, nonlocking closure is completed with 3–0 or 4–0 suture (see Fig. 27-18B). Following any repair, needle and sponge counts are reconciled and recorded in the delivery note.

FIGURE 27-18

A. Suturing of the anorectal mucosa begins above the laceration apex using a continuous, nonlocking method with fine-gauge absorbable suture such as 3–0 or 4–0 chromic gut or polyglactin 910. Sutures are placed through the anorectal submucosa approximately 0.5 cm apart down to the anal verge. **B.** A second reinforcing layer uses 3–0 delayed-absorbable suture in a continuous, nonlocking fashion. This incorporate the torn ends of the internal anal sphincter (IAS), which can be identified as the glistening white fibrous structure lying between the anal canal submucosa and the fibers of the external anal sphincter. In many cases, the IAS retracts laterally and must be sought and retrieved for repair. (Reproduced with permission from Kenton K, Mueller M: Episiotomy and obstetric anal sphincter lacerations. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



For reduction of infectious morbidity associated with anal sphincter lacerations, a single dose of antibiotic at the time of repair is recommended by the American College of Obstetricians and Gynecologists (2016c). This practice is supported by evidence (Buppasiri, 2014; Duggal, 2008; Lewicky-Gaupp, 2015; Stock, 2013). A single dose of a second-generation cephalosporin is suitable, or clindamycin for penicillin-allergic women. With OASIS, postoperatively, stool softeners are prescribed for a week, and enemas and suppositories are avoided.

Unfortunately, normal function is not always ensured even with correct and complete surgical repair. Some women may experience continuing fecal incontinence caused by injury to the innervation of the pelvic floor musculature (Roberts, 1990).

Perineal Laceration Care

Initially, locally applied ice packs help reduce swelling and allay discomfort (de Souza Bosco Paiva, 2016). In subsequent days, warm sitz baths aid comfort and hygiene. Additionally, a small squirt bottle of warm water can cleanse the site after voiding or stooling. For pain, topical application of 5-percent lidocaine ointment was not effective in relieving episiotomy or perineal laceration discomfort in one randomized trial (Minassian, 2002). Oral analgesics containing codeine provide considerable relief. For lesser degree of discomfort, NSAID tablets can be given.

Because pain may signal a large vulvar, paravaginal, or ischiorectal fossa hematoma or perineal cellulitis, these sites should be examined carefully if pain is severe or persistent. Management of these complications is discussed in Chapters 37 and 41 (Perineal Infections and Puerperal Hematomas). In addition to pain, urinary retention may complicate episiotomy recovery (Mulder, 2012, 2016). Its management is described in Chapter 36 (Perineal Care).

For those with second-degree lacerations or anal sphincter tears, intercourse is usually proscribed until after the first puerperal visit at 6 weeks. Compared with women with intact perineum, those with perineal trauma show higher rates of delayed intercourse at 3 and 6 months, but not at 1 year (McDonald, 2015; Rådestad, 2008; Signorello, 2001).

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Silverchair

CHAPTER 28: Breech Delivery

The essential prerequisite for the successful performance of breech extraction lies in the complete dilatation of the cervix and the absence of any serious mechanical obstacle. It is true that in a certain number of cases extraction through an imperfectly dilated cervix is possible, but this is usually effected only at the cost of deep cervical tears.

—J. Whitridge Williams (1903)

INTRODUCTION

Near term, the fetus typically has spontaneously assumed a cephalic presentation. Conversely, if the fetal buttocks or legs enter the pelvis before the head, the presentation is breech. This fetal lie is more common remote from term, as earlier in pregnancy each fetal pole has similar bulk. At term, breech presentation persists in approximately 3 to 5 percent of singleton deliveries (Cammu, 2014; Lyons, 2015; Macharey, 2017).

CLASSIFICATION OF BREECH PRESENTATIONS

The categories of frank, complete, and incomplete breech presentations differ in their varying relations between the lower extremities and buttocks. With a frank breech, lower extremities are flexed at the hips and extended at the knees, and thus the feet lie close to the head (Fig. 28-1). With a complete breech, both hips are flexed, and one or both knees are also flexed (Fig. 28-2). With an incomplete breech, one or both hips are extended. As a result, one or both feet or knees lie below the breech, such that a foot or knee is lowermost in the birth canal (Fig. 28-3). A footling breech is an incomplete breech with one or both feet below the breech.

FIGURE 28-1
Frank breech presentation.

FIGURE 28-2

Complete breech presentation.

FIGURE 28-3

Incomplete breech presentation.

Of term breech fetuses, the neck may be extremely hyperextended in perhaps 5 percent, and the term *stargazing fetus* is used (Cimmino, 1975). With these, fetal or uterine anomalies may be more prevalent and are sought if not previously identified (Phelan, 1983). With this hyperextension, vaginal delivery can result in injury to the cervical spinal cord. Thus, if identified at term, this is an indication for cesarean delivery (Westgren, 1981). That said, flexion itself may be implicated, as cases of spinal cord injury have been reported following uneventful cesarean delivery of such fetuses (Hernandez-Marti, 1984). With transverse lie and similar hyperextension of the fetal neck, the term *flying fetus* is applied.

DIAGNOSIS

Risk Factors

Understanding the clinical settings that predispose to breech presentation can aid early recognition. Other than early gestational age, risk factors include extremes of amnionic fluid volume, multifetal gestation, hydrocephaly, anencephaly, structural uterine abnormalities, placenta previa, pelvic tumors, and prior breech delivery. One study found that following one breech delivery, the recurrence rate for a second breech presentation was 10 percent, and for a subsequent third breech it was 28 percent (Ford, 2010).

Examination

Leopold maneuvers to ascertain fetal presentation are discussed in Chapter 22 (Diagnosis). With the first maneuver, the hard, round fetal head occupies the fundus. The second maneuver identifies the back to be on one side of the abdomen and the small parts on the other. With the third maneuver, if not engaged, the softer breech is movable above the pelvic inlet. After engagement, the fourth maneuver shows the breech to be beneath the symphysis. The accuracy of this palpation varies (Lydon-Rochelle, 1993; Nassar, 2006). Thus, with suspected breech presentation—or any presentation other than cephalic—sonographic evaluation is indicated.

During cervical examination with a frank breech, no feet are appreciated, but the fetal ischial tuberosities, sacrum, and anus are usually palpable. After further fetal descent, the external genitalia may also be distinguished. When labor is prolonged, the fetal buttocks may become markedly swollen, rendering digital differentiation of a face and breech difficult. In some cases, the anus may be mistaken for the mouth and the ischial tuberosities for the malar eminences. With careful examination, however, the finger encounters muscular resistance with the anus, whereas the hard, less yielding jaws are felt through the mouth. The finger, upon removal from the anus, may be stained with meconium. The mouth and malar eminences form a triangular shape, whereas the ischial tuberosities and anus lie in a straight line. With a complete breech, the feet may be felt alongside the buttocks. In footling presentations, one or both feet are inferior to the buttocks.

The fetal sacrum and its spinous processes are palpated to establish position. As with cephalic presentations, fetal position is designated to reflect the relations of the fetal sacrum to the maternal pelvis. Positions include left sacrum anterior (LSA), right sacrum anterior (RSA), left sacrum posterior (LSP), right sacrum posterior (RSP), and sacrum transverse (ST).

ROUTE OF DELIVERY

Multiple factors aid determination of the best delivery route for a given mother-fetus pair. These include fetal characteristics, maternal pelvic dimensions, coexistent pregnancy complications, provider experience, patient preference, hospital capabilities, and gestational age.

Compared with their term counterparts, preterm breech fetuses have distinct complications related to their small size and immaturity. For example, rates of head entrapment, birth trauma, and perinatal mortality can be greater. Accordingly, separate discussions of term and preterm breech fetuses are more appropriate.

Term Breech Fetus

Current obstetrical thinking regarding vaginal delivery of the term breech fetus has been tremendously influenced by results of the Term Breech Trial (Hannah, 2000). This trial included 1041 women randomly assigned to planned cesarean and 1042 to planned vaginal delivery. In the planned vaginal delivery group, 57 percent were actually delivered vaginally. Planned cesarean delivery was associated with a lower risk of perinatal mortality compared with planned vaginal delivery—3 per 1000 versus 13 per 1000. Cesarean delivery was also associated with a lower risk of “serious” neonatal morbidity—1.4 versus 3.8 percent. Short-term maternal morbidity was similar between groups.

Critics of the Term Breech Trial emphasize that fewer than 10 percent of candidates underwent radiological pelvimetry. Also, most of the outcomes included in the “serious” neonatal morbidity composite did not actually portend long-term infant disability (Whyte, 2004).

Since that trial, however, additional data favoring cesarean delivery has come from the World Health Organization (Lumbiganon, 2010). From their evaluation of more than 100,000 deliveries from nine participating Asian countries, they reported improved perinatal outcomes for the term breech fetus with planned cesarean compared with planned vaginal delivery. Other studies have evaluated neonatal outcome with cesarean delivery and also found lowered neonatal morbidity and mortality rates (Hartnack Tharin, 2011; Lyons, 2015; Rietberg, 2005; Vistad, 2015). From their metaanalysis, Berhan and Haileamlak (2016) calculate absolute risk of perinatal mortality to be 0.3 percent and of fetal birth trauma or neurological morbidity to be 0.7 percent.

In contrast, other studies support vaginal delivery as a suitable option at term (Hofmeyr, 2015a). The *Presentation et Mode d'Accouchement—PREMODA* study—which translates as presentation and mode of delivery—showed no differences in corrected neonatal mortality rates and neonatal outcomes according to delivery mode (Goffinet, 2006). This French prospective observational study involved more than 8000 women with term breech singletons. Strict criteria were used to select 2526 of these for planned vaginal delivery, and 71 percent of that group were delivered vaginally. Similarly, data from the Lille Breech Study Group in France showed

no excessive morbidity in term breech singletons delivered vaginally provided strict fetal biometric and maternal pelvimetry parameters were applied (Michel, 2011). Other smaller studies support these findings as long as guidelines are part of the selection process (Alarab, 2004; Giuliani, 2002; Toivonen, 2012).

Long-term evidence in support of vaginal breech delivery comes from Eide and associates (2005). These investigators analyzed intelligence testing scores of more than 8000 men delivered breech and found no differences in intellectual performance in those undergoing vaginal or cesarean delivery. Also, a 2-year follow up from the Term Breech trial showed similar risks for death and for neurodevelopmental delay between delivery groups (Whyte, 2004).

Despite evidence on both sides of the debate, at least in the United States, rates of planned vaginal delivery attempts continue to decline. And as predicted, the number of skilled providers able to safely select and vaginally deliver breech fetuses continues to dwindle (Chinnock, 2007). Moreover, obvious medicolegal concerns make physician training in such deliveries difficult. In response, some institutions have developed birth simulators to improve resident competence in vaginal breech delivery (Deering, 2006; Maslovitz, 2007).

Preterm Breech Fetus

In contrast to the term breech fetus, there are no randomized trials regarding delivery of the preterm breech fetus. Moreover, study comparisons are often made difficult by lumping, splitting, or overlapping of preterm gestational age groups. All that said, it would appear that for the preterm breech fetus, planned cesarean delivery confers a survival advantage compared with planned vaginal delivery. Reddy and associates (2012) reported data from deliveries between 24 and 32 weeks' gestation. For breech fetuses within these gestational ages, attempting vaginal delivery yielded a low success rate, and those completed were associated with higher neonatal mortality rates compared with planned cesarean delivery. Other investigations have reported similar findings (Bergenhenegouwen, 2014; Demirci, 2012; Muhuri, 2006).

For preterm fetuses in younger subgroups—23 to 28 weeks—the data are more conflicting, and some studies describe no improved survival rate with planned cesarean delivery (Bergenhenegouwen, 2015; Kayem, 2015; Thomas, 2016). For *periviable fetuses*, defined by them as 20 to $25^{6/7}$ weeks, a consensus workshop of perinatal organizations concluded that "available data do not consistently support routine cesarean delivery to improve perinatal mortality or neurological outcomes for early preterm infants" (Raju, 2014). A subsequent joint statement by the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2017) suggested consideration for cesarean delivery for periviable fetuses beginning at $23^{0/7}$ weeks, with a recommendation for cesarean delivery at $25^{0/7}$ weeks.

For more mature preterm breech fetuses, that is, between 32 and 37 weeks, again there are sparse data to guide delivery route selection. Bergenhenegouwen and coworkers (2015) studied more than 6800 breech deliveries in a subgroup between 32 and 37 weeks. With planned cesarean delivery, they found similar perinatal mortality rates but less composite mortality and severe morbidity. It appears in this subgroup that fetal weight rather than gestational age is likely more important. The Maternal-Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) states that vaginal breech delivery is reasonable when the estimated fetal weight is >2500 g (Kotaska, 2009). There are especial concerns for delivery of the second noncephalic-presenting twin fetus that are discussed in Chapter 45 (Evaluation of Fetal Presentation).

In the United States, all these findings shape practice, and cesarean delivery is almost uniformly favored for the preterm breech fetus for which resuscitation is planned.

Delivery Complications

Increased rates of maternal and perinatal morbidity can be anticipated with breech presentations. For the mother, with either cesarean or vaginal delivery, genital tract laceration can be problematic. With cesarean delivery, added stretching of the lower uterine segment by forceps or by a poorly molded fetal head can extend hysterotomy incisions. With vaginal delivery, especially with a thinned lower uterine segment, delivery of the aftercoming head through an incompletely dilated cervix or application of forceps may cause vaginal wall or cervical lacerations, and even uterine rupture. Manipulations may also extend an episiotomy, create deep perineal tears, and increase infection risks. Anesthesia sufficient to induce appreciable uterine relaxation during vaginal delivery may cause uterine atony and in turn postpartum hemorrhage. Maternal death is rare, but rates appear higher in those with planned cesarean delivery for breech presentation—a case fatality rate of 0.47 maternal deaths per 1000 births (Schutte, 2007). Last, the risks associated with vaginal breech delivery are balanced against general cesarean delivery risks described in Chapter 30 (Cesarean Delivery Risks). Long-term, cesarean risks include those associated with repeated hysterotomy or with vaginal birth after cesarean —VBAC—further described in Chapter 31 (Delivery Route Risks).

For the fetus, prematurity and its complications are frequently comorbid with breech presentation. Rates of congenital anomalies are also greater (Cammu, 2014; Mostello, 2014). Compared with cephalic presentation, umbilical cord prolapse is more frequent with breech fetuses (Behbehani, 2016; Obeidat, 2010). Birth trauma can include fractures of the humerus, clavicle, and femur (Canpolat, 2010; Matsubara, 2008). In some cases, traction may separate scapular, humeral, or femoral epiphyses (Lamrani, 2011). Trauma is more common with vaginal births, but fetal trauma is also seen with cesarean deliveries.

Rare traumatic injuries may involve soft tissues. Brachial plexus injury and paralysis is one example (Foad, 2008). The spinal cord may be injured or even severed, or vertebrae fractured, especially if great force is employed (Vialle, 2007). Hematomas of the sternocleidomastoid muscles occasionally develop after delivery but usually disappear spontaneously. Last, genital injury may follow breech delivery (Saroha, 2015).

Some perinatal outcomes may be inherent to the breech position rather than delivery. For example, development of hip dysplasia is more common in breech compared with cephalic presentation and is unaffected by delivery mode (de Hundt, 2012; Fox, 2010; Ortiz-Neira, 2012).

Imaging Techniques

In many fetuses—especially those that are preterm—the breech is smaller than the aftercoming head. Moreover, unlike cephalic presentations, the head of a breech-presenting fetus does not undergo appreciable molding during labor. Thus, if vaginal delivery is considered, fetal size, type of breech, and degree of neck flexion or extension are evaluated. In addition, pelvic dimensions are assessed to avoid head entrapment from cephalopelvic disproportion. Sonography and fetal pelvimetry are options.

Sonographic fetal evaluation will have been performed in most cases as part of prenatal care. If not, gross fetal abnormalities, such as hydrocephaly or anencephaly, can be rapidly ascertained with sonography. This will identify many fetuses not suitable for vaginal delivery. It will also help to ensure that a cesarean delivery is not performed under emergency conditions for an anomalous fetus with no chance of survival.

Head flexion can usually also be determined sonographically, and for vaginal delivery, the fetal head should not be extended (Fontenot, 1997; Rojansky, 1994). If imaging is uncertain, then simple two-view radiography of the maternal abdomen is useful to define fetal head inclination. Sonographic identification of a nuchal arm may warrant cesarean delivery to avoid neonatal harm (Sherer, 1989).

The accuracy of fetal weight estimation by sonography is not altered by breech presentation (McNamara, 2012). Although variable, many protocols use fetal weights >2500 g and <3800 to 4000 g or evidence of growth restriction as exclusion criteria for planned vaginal delivery (Azria, 2012; Kotaska, 2009). Similarly, a biparietal diameter (BPD) >90 to 100 mm is often considered exclusionary (Giuliani, 2002; Roman, 2008).

Pelvimetry assesses the maternal bony pelvis before vaginal delivery, and one-view computed tomography (CT), magnetic resonance (MR) imaging, or plain film radiography is suitable. Comparative data among these modalities for pelvimetry are lacking, but CT is favored due to its accuracy, low radiation dose, and widespread availability (Thomas, 1998). At Parkland Hospital, we use CT pelvimetry when possible to assess the critical dimensions of the pelvis (Chap. 2, Planes and Diameters of the Pelvis). Although variable, some suggest specific measurements to permit a planned vaginal delivery: inlet anteroposterior diameter ≥10.5 cm; inlet transverse diameter ≥12.0 cm; and midpelvic interspinous distance ≥10.0 cm (Azria, 2012; Vendittelli, 2006). Some have recommended maternal-fetal biometry correlation. Appropriate values include: the sum of the inlet obstetrical conjugate minus the fetal BPD is ≥15 mm; the inlet transverse diameter minus the BPD is ≥25 mm; and the midpelvis interspinous distance minus the BPD is ≥0 mm (Michel, 2011). With MR imaging, Hoffmann and colleagues (2016) found vaginal delivery success rates of 79 percent in selected candidates if the interspinous distance exceeded 11 cm.

Decision-Making Summary

Currently, the American College of Obstetricians and Gynecologists (2016b) recommends that “the decision regarding the mode of delivery should depend on the experience of the health-care provider” and that “planned vaginal delivery of a term singleton breech fetus may be reasonable under hospital-specific protocol guidelines.” These guidelines have been echoed by other obstetrical organizations (Kotaska, 2009; Royal College of Obstetricians and Gynaecologists, 2006). Risks versus benefits are weighed and discussed with the patient. If possible, this is preferably done before admission. A diligent search is made for other complications, actual or anticipated, that might warrant cesarean delivery. Common circumstances are listed in Table 28-1. For a favorable outcome with any breech delivery, at the very minimum, the birth canal must be sufficiently large to allow passage of the fetus without trauma. The cervix must be fully dilated, and if not, then a cesarean delivery nearly always is the more appropriate method of delivery if suspected fetal compromise develops.

TABLE 28-1

Factors Favoring Cesarean Delivery of the Breech Fetus

Lack of operator experience
Patient request for cesarean delivery
Large fetus: >3800 to 4000 g
Apparently healthy and viable preterm fetus either with active labor or with indicated delivery
Severe fetal-growth restriction
Fetal anomaly incompatible with vaginal delivery
Prior perinatal death or neonatal birth trauma
Incomplete or footling breech presentation
Hyperextended head
Pelvic contraction or unfavorable pelvic shape determined clinically or with pelvimetry
Prior cesarean delivery

LABOR AND DELIVERY MANAGEMENT

Vaginal Delivery Methods

The conduct of both labor and delivery differ between cephalic and breech presentations. First, breech labor in general proceeds more slowly, but steady cervical progress is a positive indicator of adequate pelvic proportions (Lennox, 1998). Vaginal breech delivery is accomplished by one of three methods. With *spontaneous breech delivery*, the fetus is expelled entirely without any traction or manipulation other than support of the newborn. With *partial breech extraction*, the fetus is delivered spontaneously as far as the umbilicus, but the remainder of the body is delivered by provider traction and assisted maneuvers, with or without maternal expulsive efforts. With *total breech extraction*, the entire fetal body is extracted by the provider.

Labor Induction and Augmentation

As with many other aspects of breech position, induction or augmentation of labor is controversial. Here again, data are limited and mostly retrospective. With labor induction, Burgos and coworkers (2017) reported equivalent vaginal delivery rates compared with spontaneous labor. With induction, however, they reported higher rates of neonatal intensive care unit admission. But, others have found similar perinatal outcome and cesarean delivery rates (Jarniat, 2017; Marzouk, 2011). Finally, others described greater cesarean delivery rates with induction but similar neonatal outcomes (Macharey, 2016).

In many studies, successful vaginal delivery is associated with orderly labor progression. Thus, some protocols avoid augmentation for the breech-presenting fetus, whereas others recommend it only for hypotonic contractions (Alarab, 2004; Kotaska, 2009). In women with a viable fetus, at Parkland Hospital, we attempt amniotomy induction but prefer cesarean delivery instead of pharmacological labor induction or augmentation.

Labor Management

On arrival to the labor unit, surveillance of fetal heart rate and uterine contractions begins, and immediate recruitment of necessary staff includes: (1) a provider skilled in the art of breech extraction, (2) an associate to assist with the delivery, (3) anesthesia personnel who can ensure adequate analgesia or anesthesia when needed, and (4) an individual trained in newborn resuscitation. For the mother, intravenous access is obtained. This allows, if needed, emergency induction of anesthesia or maternal resuscitation following hemorrhage from lacerations or from uterine atony.

At admission, the status of the membranes and progression of labor are assessed. Knowledge regarding cervical dilatation, cervical effacement, and presenting part station is essential for preparation. If labor is too far advanced, pelvimetry may be unsafe if fetal expulsion in the radiology department is a possibility. This alone, however, should not force the decision for cesarean delivery. As mentioned, stepwise labor progression itself is a good indicator of pelvic adequacy (Biswas, 1993). Sonographic assessment, described earlier, is completed. Ultimately, the choice of abdominal or vaginal delivery is based on factors discussed earlier and listed in Table 28-1.

During labor, one-on-one nursing is ideal because of cord prolapse risks, and physicians must be readily available for such emergencies. Guidelines for monitoring the high-risk fetus are applied (Chap. 24, Intrapartum Surveillance of Uterine Activity). For first-stage labor, while most clinicians prefer continuous electronic monitoring, the fetal heart rate is recorded at a minimum of every 15 minutes. A scalp electrode can be safely affixed to the buttock, but genitalia are avoided. If a nonreassuring fetal heart rate pattern develops, then a decision must be made regarding the necessity of cesarean delivery.

When membranes rupture, either spontaneously or artificially, the cord prolapse risk is appreciable and is increased when the fetus is small or when the breech is not frank. Therefore, vaginal examination is performed immediately following rupture, and special attention is directed to the fetal heart rate for the first 5 to 10 minutes thereafter.

For women in labor with a breech presentation, continuous epidural analgesia is advocated by some. This may increase the need for labor augmentation and prolong second-stage labor (Chadha, 1992; Confino, 1985). These potential disadvantages are weighed against the advantages of better pain relief and increased pelvic relaxation should extensive manipulation be required. Analgesia must be sufficient for episiotomy, for breech extraction, and for Piper forceps application. Nitrous oxide plus oxygen inhalation can provide further relief from pain. If general anesthesia is required, it must be induced quickly.

Spontaneous Breech Delivery

Similar to vertex delivery, spontaneous expulsion of a breech fetus entails sequential cardinal movements. First, engagement and descent of the breech usually take place with the bitrochanteric diameter in one of the oblique pelvic diameters. The anterior hip usually descends more rapidly than the posterior hip, and when the resistance of the pelvic floor is met, internal rotation of 45 degrees usually follows, bringing the anterior hip toward the pubic arch and allowing the bitrochanteric diameter to occupy the anteroposterior diameter of the pelvic outlet. If the posterior extremity is prolapsed, however, it, rather than the anterior hip, rotates to the symphysis pubis.

After rotation, descent continues until the perineum is distended by the advancing breech, and the anterior hip appears at the vulva. By lateral flexion of the fetal body, the posterior hip then is forced over the perineum, which retracts over the fetal buttocks, thus allowing the fetus to straighten out when the anterior hip is born (Fig. 28-4). The legs and feet follow the breech and may be born spontaneously or require aid.

After the birth of the breech, there is slight external rotation, with the back turning anteriorly as the shoulders are brought into relation with one of the oblique diameters of the pelvis. The shoulders then descend rapidly and undergo internal rotation, with the bisacromial diameter occupying the anteroposterior plane. Immediately following the shoulders, the head, which is normally sharply flexed on the thorax, enters the pelvis in one of the oblique diameters and then rotates to bring the posterior portion of the neck under the symphysis pubis. The head is then born in flexion.

The breech may engage in the transverse diameter of the pelvis, with the sacrum directed anteriorly or posteriorly. The mechanism of labor in the transverse position differs only in that internal rotation is through an arc of 90 rather than 45 degrees. Infrequently, rotation renders the back of the fetus to lie posteriorly

instead of anteriorly. Such rotation is prevented if possible. Although the head can be delivered by allowing the chin and face to pass beneath the symphysis, the slightest traction on the body may cause extension of the head, which increases the diameter of the head that must pass through the pelvis.

Partial Breech Extraction

With breech delivery, successively larger and less compressible parts are born. Thus, spontaneous expulsion is the exception, and vaginal delivery typically requires skilled provider participation for the fetus to navigate the birth canal. Noteworthy clinical pearls are provided by Yeomans (2017) in the third edition of *Cunningham and Gilstrap's Operative Obstetrics*.

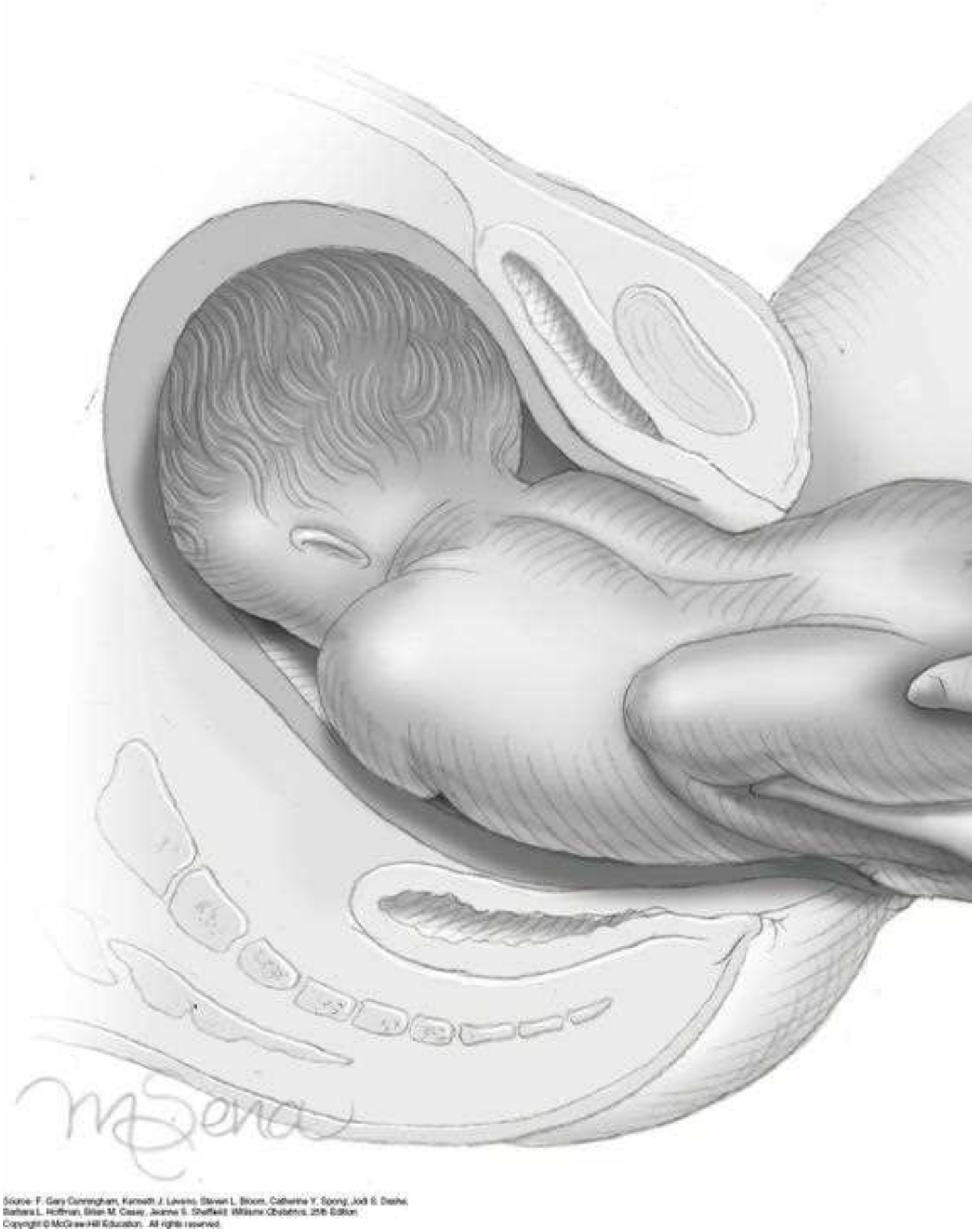
First, with all breech deliveries, unless the perineum is considerably lax, an episiotomy is made and is an important adjunct to delivery. As discussed in Chapter 27 (Episiotomy), mediolateral episiotomy may be preferred for its lower associated risk of anal sphincter lacerations. Ideally, the breech is allowed to deliver spontaneously to the umbilicus. Delivery of the breech draws the umbilicus and attached cord into the pelvis. Therefore, once the breech has passed beyond the vaginal introitus, the abdomen, thorax, arms, and head must be delivered promptly either spontaneously or assisted.

The posterior hip will deliver, usually from the 6 o'clock position, and often with sufficient pressure to evoke passage of thick meconium (see Fig. 28-4). The anterior hip then delivers, followed by external rotation to a sacrum anterior position. The mother is encouraged to continue to push as the fetus descends until the legs are accessible. The legs are sequentially delivered by splinting the femur with the operator's fingers positioned parallel to the long axis of the femur, and by exerting pressure upward and laterally to sweep each leg away from the midline (Fig. 28-5).

FIGURE 28-4
The hips of the frank breech are delivering over the perineum. The anterior hip usually delivers first.

FIGURE 28-5
To deliver the left leg, two fingers of the provider's left hand are placed beneath and parallel to the femur. The thigh is then slightly abducted and pressure from the fingertips in the popliteal fossa should induce knee flexion and bring the foot within reach. The foot is then grasped to gently deliver the entire leg outside the vagina.

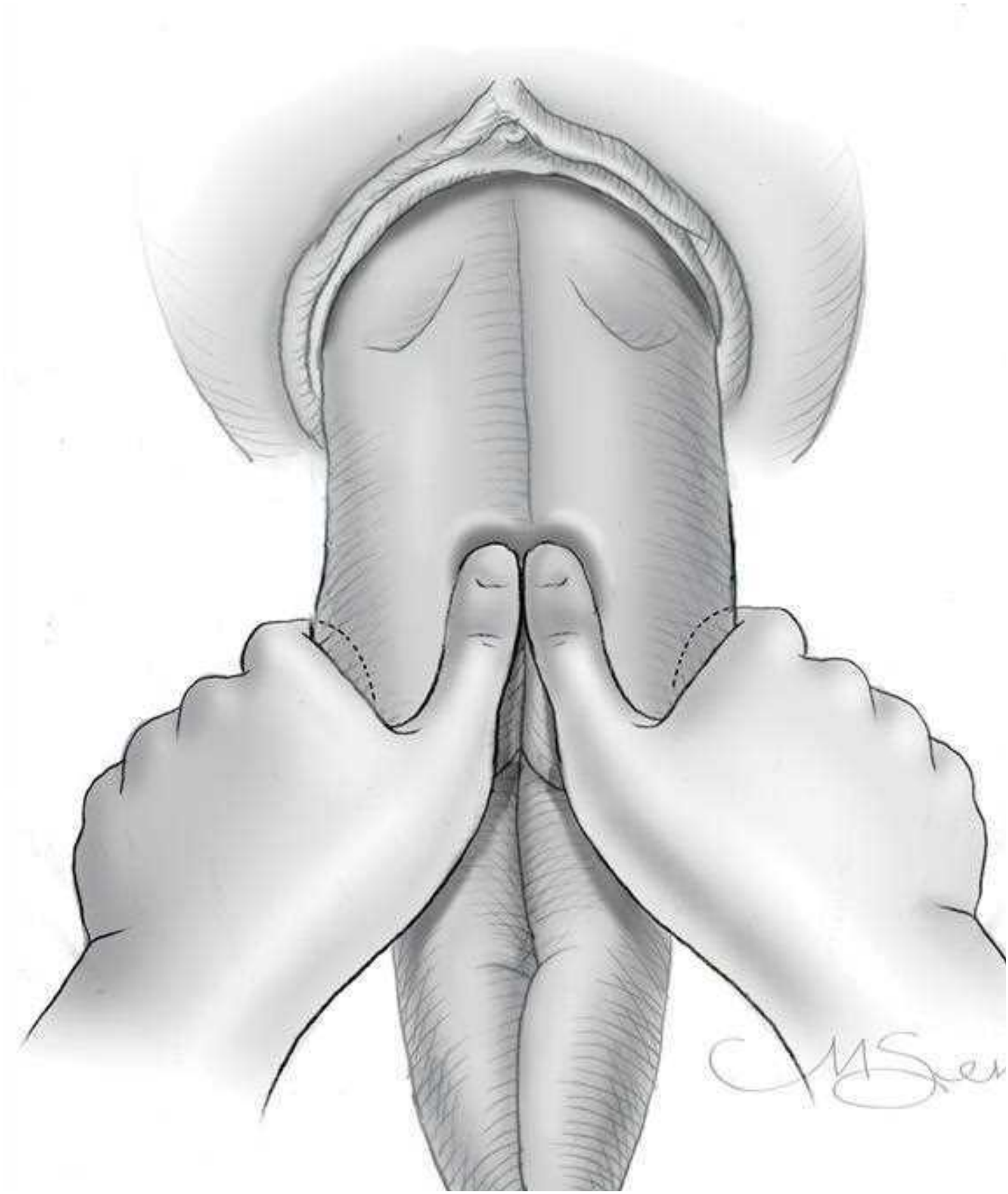
A similar procedure is followed on the right. (Figures 28-5 though 28-8: Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Following delivery of the legs, the fetal bony pelvis is grasped with both hands. The fingers should rest on the anterior superior iliac crests and the thumbs on the sacrum. This minimizes the chance of fetal abdominal soft-tissue injury (Fig. 28-6). Maternal expulsive efforts are again used in conjunction with downward traction to affect delivery.

FIGURE 28-6

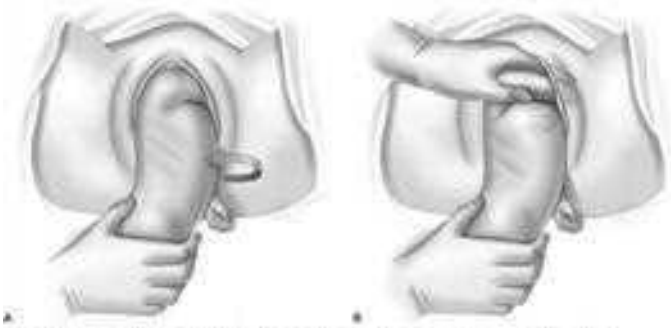
To deliver the body, thumbs are placed over the sacrum, and each index finger wraps over the top of the corresponding fetal iliac crest. Gentle downward traction is applied until the scapulas are clearly visible.



A cardinal rule in successful breech extraction is to employ steady, gentle, downward traction until the lower halves of the scapulas are delivered, making no attempt at delivery of the shoulders and arms until one axilla becomes visible. It makes little difference which shoulder is delivered first, and two methods are suitable for their delivery. In the first method, with the scapulas visible, the trunk is rotated either clockwise or counterclockwise to bring the anterior shoulder and arm into view (Fig. 28-7). During delivery of the arm, fingers and hand are aligned parallel to the humerus and act to splint and prevent humeral fracture. The body of the fetus is then rotated 180 degrees in the reverse direction to bring the other shoulder and arm into position for delivery.

FIGURE 28-7

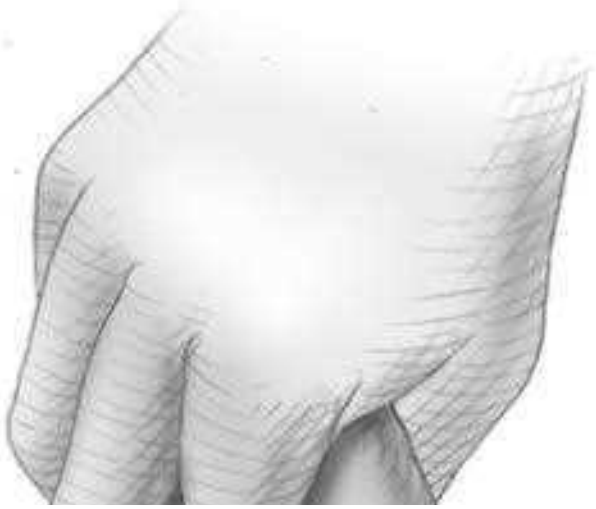
A. After delivery of the first arm, 180-degree rotation of the fetal body brings the sacrum to a right sacrum transverse (RST) position. **B.** Fingers of the provider's hand extended over the right shoulder and parallel to the humerus. These sweep the arm downward across the chest and out.

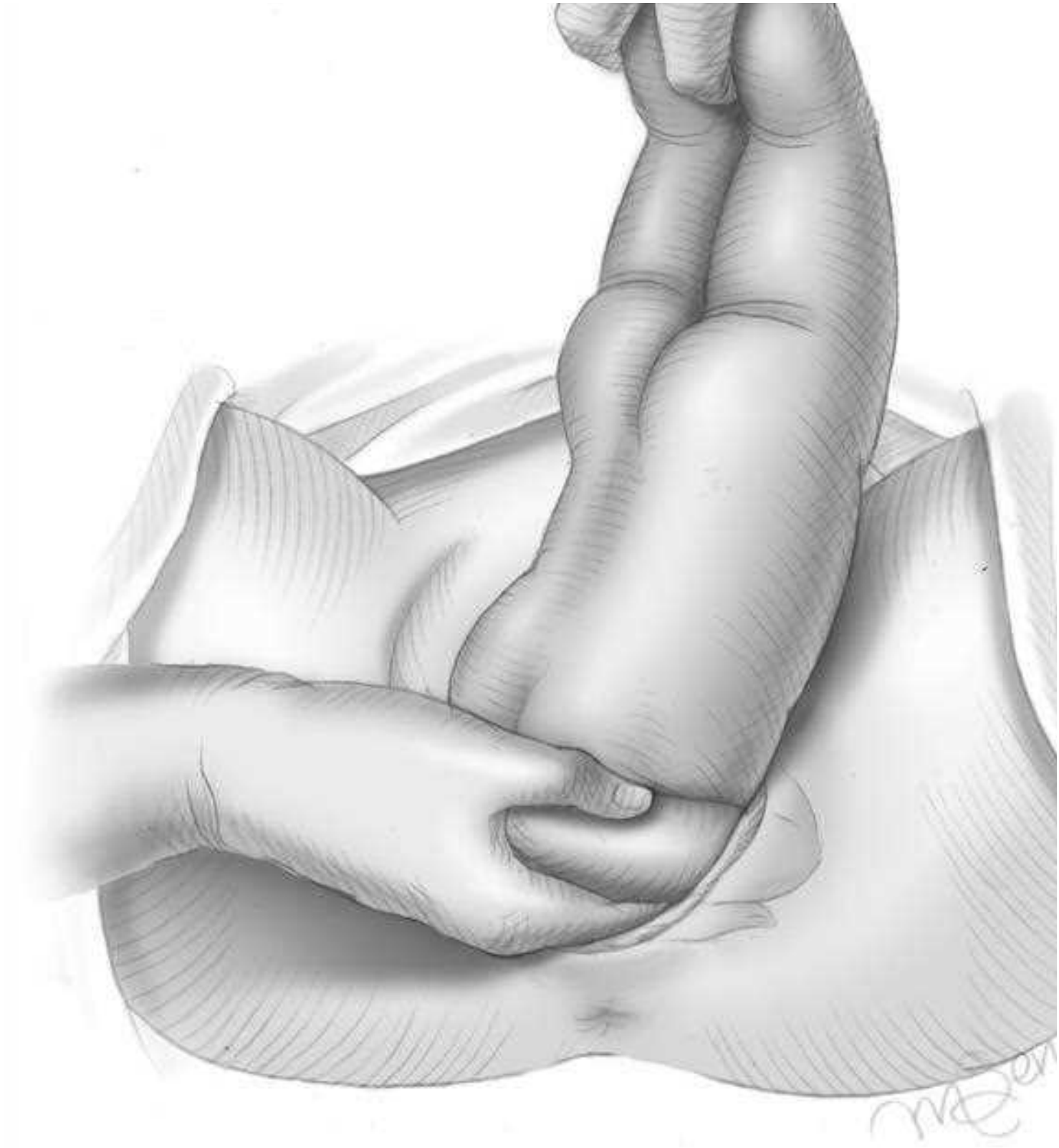


The second method is employed if trunk rotation is unsuccessful. With this maneuver, the posterior shoulder is delivered first. For this, the feet are grasped in one hand and drawn upward over the inner thigh of the mother (Fig. 28-8). The hand enters over the shoulder, fingers are aligned parallel to the long axis of the humerus, and the fetal arm is swept upward. The posterior shoulder slides out over the perineal margin and is usually followed by the arm and hand. Then, by depressing the body of the fetus, the anterior shoulder emerges beneath the pubic arch, and the arm and hand usually follow spontaneously. After both shoulders are delivered, the back of the fetus tends to rotate spontaneously to the symphysis. Delivery of the head may then be accomplished.

FIGURE 28-8

Infrequently, the posterior arm must be delivered first. For this, the lower half of the fetal body is raised up and over the maternal groin. The provider's fingers are inserted under the posterior shoulder and aligned with the humerus.



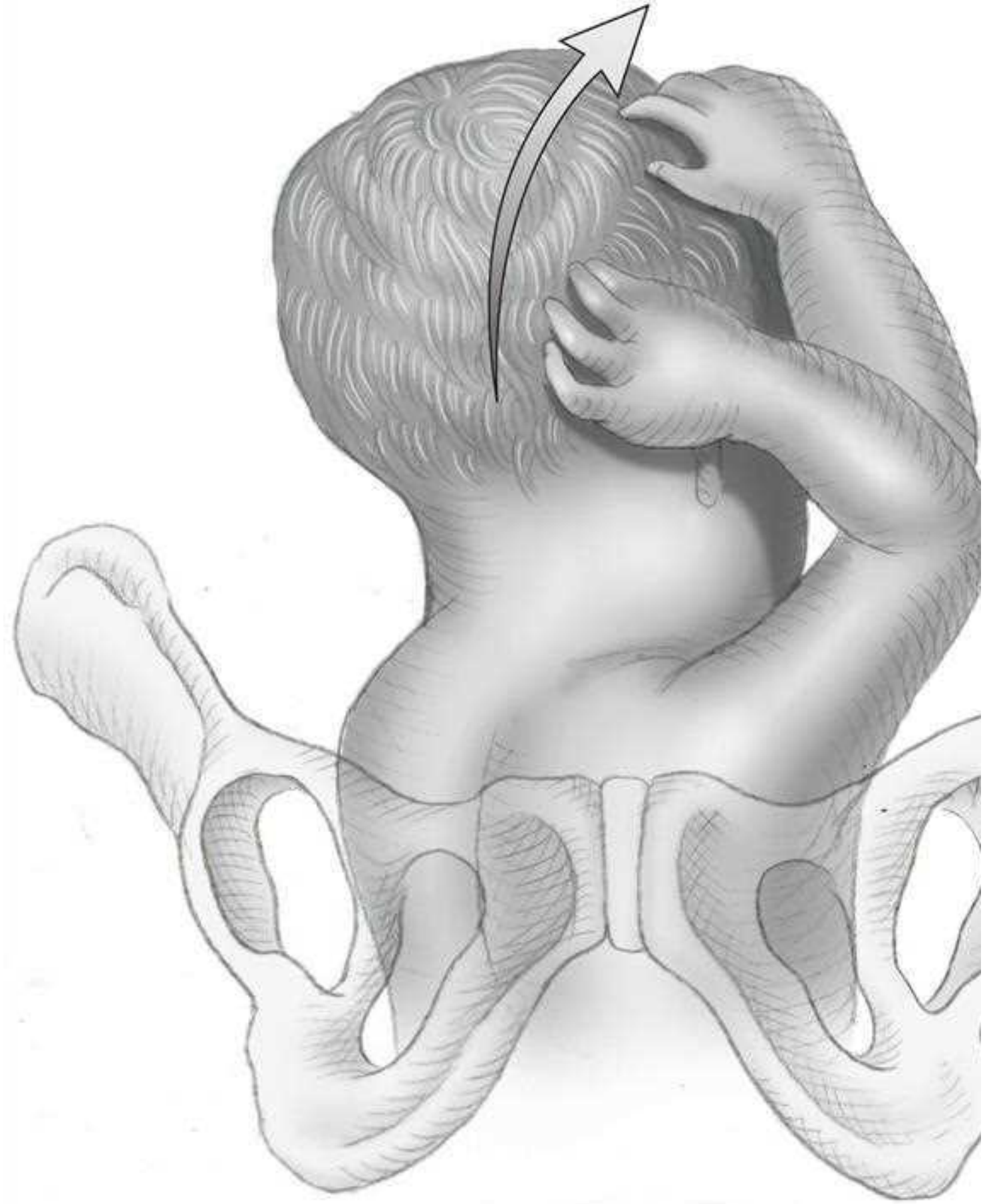


Nuchal Arm

During delivery, one or both fetal arms occasionally may lie across the back of the neck and become impacted at the pelvic inlet. With such a nuchal arm, delivery is more difficult and can be aided by rotating the fetus through a half circle in such a direction that the friction exerted by the birth canal will draw the elbow toward the face (Fig. 28-9). With a right nuchal arm, the body should be rotated counterclockwise, which rotates the fetal back toward the maternal right. With a left nuchal arm, the rotation is clockwise. If rotation fails to free the nuchal arm, it may be necessary to push the fetus upward to a roomier part of the pelvis. If the rotation is still unsuccessful, the nuchal arm often is extracted by hooking a finger(s) over it and forcing the arm over the shoulder, and down the ventral surface for delivery of the arm. In this event, fracture of the humerus or clavicle is common.

FIGURE 28-9

Reduction of a right nuchal arm is accomplished by rotating the fetal body 180 degrees counterclockwise, which directs the fetal back to the maternal right. Friction exerted by the birth canal will draw the elbow toward the face. (Reproduced with permission from Yeomans ER: Vaginal breech delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Delivery of the Aftercoming Head

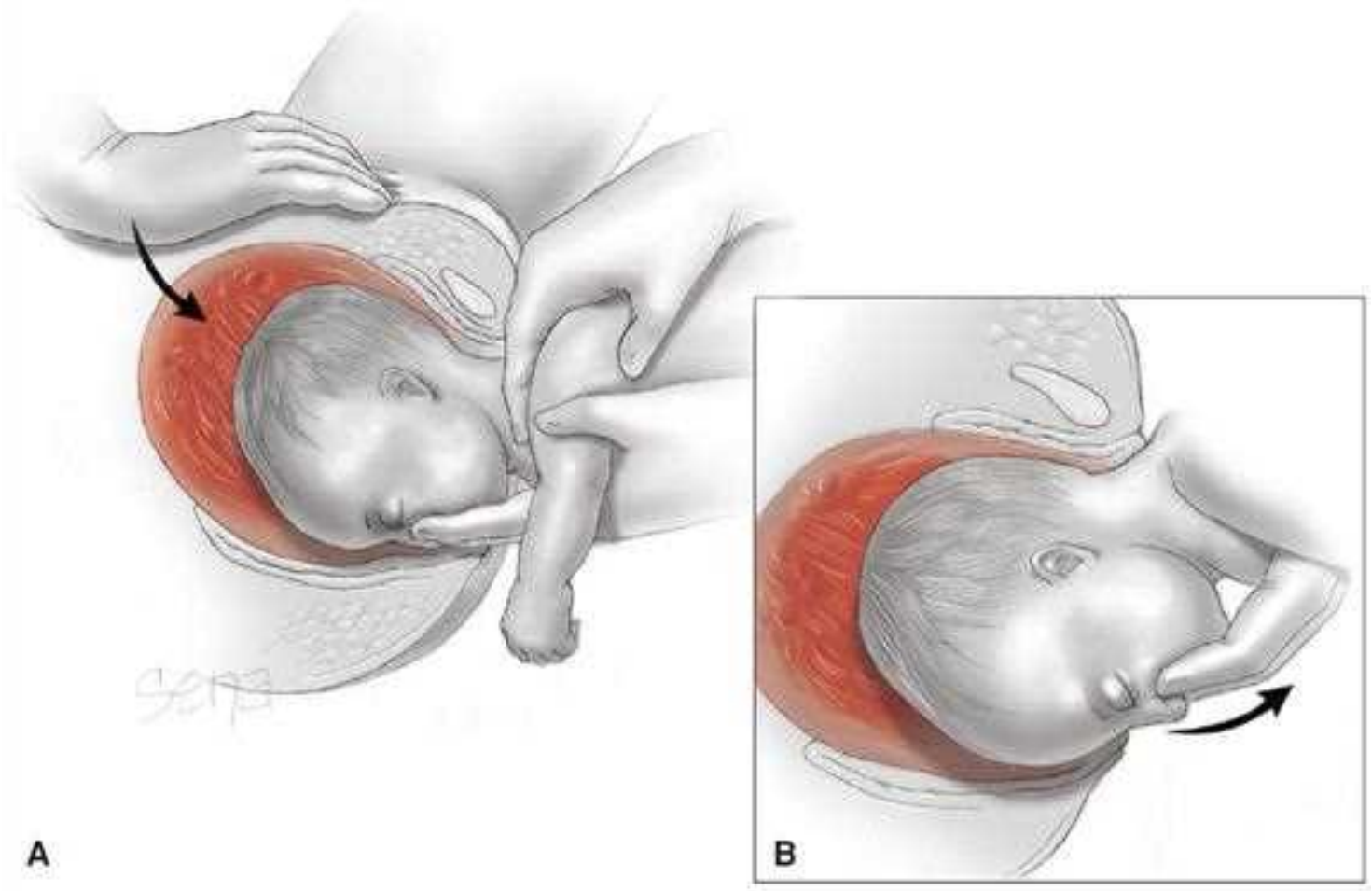
Mauriceau Maneuver

The fetal head is normally extracted with forceps or by one of several maneuvers. With any of these techniques, hyperextension of the fetal neck is avoided.

With the Mauriceau maneuver, the index and middle finger of one hand are applied over the maxilla, to flex the head, while the fetal body rests on the palm of the same hand and forearm (Fig. 28-10). Fetal legs straddle the forearm. Two fingers of the other hand then are hooked over the fetal neck and grasp the shoulders. Downward traction is concurrently applied until the suboccipital region appears under the symphysis. Gentle suprapubic pressure simultaneously applied by an assistant helps keep the head flexed. The body then is slightly elevated toward the maternal abdomen, and the mouth, nose, brow, and eventually the occiput emerge successively over the perineum. With this maneuver, the provider uses both hands simultaneously to exert continuous downward gentle traction while balancing forces between the fetal neck and maxilla to avoid neck hyperextension.

FIGURE 28-10

A. Delivery of the aftercoming head using the Mauriceau maneuver. Note that as the fetal head is being delivered, flexion of the head is maintained by suprapubic pressure provided by an assistant. **B.** Pressure on the maxilla is applied simultaneously by the operator as upward and outward traction is exerted.

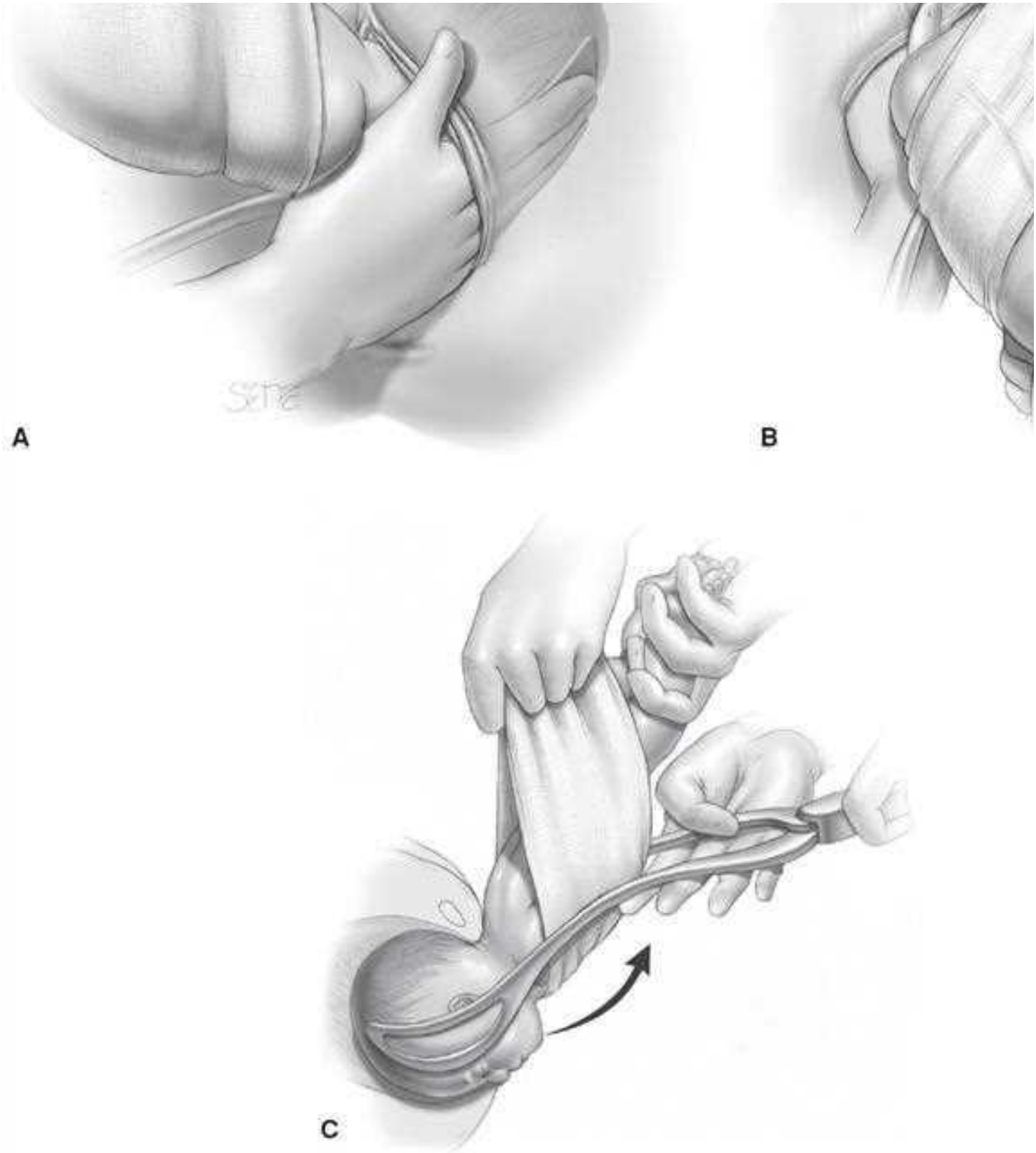


Forceps

Specialized forceps can be used to deliver the aftercoming head. Piper forceps, shown in Figure 28-11, or Laufe-Piper forceps may be applied electively or when the Mauriceau maneuver cannot be accomplished easily. The blades of the forceps are not applied to the aftercoming head until it has been brought into the pelvis by gentle traction, combined with suprapubic pressure, and is engaged. Suspension of the body of the fetus in a towel effectively holds the fetus up and helps keep the arms and cord out of the way as the forceps blades are applied.

FIGURE 28-11

Piper forceps for delivery of the aftercoming head. **A.** The fetal body is held elevated using a warm towel and the left blade of forceps is applied to the aftercoming head. **B.** The right blade is applied with the body still elevated. **C.** Forceps delivery of the aftercoming head. Note the direction of movement shown by the arrow.



Because the forceps blades are directed upward from the level of the perineum, some choose to apply them from a one-knee kneeling position. Piper forceps have a downward arch in the shank to accommodate the fetal body and lack a pelvic curve. This shape permits direct application of the cephalic curve of the blade along the length of the maternal vagina and fetal parietal bone. The blade to be placed on the maternal left is held in the provider's left hand. The right hand slides between the fetal head and left maternal vaginal sidewall to guide the blade inward and around the parietal bone. The opposite blade mirrors this application.

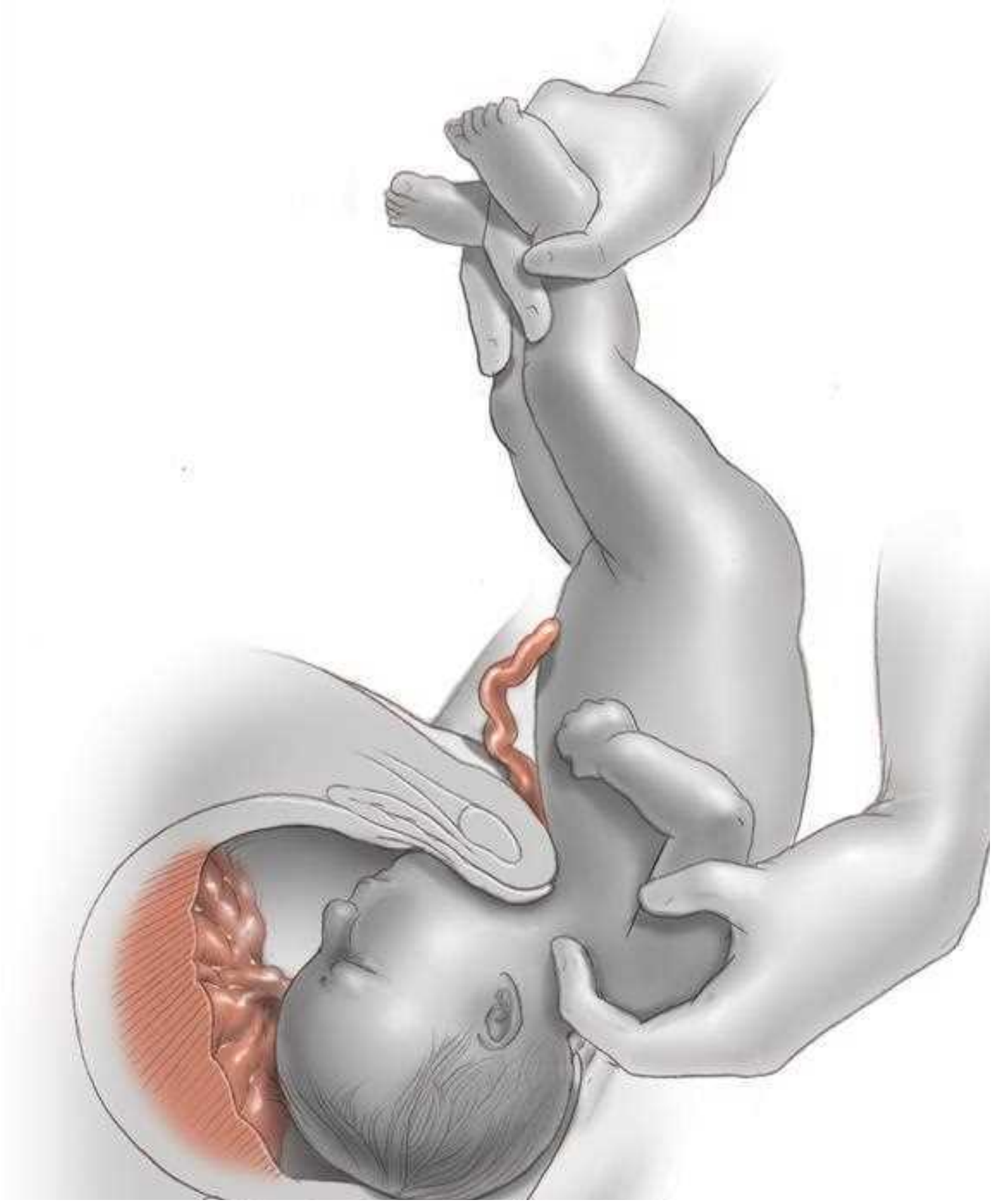
Once in place, the blades are articulated, and the fetal body rests across the shanks. The head is delivered by pulling gently outward and slightly raising the handle simultaneously. This rolls the face over the perineum, while the occiput remains beneath the symphysis until after the brow delivers. Ideally, the head and body move in unison to minimize neck hyperextension.

Modified Prague Maneuver

Rarely, the back of the fetus fails to rotate to the symphysis. The fetus still may be delivered using the modified Prague maneuver. With this, two fingers of one hand grasp the shoulders of the back-down fetus from below while the other hand draws the feet up and over the maternal abdomen (Fig. 28-12).

FIGURE 28-12

Delivery of the aftercoming head using the modified Prague maneuver necessitated by failure of the fetal trunk to rotate anteriorly.

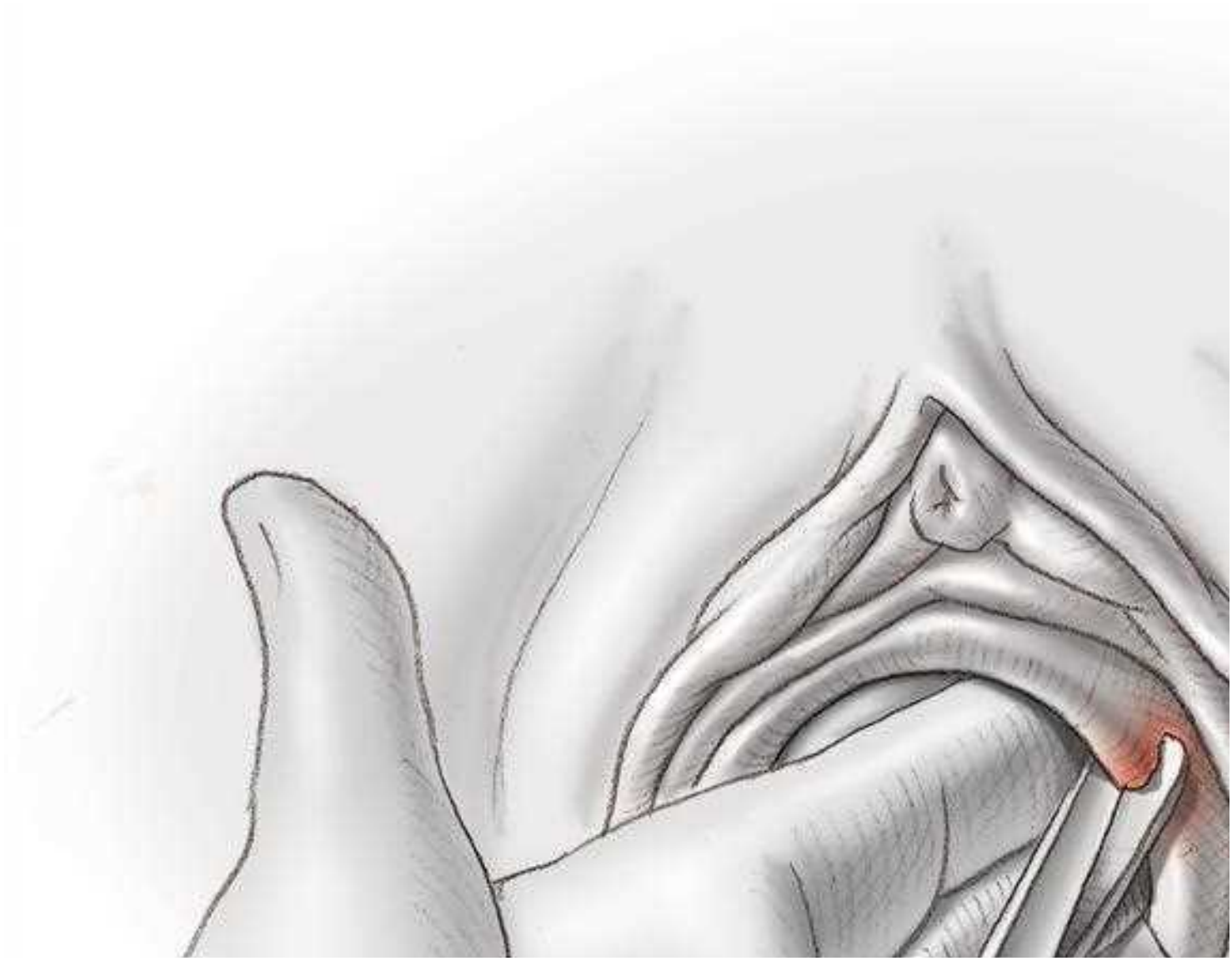


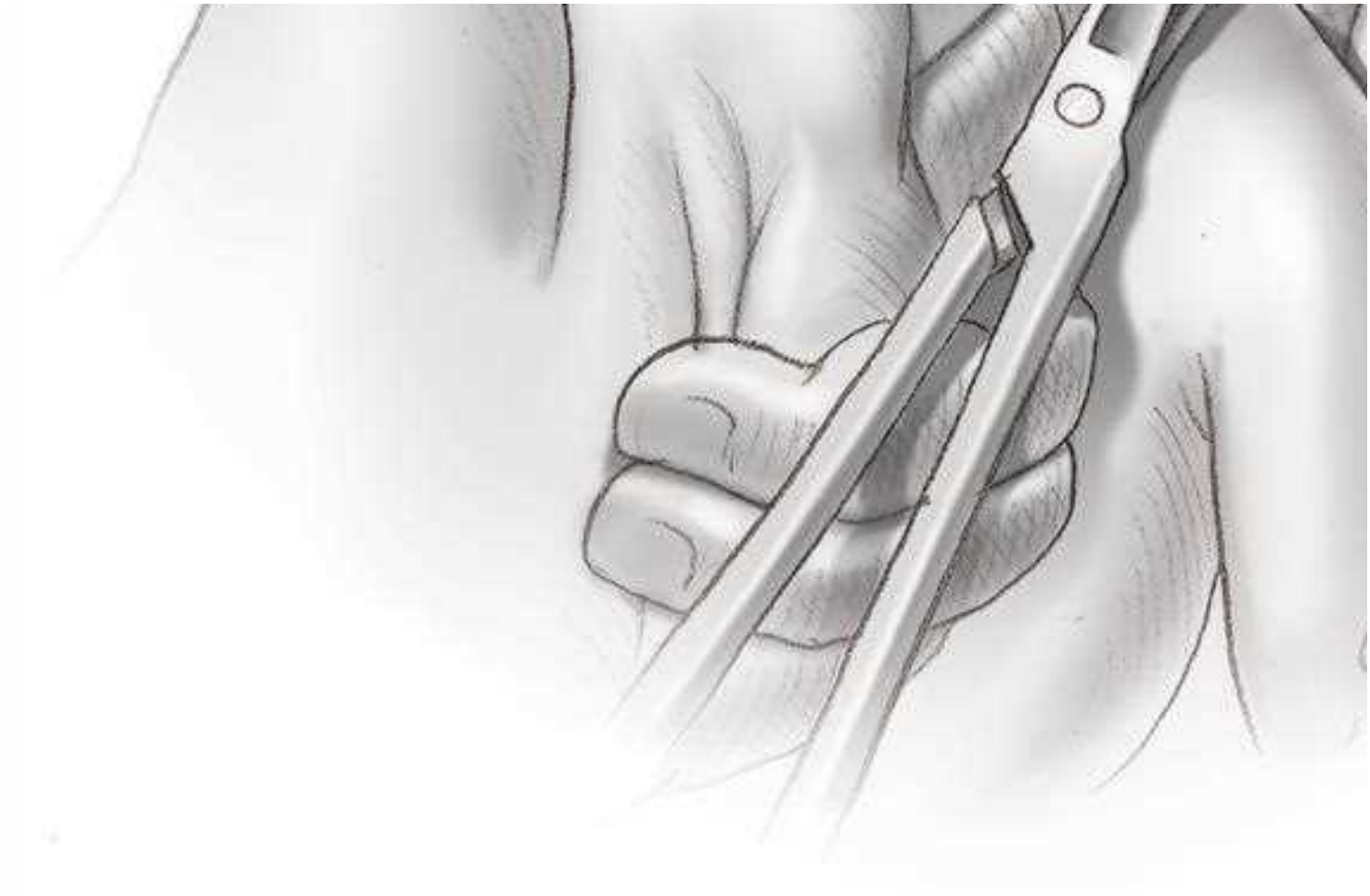
Head Entrapment

This emergency reflects either an incompletely dilated cervix or cephalopelvic disproportion. First, especially with a small preterm fetus, an incompletely dilated cervix can constrict around the neck and impede delivery of the aftercoming head. At this point, significant cord compression must be assumed, and time management is essential. With gentle traction on the fetal body, the cervix, at times, may be manually slipped over the occiput. If unsuccessful, then Dührssen incisions may be necessary (Fig. 28-13). General anesthesia with halogenated agents or intravenous nitroglycerin is another option to aid lower uterine segment relaxation. As an extreme measure, replacement of the fetus higher into the vagina and uterus, followed by cesarean delivery, can rescue an entrapped breech fetus. This *Zavanelli maneuver* is classically performed to relieve intractable shoulder dystocia (Sandberg, 1988). However, case reports also have described its use for an entrapped aftercoming head (Sandberg, 1999; Steyn, 1994).

FIGURE 28-13

Dührssen incision being cut at 2 o'clock, which is followed by a second incision at 10 o'clock. Infrequently, an additional incision is required at 6 o'clock. The incisions are so placed as to minimize bleeding from the laterally located cervical branches of the uterine artery. After delivery, the incisions are repaired as described in Chapter 41 (Injuries to the Birth Canal).





In cases with cephalopelvic disproportion and arrest of aftercoming head, the Zavanelli maneuver or symphysiotomy are options (Sunday-Adeoye, 2004; Wery, 2013). Using local analgesia, symphysiotomy surgically divides the intervening symphyseal cartilage and much of its ligamentous support to widen the symphysis pubis up to 2.5 cm (Basak, 2011). Lack of provider training and potentially serious maternal pelvic or urinary tract injury explain its rare use in the United States. That said, if cesarean delivery is not possible, symphysiotomy may be lifesaving for both mother and baby (Hofmeyr, 2012).

Total Breech Extraction

Complete or Incomplete Breech

At times, total extraction of a complete or incomplete breech may be required. A hand is introduced through the vagina, and both fetal feet are grasped. The ankles are held with the middle finger lying between them. With gentle traction, the feet are brought through the introitus (Fig. 28-14). As the legs begin to emerge through the vulva, downward gentle traction is continued. As the legs emerge, successively higher portions are grasped, first the calves and then the thighs. When the breech appears at the vaginal outlet, gentle traction is applied until the hips are delivered. The thumbs are then placed over the sacrum and the fingers over the iliac crests. Breech extraction is then completed, as described for partial breech extraction (Partial Breech Extraction).

FIGURE 28-14
Complete breech extraction begins with traction on the feet and ankles.

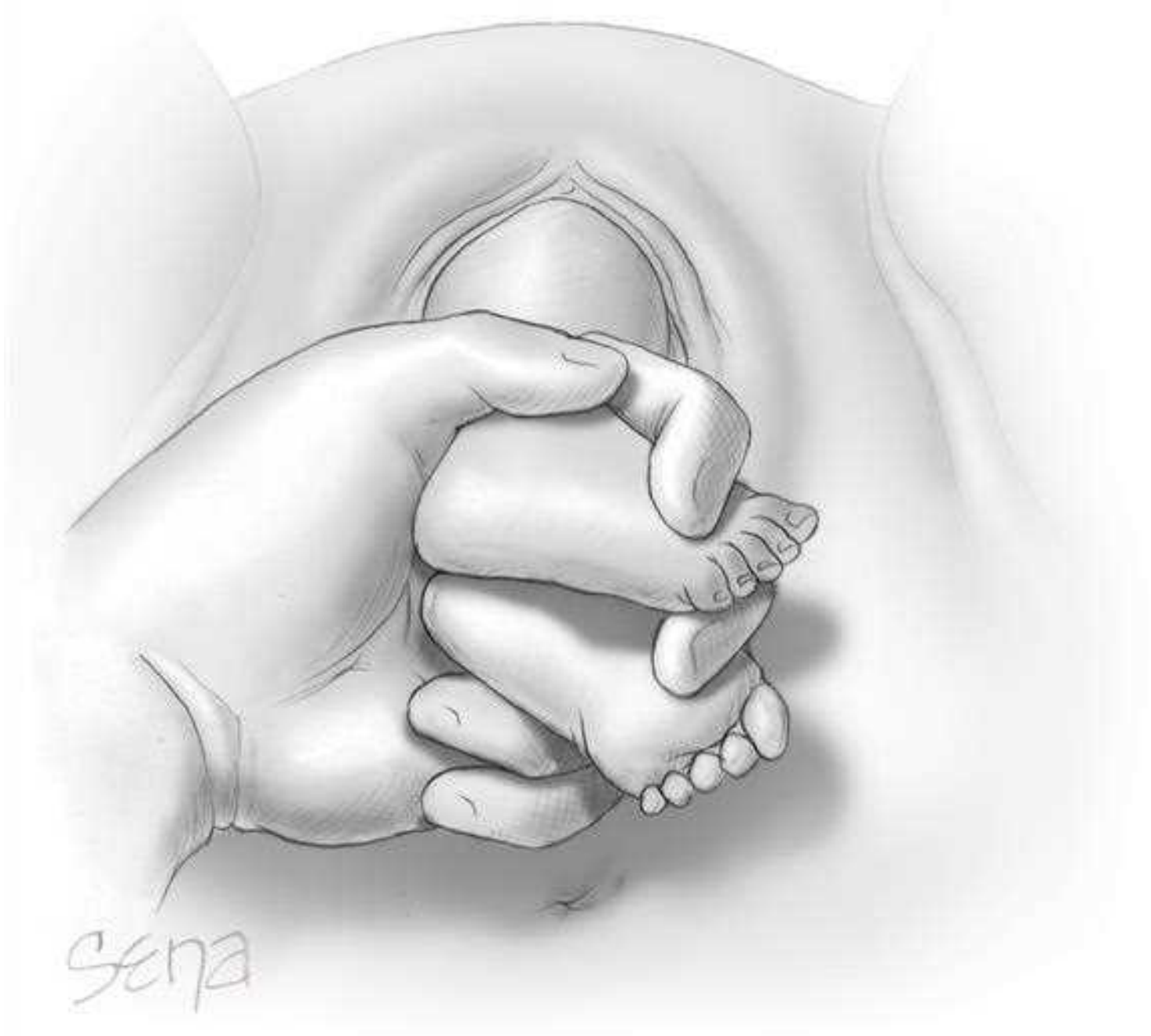
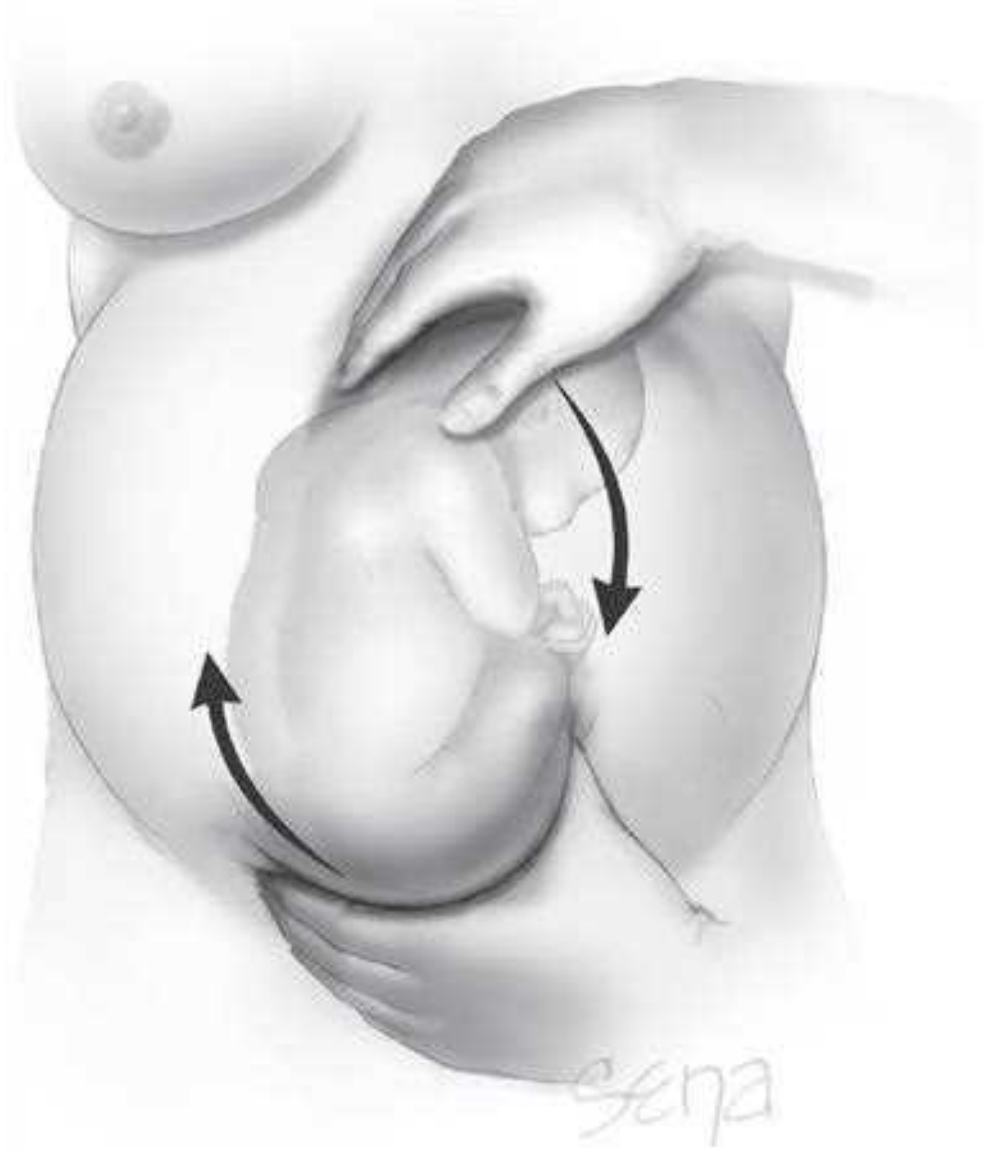


FIGURE 28-15

External cephalic version. With an attempted forward roll, clockwise pressure is exerted against the fetal poles.



If only one foot can be grasped, it can be brought down into the vagina and held with the appropriate hand, right hand for right foot and left hand for left foot (Yeomans, 2017). With the first foot secure, the opposite hand is introduced, passed upward along the leg, and guided to locate the other foot. If the remaining hip is extended, the second foot is usually easily grasped and brought down. If the hip is flexed and knee extended, a finger is hooked into that groin, and traction will bring the lower half of the fetus down until the leg can be reached. For cesarean delivery, these total breech extraction maneuvers can be used to deliver a complete, incomplete, or footling breech through the hysterotomy incision.

Frank Breech

During complete extraction of a frank breech, moderate traction is exerted by a finger in each groin and aided by a generous episiotomy. Once the breech is pulled through the introitus, the steps described for partial breech extraction are then completed (Partial Breech Extraction). These maneuvers are also used during cesarean delivery of a frank breech through a hysterotomy incision.

Rarely during vaginal delivery, a frank breech will require decomposition inside the uterine cavity. Attributed to Pinard (1889), this procedure converts a frank breech into a footling breech. It is accomplished more readily if the membranes have ruptured only recently. It becomes extremely difficult if amnionic fluid is scant and the uterus is tightly contracted around the fetus. Pharmacological relaxation by general anesthesia or intravenous magnesium sulfate, nitroglycerin, or a betamimetic agent may be required. To begin, two fingers are carried up along one leg to externally rotate the hip by pressing on the medial side of the thigh parallel to the femur. Simultaneously, pressure in the popliteal fossa should prompt spontaneous knee flexion, which brings the corresponding foot into contact with the back of the provider's hand. The fetal foot then may be grasped and brought down.

EXTERNAL CEPHALIC VERSION

With *version*, fetal presentation is altered by physically substituting one pole of a longitudinal presentation for the other, or converting an oblique or transverse lie into a longitudinal presentation. Manipulations performed through the abdominal wall that yield a cephalic presentation are termed *external cephalic version*.

Manipulations accomplished inside the uterine cavity that yield a breech presentation are designated *internal podalic version*. This latter procedure is reserved for delivery of a second twin and described in Chapter 45 (Vaginal Birth after Cesarean Delivery).

Indications

External cephalic version (ECV) reduces the rate of noncephalic presentation at birth (Hofmeyr, 2015b). For breech fetuses near term, the American College of Obstetricians and Gynecologists (2016a,b) recommends that version be offered and attempted whenever possible. Its success rate averages about 60 percent (de Hundt, 2014). For women with a transverse lie, the overall success rate is significantly higher.

In general, ECV is attempted before labor in a woman who has reached 37 weeks' gestation. Before this time, breech presentation still has a high likelihood of correcting spontaneously. And, if ECV is performed too early, time may allow a reversion back to breech (Bogner, 2012). Last, if attempts at version cause a need for immediate delivery, complications of iatrogenic late-preterm delivery generally are not severe.

Absolute contraindications to external version are few. It is contraindicated if vaginal delivery is not an option, such as with placenta previa. Another is multifetal gestation. Relative contraindications are early labor, oligohydramnios or rupture of membranes, known nuchal cord, structural uterine abnormalities, fetal-growth restriction, and prior abruption or its risks (Rosman, 2013). While many consider a prior cesarean delivery a contraindication, a few small studies found ECV was not associated with uterine rupture (Burgos, 2014; Keepanasseril, 2017; Weill, 2017). At Parkland Hospital, we do not attempt version in these women. More data from clinical studies are needed.

Several factors can improve the chances of a successful attempt. These include multiparity, unengaged presenting part, nonanterior placenta, nonobese patient, and abundant amnionic fluid (Kok, 2009, 2011; Velzel, 2015). To augment the last parameter, Burgos and coworkers (2014) administered a preprocedural 2-L intravenous fluid bolus. While this improved amnionic fluid volume, it did not increase version success rates.

Complications

Patient counseling includes a discussion regarding small but real risks for placental abruption, preterm labor, and fetal compromise. Rarely, uterine rupture, fetomaternal hemorrhage, alloimmunization, amnionic fluid embolism, and even death may also complicate attempts at external version. That said, fetal deaths are rare, serious complication rates are typically very low, and emergent cesarean rates are 0.5 percent or less (Grootscholten, 2008; Rodgers, 2017). And even after successful ECV, several reports suggest that the cesarean delivery rate does not completely revert to the baseline for vertex presentations. Specifically, dystocia, malpresentation, and nonreassuring fetal heart patterns may be more common in these fetuses completing successful version (Chan, 2004; de Hundt, 2014; Vézina, 2004).

Technique

ECV should be carried out in an area that has ready access to a facility equipped to perform emergency cesarean delivery (American College of Obstetricians and Gynecologists, 2016a). Because of the risk for surgical intervention, intravenous access is obtained, and patients abstain from eating for 6 or more hours. Sonographic examination is performed to confirm nonvertex presentation, document amnionic fluid volume adequacy, exclude obvious fetal anomalies if not done previously, and identify placental location and fetal spine orientation. Preprocedural external monitoring is performed to assess fetal heart rate reactivity. Anti-D immune globulin is given to Rh-D negative women. Tocolysis and regional analgesia may be elected, and rationale for these is provided in subsequent sections.

The woman is placed in left lateral tilt to aid uteroplacental perfusion, and Trendelenburg positioning helps during elevation of the breech. During the procedure, we prefer to monitor fetal heart motion sonographically. An abundant abdominal coating of ultrasound gel permits this and also minimizes painful skin friction (Vallikkannu, 2014).

A forward roll of the fetus usually is attempted first. One or two providers may participate, and one hand grasps the head. The fetal buttocks are then elevated from the maternal pelvis and displaced laterally (Fig. 28-15). The buttocks are then gently guided toward the fundus, while the head is simultaneously directed toward the pelvis. If the forward roll is unsuccessful, a backward flip is attempted. ECV attempts are discontinued for excessive discomfort, persistently abnormal fetal heart rate, or after multiple failed attempts. Failure is not always absolute. Ben-Meir and colleagues (2007) reported a spontaneous version rate of 7 percent among 226 failed versions—2 percent among nulliparas and 13 percent among multiparas.

If ECV is successful, a nonstress test is repeated until a normal test result is obtained. If version is completed before 39 weeks' gestation, then awaiting spontaneous labor and fetal maturity is preferred. In some studies, immediate labor induction is linked to higher cesarean delivery rates (Burgos, 2015; Kuppens, 2013).

Tocolysis

To relax the uterus prior to an ECV attempt, existing evidence supports the use of tocolysis (American College of Obstetricians and Gynecologists, 2016a). Most data support the use of the beta-mimetics terbutaline and ritodrine (Cluver, 2015). In one such trial, Fernandez and coworkers (1996) reported that the success rate with subcutaneous terbutaline—52 percent—was significantly higher than without—27 percent. Our policy at Parkland Hospital is to administer 250 µg of terbutaline subcutaneously to most women before attempted ECV. When maternal tachycardia—a known side effect of terbutaline—is noted, the attempt is begun. Data are limited and, in some cases nonsupportive, for alternate agents that include calcium-channel blockers, such as nifedipine; nitric oxide donors, such as nitroglycerin; the oxytocin-receptor antagonist atosiban; and another betamimetic salbutamol (Burgos, 2010; Hilton, 2009; Kok, 2008; Vani, 2009; Velzel, 2017; Wilcox, 2011).

Conduction Analgesia

Epidural analgesia coupled with tocolysis has been reported to increase version success rates compared with tocolysis alone (Goetzinger, 2011; Magro-Malosso, 2016). Moreover, rates of complications that include fetal heart rate aberrations, emergency cesarean delivery, or placental abruption were not greater with regional analgesia. Of randomized trials, spinal and epidural have both shown success (Khaw, 2015; Weiniger, 2010). Currently, the superior technique and best drugs to administer are unclear. In contrast, from limited data, intravenous sedation does not appear to improve success rates (Burgos, 2016; Khaw, 2015).

Moxibustion

This is a traditional Chinese medicine technique that burns a cigarette-shaped stick of ground *Artemisia vulgaris*—which is also known as mugwort or in Japanese as *moxa.* At the BL 67 acupuncture point, the stick is directly placed against the skin or indirectly heats an acupuncture needle at the site to increase fetal movement and promote spontaneous breech version (Ewies, 2002). It is performed usually between 33 and 36 weeks' gestation to permit a trial of ECV if not successful. Results from randomized controlled studies are conflicting (Bue, 2016; Coulon, 2014; Coyle, 2012; Sananes, 2016; Vas, 2013).

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CHAPTER 29: Operative Vaginal Delivery

The most important function of forceps is traction exercised for the purpose of drawing the head through the genital tract. In not a few cases, however, particularly in occipito-posterior presentations, its employment as a rotator is attended by most happy results.

—J. Whitridge Williams (1903)

INTRODUCTION

Operative deliveries are vaginal deliveries accomplished with the use of forceps or a vacuum device. Once either is applied to the fetal head, outward traction generates forces that augment maternal pushing to deliver the fetus vaginally. The most important function of both devices is traction. In addition, forceps may also be used for rotation, particularly from occiput transverse and posterior positions.

According to the birth certificate data from the National Vital Statistics Report, forceps- or vacuum-assisted vaginal delivery was used for 3.2 percent of births in the United States in 2014. This is a decline from 9.0 percent in 1990 (Hamilton, 2015). For these deliveries, a vacuum is disproportionately selected, and the vacuum-to-forceps delivery ratio is nearly 5:1 (Merriam, 2017). In general, most of these attempts are successful. In 2006, only 0.4 percent of forceps trials in the United States and 0.8 percent of vacuum extraction attempts failed to result in vaginal delivery (Osterman, 2009).

INDICATIONS

If it is technically feasible and can be safely accomplished, termination of second-stage labor by traction instruments is indicated in any condition threatening the mother or fetus that is likely to be relieved by delivery. Some fetal indications include nonreassuring fetal heart rate pattern and premature placental separation (Schuit, 2012). In the past, forceps delivery was believed to be somewhat protective of the fragile preterm infant head. However, outcomes for neonates who weigh 500 to 1500 g do not significantly differ if delivered spontaneously or by outlet forceps (Fairweather, 1981; Schwartz, 1983).

Some maternal indications include heart disease, pulmonary compromise, intrapartum infection, and certain neurological conditions. The most common are exhaustion and prolonged second-stage labor. However, a specific maximum length beyond which all women should be considered for operative vaginal delivery has not been identified (American College of Obstetricians and Gynecologists, 2016).

Operative delivery is generally performed from either a low or outlet station. Additionally, forceps or vacuum delivery should not be used *electively* until the criteria for an outlet delivery have been met. In these circumstances, operative delivery is a simple and safe operation, although with some risk of maternal lower reproductive tract injury (Yancey, 1999).

CLASSIFICATION AND PREREQUISITES

Classification for operative vaginal delivery is summarized in Table 29-1. It emphasizes that the two most important discriminators of risk for both mother and neonate are station and rotation. Station is measured in centimeters, –5 to 0 to +5. Zero station reflects a line drawn between the ischial spines. Deliveries are categorized as outlet, low, and midpelvic procedures. *High forceps, in which instruments are applied above 0 station, have no place in contemporary obstetrics.*

TABLE 29-1

Operative Vaginal Delivery Prerequisites and Classification According to Station and Rotation[a]

Procedure	**Criteria**	
Outlet forceps	Scalp is visible at the introitus without separating the labia Fetal skull has reached pelvic floor Fetal head is at or on perineum Head is OA or OP ***or*** Head is right or left OA or OP position but rotation ≤45 degrees	
Low forceps (2 types)	Leading point of fetal skull is at station ≥+2 cm, and not on the pelvic floor, and: (a) Rotation is ≤45 degrees, ***or*** (b) Rotation is >45 degrees	
Midforceps	Station is between 0 and +2 cm	
Prerequisites		
Engaged head	Experienced operator	No fetal coagulopathy
Vertex presentation[b,c]	Ruptured membranes	No fetal demineralization disorder
Known fetal head position	Completely dilated cervix	Willingness to abandon OVD
CPD not suspected	Adequate anesthesia	Informed consent completed
Fetal weight estimated	Emptied maternal bladder	

[a]Classification for the vacuum delivery system is the same as for forceps except that vacuum is used for traction but not rotation.

[b]Forceps, but not vacuum extractor, may be used for delivery of a face presentation with mentum anterior.

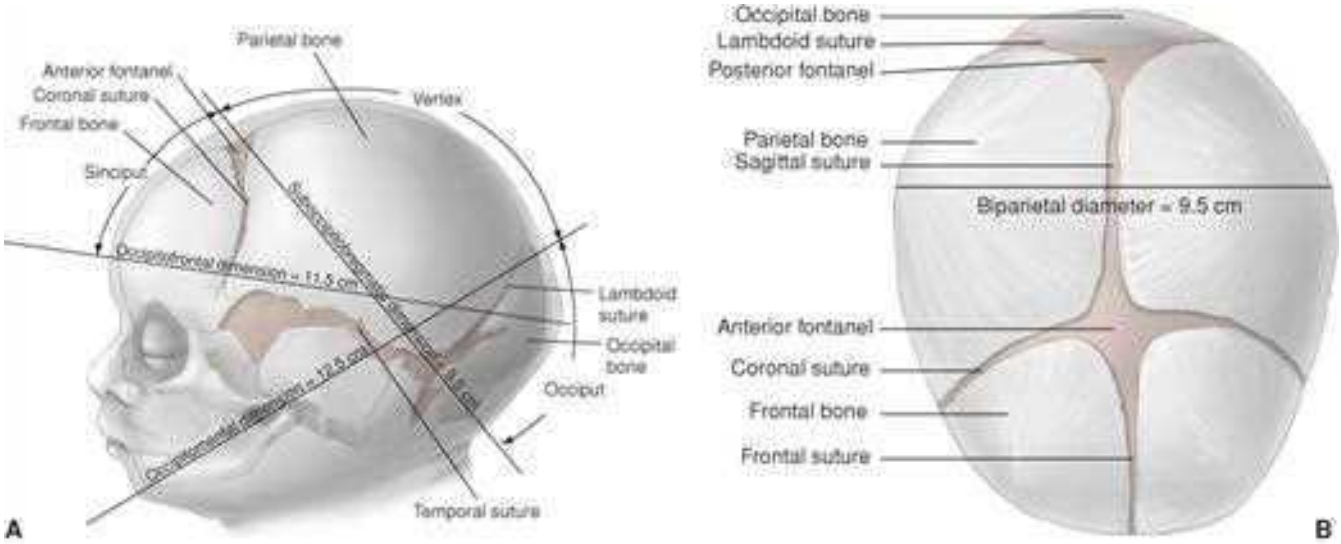
[c]Piper forceps may be used to deliver the head during breech delivery.

CPD = cephalopelvic disproportion; OA = occiput anterior; OP = occiput posterior; OVD = operative vaginal delivery.

Once station and rotation are assessed, several prerequisites are met and are listed in Table 29-1. For vacuum extraction, fetuses should also be at least 34 weeks' gestation, and although infrequently used in the United States, fetal scalp blood sampling should not have been recently performed. Of requisites, ascertaining correct head position is essential, and the anatomy of the fetal skull is described in Figure 29-1. In unclear cases, sonography is useful to identify fetal orbits and nasal bridge to aid orientation (Malvasi, 2014).

FIGURE 29-1

Fetal head (**A, B**) at term showing fontanels, sutures, and various dimensions.



Regional analgesia or general anesthesia is preferable for low forceps or midpelvic procedures, although pudendal blockade may prove adequate for outlet forceps. As discussed in Chapter 25 (Effects on Labor), regional analgesia during labor does not appear to increase the risk for operative delivery (Halpern, 2004; Marucci, 2007; Wassen, 2014).

The bladder is emptied to provide additional pelvic space and minimize bladder trauma. Urinary retention and bladder dysfunction are often short-term effects of forceps and vacuum deliveries (Mulder, 2012; Pifarotti, 2014). Notably, episiotomy and epidural analgesia, both common associates, are also identified risks for urinary retention. Symptoms are brief and typically resolve with 24 to 48 hours of passive Foley catheter bladder drainage.

MORBIDITY

There is an increased risk of certain morbidities for both mother and fetus when operative delivery is employed. In general, these are related to the ease with which the delivery is accomplished.

Maternal Morbidity

In general, a higher station and/or greater degrees of rotation increase the chance of maternal or fetal injury. Morbidity is most properly compared with morbidity from cesarean delivery, and not with that from spontaneous vaginal delivery. This is the most appropriate comparator because the alternative to indicated operative delivery is cesarean delivery. For example, postpartum wound or uterine infection is more frequent in women following cesarean compared with operative vaginal delivery (Bailit, 2016; Halscott, 2015). Moreover, in a study of more than 1 million births, Spiliopoulos and associates (2011) reported cesarean delivery, but not operative vaginal delivery, as a risk for peripartum hysterectomy.

Lacerations

The very conditions that lead to indications for operative delivery also increase the need for episiotomy and the likelihood of lacerations (de Leeuw, 2008). That said, forceps and vacuum deliveries are associated with higher rates of third- and fourth-degree lacerations as well as vaginal wall and cervical lacerations (Gurol-Urganci, 2013; Hirayama, 2012; Landy, 2011; Pergialiotis, 2014). These appear to occur more frequently with forceps compared with vacuum extraction, and especially if there is a midline episiotomy (Kudish, 2006; O'Mahony, 2010). Hagadorn-Freathy and coworkers (1991) reported a 13-percent rate of third- and fourth-degree episiotomy extensions and vaginal lacerations for outlet forceps, 22 percent for low forceps with less than 45-degree rotation, 44 percent for low forceps with more than 45-degree rotation, and 37 percent for midforceps deliveries.

In an effort to lower rates of third- and fourth-degree lacerations, and coincident with overall efforts to reduce routine episiotomy use, many advocate only indicated episiotomy with operative delivery. If episiotomy is required, a protective effect against these more extensive perineal lacerations may be afforded by mediolateral episiotomy (de Leeuw, 2008; de Vogel, 2012; Hirsch, 2008). Early disarticulation of forceps and cessation of maternal pushing during disarticulation can also be protective. Last, these injuries are more common with an occiput posterior position (Damron, 2004). Thus, manual or forceps rotation to an occiput anterior position and then subsequent traction delivery may decrease rates of lower reproductive tract injury (Bradley, 2013).

Pelvic Floor Disorders

This term encompasses urinary incontinence, anal incontinence, and pelvic organ prolapse. Operative vaginal delivery has been suggested as a possible risk for each of these. Proposed mechanisms include structural compromise and/or pelvic floor denervation secondary to forces exerted during delivery.

Parity and specifically vaginal delivery are risk factors for urinary incontinence (Gyhagen, 2013; Rortveit, 2003). But, many studies do not support an increased risk compared with vaginal delivery alone (Gartland, 2016; Leijonhufvud, 2011; MacArthur, 2016; Tähtinen, 2016).

Evidence linking anal incontinence with operative vaginal delivery is conflicting. Some studies show that anal sphincter disruption caused by higher-order episiotomy, but not delivery mode, is the main etiological factor strongly associated with anal incontinence (Bols, 2010; Evers, 2012; Nygaard, 1997). In contrast, others directly link operative delivery with this complication (Dolan, 2010; MacArthur, 2013). But, these studies may not be incongruous—recall that operative delivery is associated with increased rates of higher-order episiotomy. Importantly, several studies and reviews have not found cesarean delivery to be protective for anal incontinence (Nelson, 2010). Last, evidence linking pelvic organ prolapse with operative delivery also indicates mixed results (Gyhagen, 2013; Handa, 2012; Volløyhaug, 2015).

Perinatal Morbidity

Acute Perinatal Injury

These injuries are more frequent with operative vaginal delivery than with cesarean delivery or spontaneous vaginal delivery. Injuries may be seen with either method. They are more common with vacuum extraction, and types associated with this device include cephalohematoma, subgaleal hemorrhage, retinal hemorrhage, neonatal jaundice secondary to these hemorrhages, shoulder dystocia, clavicular fracture, and scalp lacerations. Cephalohematoma and subgaleal hemorrhage are both extracranial lesions described in Chapter 33 (Intracranial Hemorrhage). Forceps-assisted vaginal delivery has higher rates of facial nerve injury, brachial plexus injury, depressed skull fracture, and corneal abrasion (American College of Obstetricians and Gynecologists, 2015; Demissie, 2004; Dupuis, 2005). For intracranial hemorrhage, some studies have associated vacuum extraction with higher rates, whereas others show similar rates with either of the two methods (Towner, 1999; Wen, 2001; Werner, 2011).

Comparing operative vaginal with cesarean delivery, rates of extracranial hematoma, skull fracture, facial nerve or brachial plexus injury, retinal hemorrhage, and facial or scalp laceration are lower with cesarean delivery, and shoulder dystocia is eliminated. Importantly, however, fetal acidemia rates are not increased with operative delivery (Contag, 2010; Walsh, 2013). Intracranial hemorrhage rates are similar among newborns delivered by vacuum extraction, forceps, or cesarean delivery during labor (Towner, 1999). But, these rates are higher than among those delivered spontaneously or by cesarean delivery before labor. These authors suggest that the common risk factor for intracranial hemorrhage is abnormal labor. Werner and associates (2011), in their evaluation of more than 150,000 singleton deliveries, reported that forceps-assisted delivery was associated with fewer total neurological complications compared with vacuum-assisted or cesarean delivery. However, as a subset, subdural hemorrhage was significantly more frequent in both instrumental cohorts compared with neonates in the cesarean delivery group.

Comparing rotational operative delivery and second-stage cesarean delivery, maternal and neonatal morbidity rates are similar (Aiken, 2015; Bahl, 2013; Stock, 2013). For example, in their large series, Tempest and associates (2013) found similar morbidity rates among malpositioned fetuses during second-stage labor that underwent Kielland rotation, rotational vacuum extraction, or emergency cesarean delivery.

Comparing midforceps and cesarean delivery, reports of neonatal morbidity rates are from older studies and are conflicting. In the study by Towner and colleagues (1999), similar risks were reported for intracranial hemorrhage. Bashore and associates (1990) observed comparable Apgar scores, cord blood acid-base values, neonatal intensive care unit admission, and birth trauma between these two. In another study, however, Robertson and coworkers (1990) reported significantly higher rates of these adverse outcomes in the midforceps group. Hagadorn-Freathy and colleagues (1991) reported an increased risk for facial nerve palsy—9 percent—with midforceps delivery. In a recent report comparing low and midforceps procedures, Ducarme and coworkers (2015) found comparable morbidity rates.

Mechanisms of Acute Injury

The types of fetal injury with operative delivery can usually be explained by the forces exerted. In cases of cephalohematoma or subgaleal hemorrhage, suction and perhaps rotation during vacuum extraction may lead to a primary vessel laceration. Intracranial hemorrhage may result from skull fracture and vessel laceration or from vessel laceration alone due to exerted forces. With facial nerve palsy, one of the forceps blades may compress the nerve against the facial bones. The higher rates of shoulder dystocia seen with vacuum extraction may result from the angle of traction. With the vacuum, this angle creates vector forces that actually pull the anterior shoulder into the symphysis pubis (Caughey, 2005). To explain brachial plexus injury, Towner and Ciotti (2007) proposed that as the fetal head descends down the birth canal, the shoulders may stay above the pelvic inlet. Thus, similar to shoulder dystocia at the symphysis, this “shoulder dystocia at the pelvic inlet” is overcome by traction forces but with concomitant stretch on the brachial plexus.

Long-Term Infant Morbidity

Evidence regarding long-term neurodevelopmental outcomes in children born by operative delivery is reassuring. In an older study, Seidman and colleagues (1991) evaluated more than 52,000 Israeli Defense Forces draftees at age 17 years and found that regardless of delivery mode, rates of physical or cognitive impairments were similar. Wesley and associates (1992) noted similar intelligence scores among 5-year-olds following spontaneous, forceps, or vacuum deliveries. Murphy and coworkers (2004) found no association between forceps delivery and epilepsy in a cohort of more than 21,000 adults. In their epidemiological review, O’Callaghan and colleagues (2011) found no association between cerebral palsy and operative delivery. Last, Bahl and associates (2007) noted that the incidence of neurodevelopmental morbidity was similar in those undergoing successful forceps delivery, failed forceps with cesarean delivery, or cesarean delivery without forceps.

Data regarding midforceps deliveries are for the most part reassuring. Broman and coworkers (1975) reported that infants delivered by midforceps had slightly higher intelligence scores at age 4 years compared with those of children delivered spontaneously. Using the same database, however, Friedman and associates (1977, 1984) analyzed intelligence scores at or after age 7 years. They concluded that children delivered by midforceps had lower mean intelligence quotients compared with those delivered by outlet forceps. In yet another report from this database, Dierker and colleagues (1986) compared long-term outcomes of children delivered by midforceps with those delivered by cesarean after dystocia. The strength of this study is the appropriateness of the control group. These investigators reported that delivery by midforceps was not associated with neurodevelopmental disability. Last, Nilsen (1984) evaluated 18-year-old men and found that those delivered by Kielland forceps had higher intelligence scores than those delivered spontaneously, by vacuum extraction, or by cesarean.

TRIAL OF OPERATIVE VAGINAL DELIVERY

If an attempt to perform an operative delivery is expected to be difficult, then it should be considered a trial. Moving the woman to an operating room for this attempt, which could be followed by immediate cesarean delivery if operative delivery fails, has merit. If forceps cannot be satisfactorily applied, then the procedure is stopped and either vacuum extraction or cesarean delivery is performed. With the former, if the fetus does not descend with traction, the trial should be abandoned and cesarean delivery performed.

With such caveats, cesarean delivery after an attempt at operative vaginal delivery was not associated with adverse neonatal outcomes if there was a reassuring fetal heart rate tracing (Alexander, 2009). A similar study evaluated 122 women who had a trial of midcavity forceps or vacuum extraction in a setting with full preparations for cesarean delivery (Lowe, 1987). Investigators found no significant difference in immediate neonatal or maternal morbidity compared with that of 42 women delivered for similar indications by cesarean but without such a trial. Conversely, in 61 women who had "unexpected" vacuum or forceps failure in which there was no prior preparation for immediate cesarean delivery, neonatal morbidity was higher.

Some factors associated with operative delivery failure are persistent occiput posterior position and birthweight >4000 g (Ben-Haroush, 2007; Verhoeven, 2016). However, Palatnik and associates (2016) found that risk factors poorly predicted success. In general, to avert morbidity with failed forceps or vacuum delivery, the American College of Obstetricians and Gynecologists (2015) cautions that these trials should be attempted only if the clinical assessment suggests a successful outcome. We also emphasize proper training.

Sequential instrumentation most often involves an attempt at vacuum extraction followed by one with forceps. This most likely stems from the higher completion rate with forceps compared with vacuum extraction noted earlier. This practice significantly increases risks for fetal trauma (Dupuis, 2005; Gardella, 2001; Murphy, 2011). Because of these adverse outcomes, the American College of Obstetricians and Gynecologists (2015) recommends against the sequential use of instruments unless there is a "compelling and justifiable reason."

TRAINING

As the rate of operative vaginal delivery has declined, so have opportunities for training (Fitzwater, 2015; Kyser, 2014). In many programs, training in even low and outlet forceps procedures has reached critically low levels. For residents completing training in 2015, the Accreditation Council for Graduate Medical Education reported a median of only five forceps deliveries, and that for vacuum deliveries was 16.

Because traditional hands-on training has evolved, residency programs should have readily available skilled operators to teach these procedures by simulation as well as through actual cases (Skinner, 2017; Spong, 2012). And, the effectiveness of simulation training has been reported (Dupuis, 2006, 2009; Leslie, 2005). In one program, maternal and neonatal morbidity rates with operative delivery decreased after the implementation of a formal education program that included a manikin and pelvic model (Cheong, 2004). In another, a 59-percent increase in forceps deliveries over 2 years was related to a single experienced and proactive instructor assigned to teach forceps to residents in labor and delivery (Solt, 2011).

FORCEPS DELIVERY

Design

Forceps refers to the paired instrument, and each member of this pair is called a branch. Branches are designated left or right according to the side of the maternal pelvis to which they are applied (Fig. 29-2). Each branch has four components: blade, shank, lock, and handle (Fig. 29-3). Each blade has a toe, a heel, and two curves. Of these, the outward cephalic curve conforms to the round fetal head, whereas the upward pelvic curve corresponds more or less to the curve of the birth canal. Some blades have an opening within or a depression along the blade surface and are termed *fenestrated* or *pseudofenestrated*, respectively. True fenestration reduces the degree of head slippage during forceps rotation. Disadvantageously, it can increase friction between the blade and vaginal wall. With pseudofenestration, the forceps blade is smooth on the outer maternal side but indented on the inner fetal surface. The goal is to reduce head slipping yet improve the ease and safety of application and removal of forceps compared with pure fenestrated blades. In general, fenestrated blades are used for a fetus with a molded head or for rotation. In most situations, however, despite these subtle differences any are appropriate.

FIGURE 29-2
Simpson forceps have fenestrated blades, parallel shanks, and English lock. The cephalic curve accommodates the fetal head.

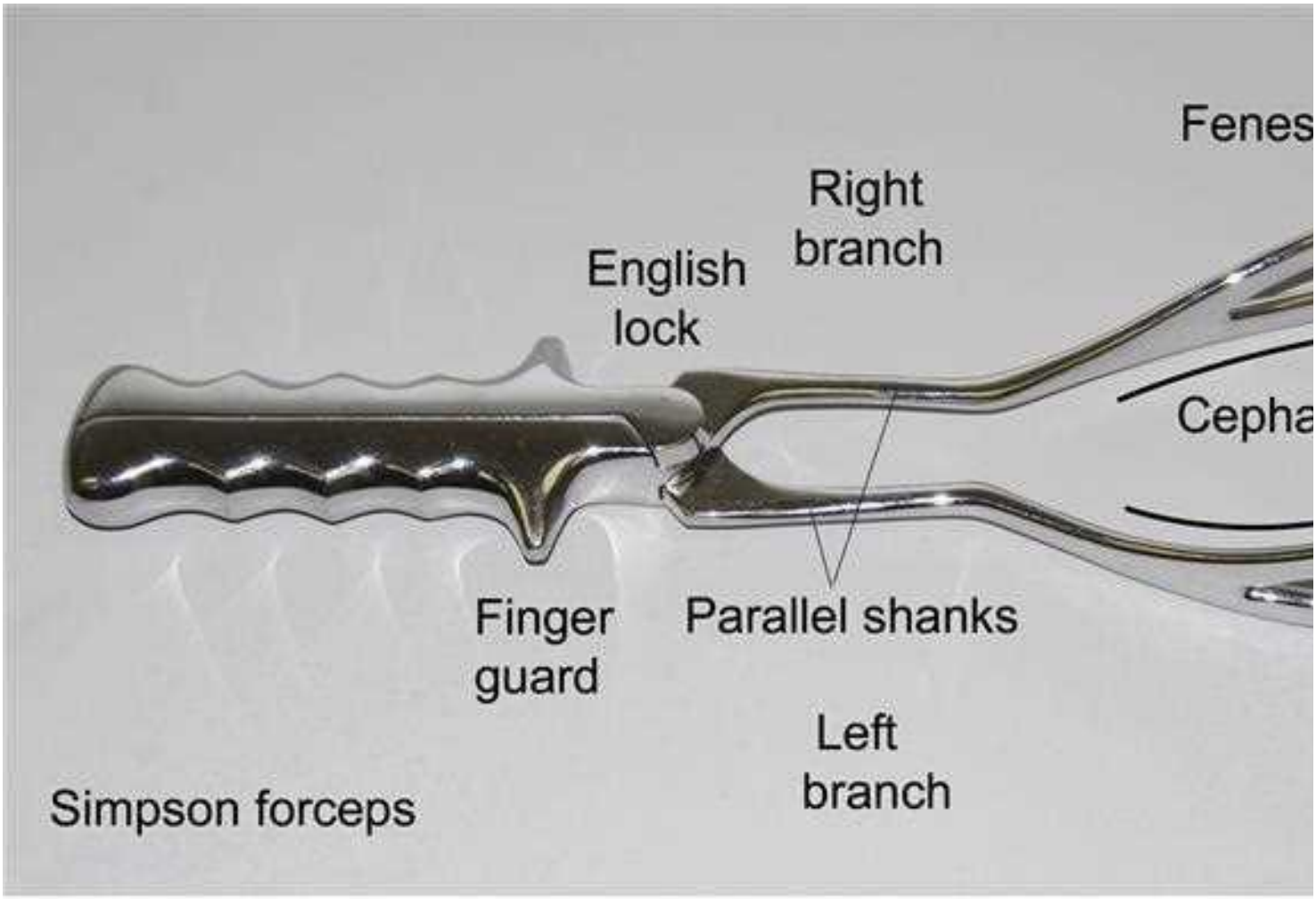
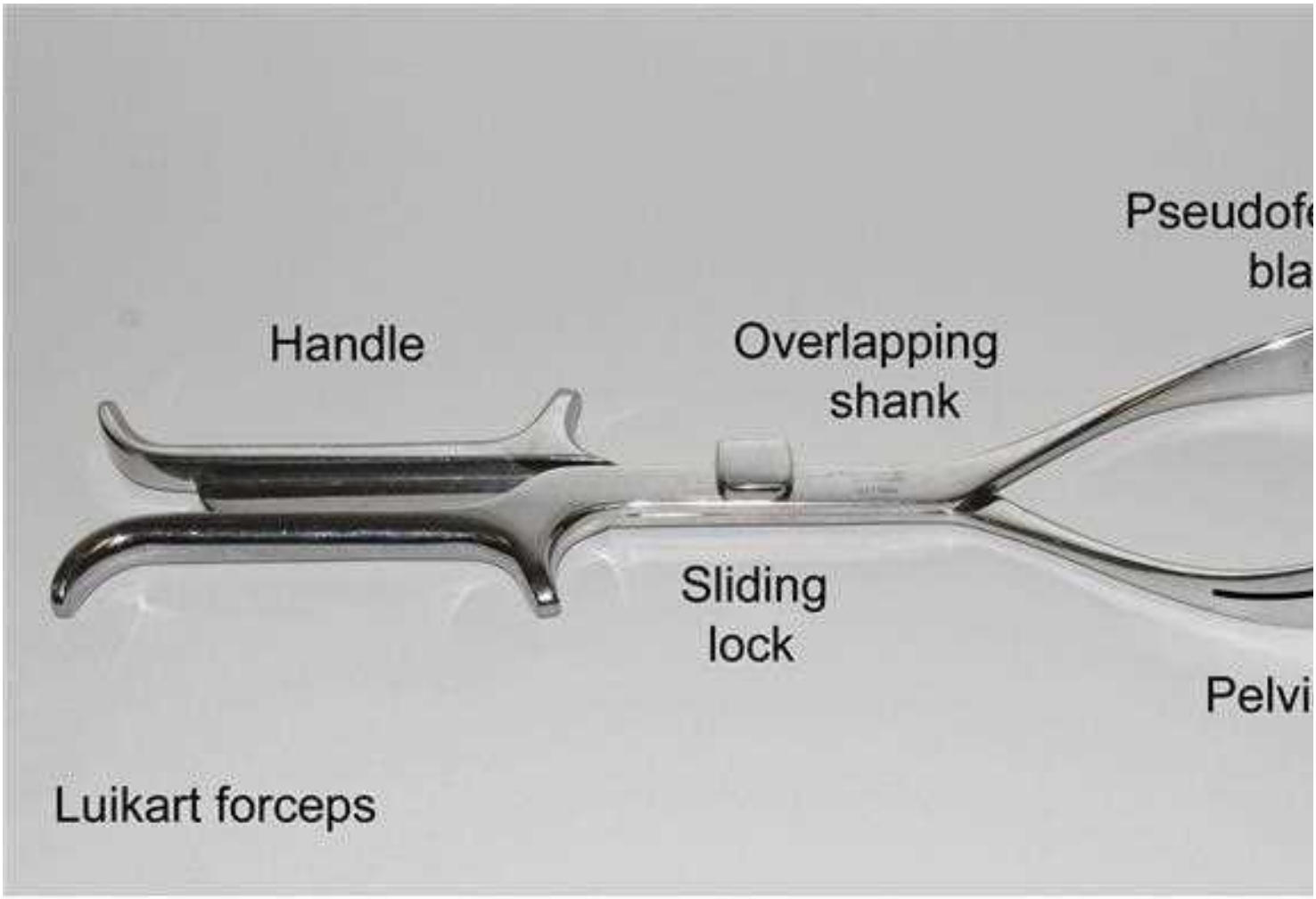


FIGURE 29-3

Luikart forceps have pseudofenestrated blades, overlapping shanks, sliding lock, tongue groove handles. The pelvic curve is marked in this example by the black line.



The blades are connected to shanks, which may be parallel or overlapping. Locks are found on all forceps and help to connect the right and left branches and stabilize the instrument. They can be located at the end of the shank nearest to the handles (English lock), at the ends of the handles (pivot lock), or along the shank (sliding lock). Although varied in design, handles, when squeezed, raise compression forces against the fetal head. Thus, forces to consider include traction and compression.

Blade Application and Delivery

Forceps blades grasp the head and are applied according to fetal head position. If the head is in an occiput anterior (OA) position, two or more fingers of the right hand are introduced inside the left posterior portion of the vulva and then into the vagina beside the fetal head. The handle of the left branch is grasped between the thumb and two fingers of the left hand (Fig. 29-4). The blade tip is then gently passed into the vagina between the fetal head and the palmar surface of the fingers of the right hand (Fig. 29-5). For application of the right blade, two or more fingers of the left hand are introduced into the right posterior portion of the vagina to serve as a guide for the right blade. This blade is held in the right hand and introduced into the vagina. With each blade, the thumb is positioned behind the heel, and most of the insertion force comes from this thumb (Fig. 29-6). If the head is positioned in a left OA (LOA) or right OA (ROA) position, then the lower of the two blades is typically placed first. After positioning, the branches are articulated.

FIGURE 29-4

For OA or LOA positions, the left handle of the forceps is held in the left hand. The blade is introduced into the left side of the pelvis between the fetal head and the fingers of the operator's right hand.

FIGURE 29-5

Insertion arc of the blade. Importantly, the thumb of the right hand, guides the blade during placement, as shown in Figure 29-6.

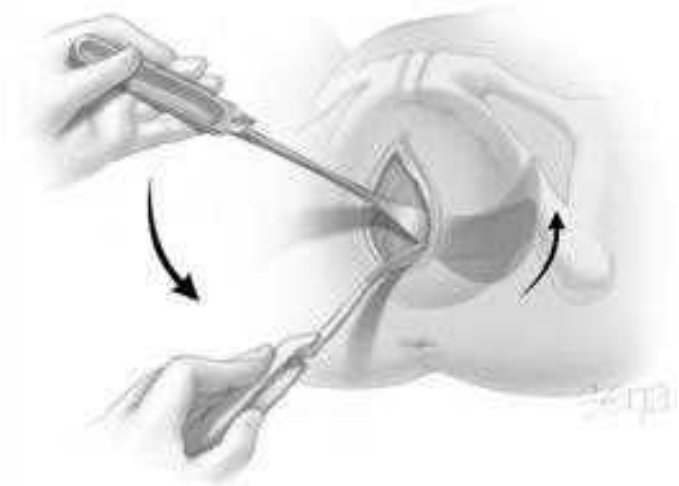
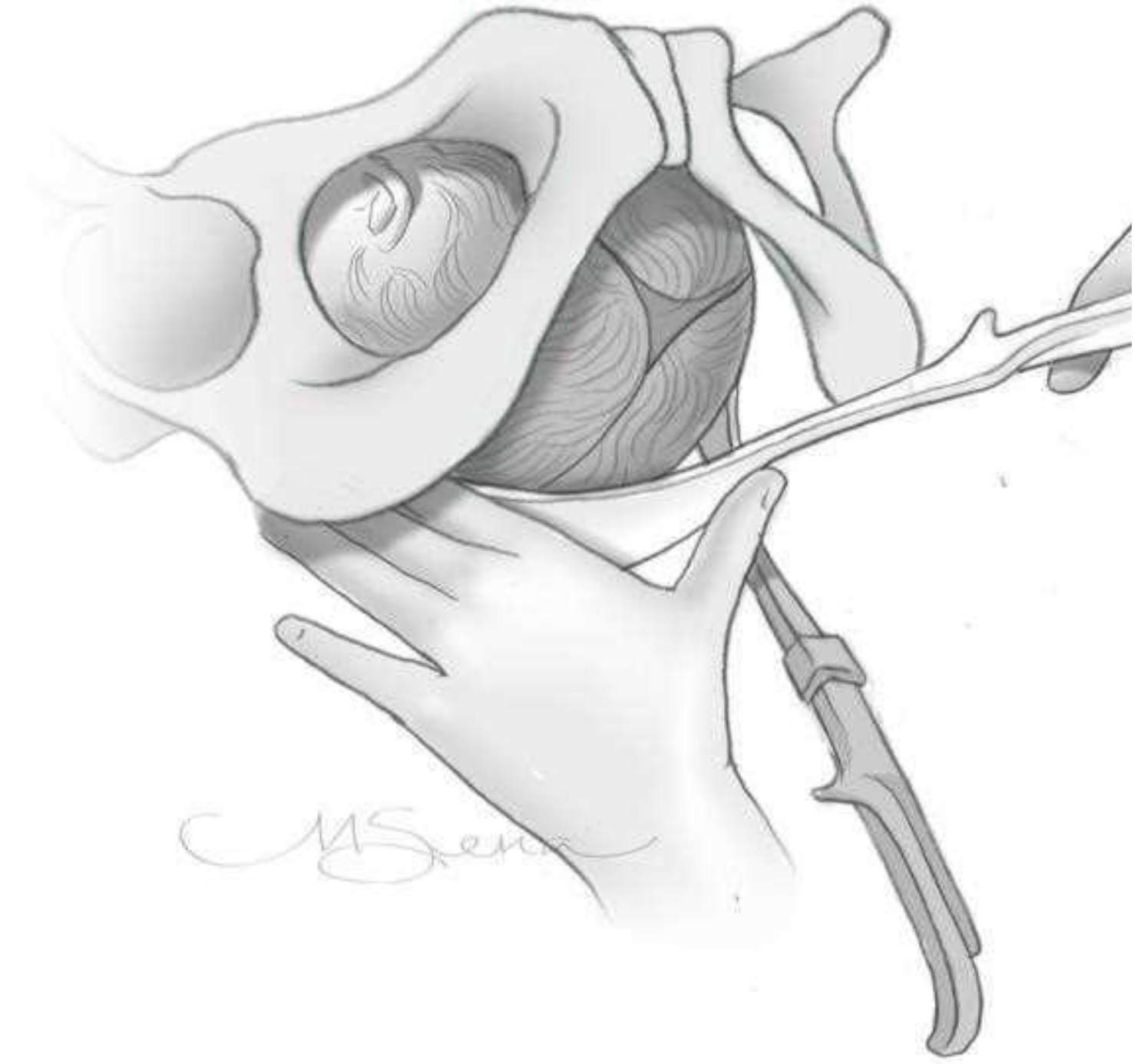


FIGURE 29-6

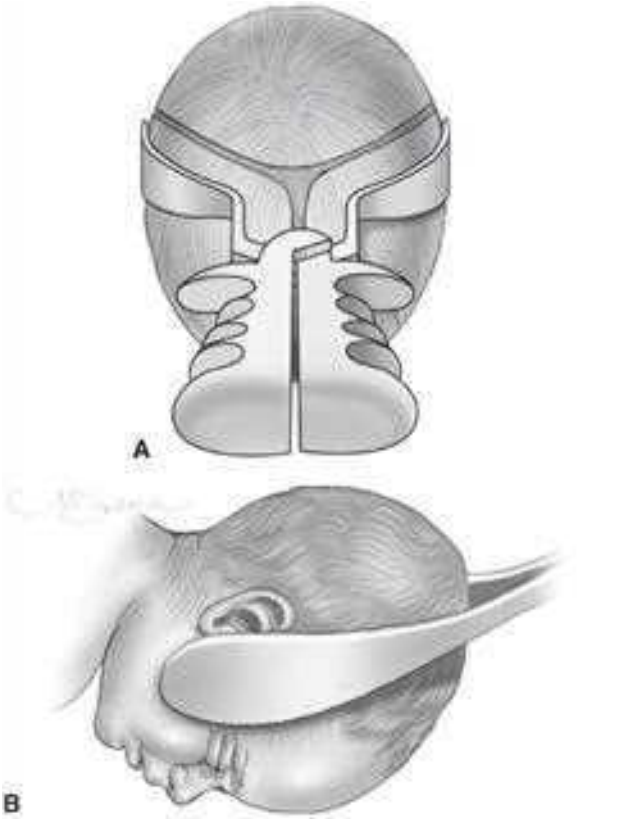
In applying the second blade, insertional force is generated mainly by the thumb. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



The blades are constructed so that their cephalic curve is closely adapted to the sides of the fetal head (Fig. 29-7). The fetal head is perfectly grasped only when the long axis of the blades corresponds to the occipitomental diameter (see Fig. 29-1). As a result, most of the blade lies over the lateral face. If the fetus is in an OA position, then the concave arch of the blades is directed toward the sagittal suture. If the fetus is in an occiput posterior (OP) position, then the concave arch is directed toward the midline face.

FIGURE 29-7

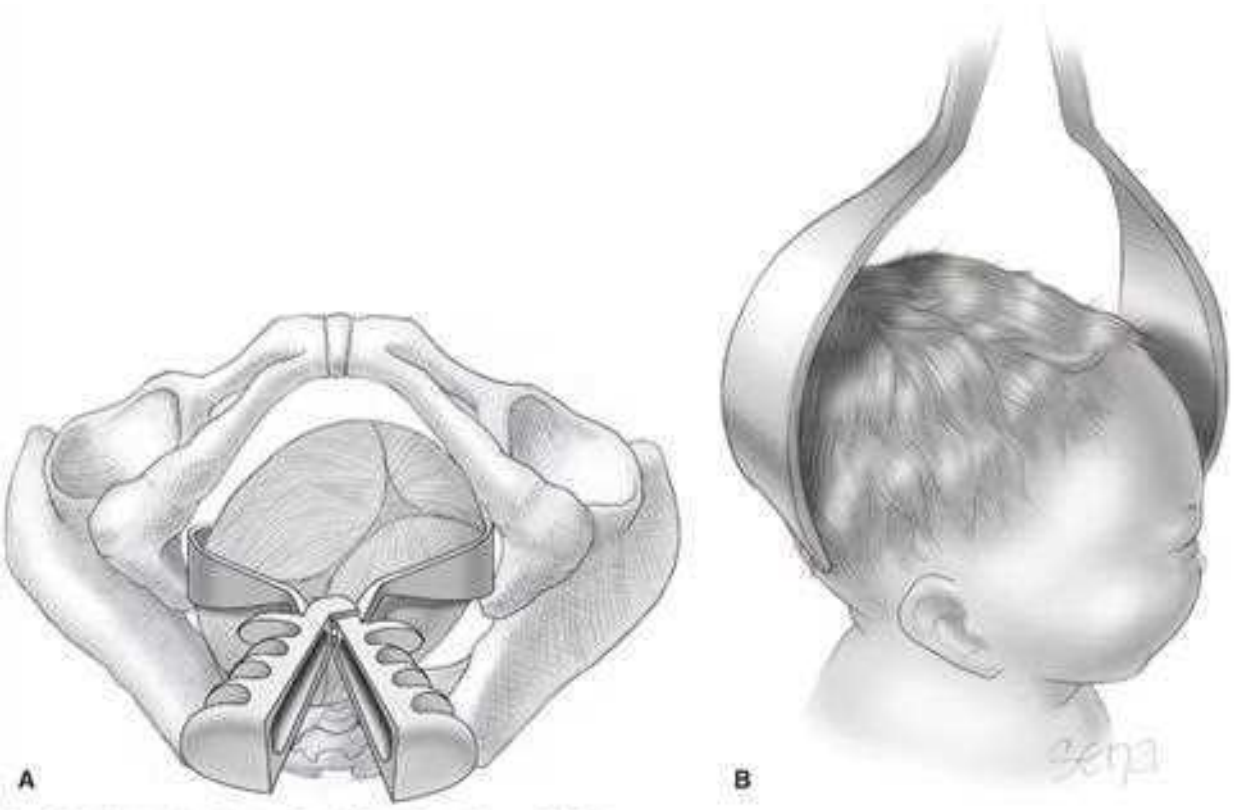
A. The forceps are symmetrically placed and articulated. **B.** The vertex is OA. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Suboptimal blade placement can increase morbidity (Ramphul, 2015). For OA position, appropriately applied blades are equidistant from the sagittal suture, and each blade is equidistant from its adjacent lambdoidal suture. In the OP position, the blades are equidistant from the midline of the face and brow. Also for OP position, blades are symmetrically placed relative to the sagittal suture and each coronal suture. Applied in this way, the forceps should not slip, and traction may be applied most advantageously. With most forceps, if one blade is applied over the brow and the other over the occiput, the instrument cannot be locked, or if locked, the blades will slip off when traction is applied (Fig. 29-8).

FIGURE 29-8

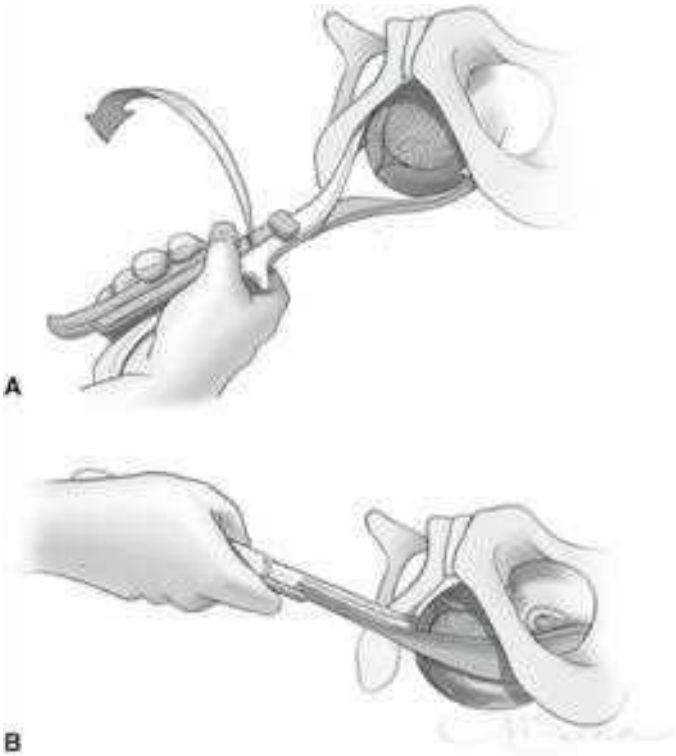
Incorrect application of forceps. **A.** One blade over the occiput and the other over the brow. Forceps cannot be locked. **B.** With incorrect placement, blades tend to slip off with traction.



With both branches in place, it should be an easy matter to articulate the handles, engage the lock, and correct asynclitism if present. Asynclitism is resolved by pulling and/or pushing each branch along the long axis of the instrument until the finger guards align. If necessary, rotation to OA position is performed before traction is applied (Fig. 29-9).

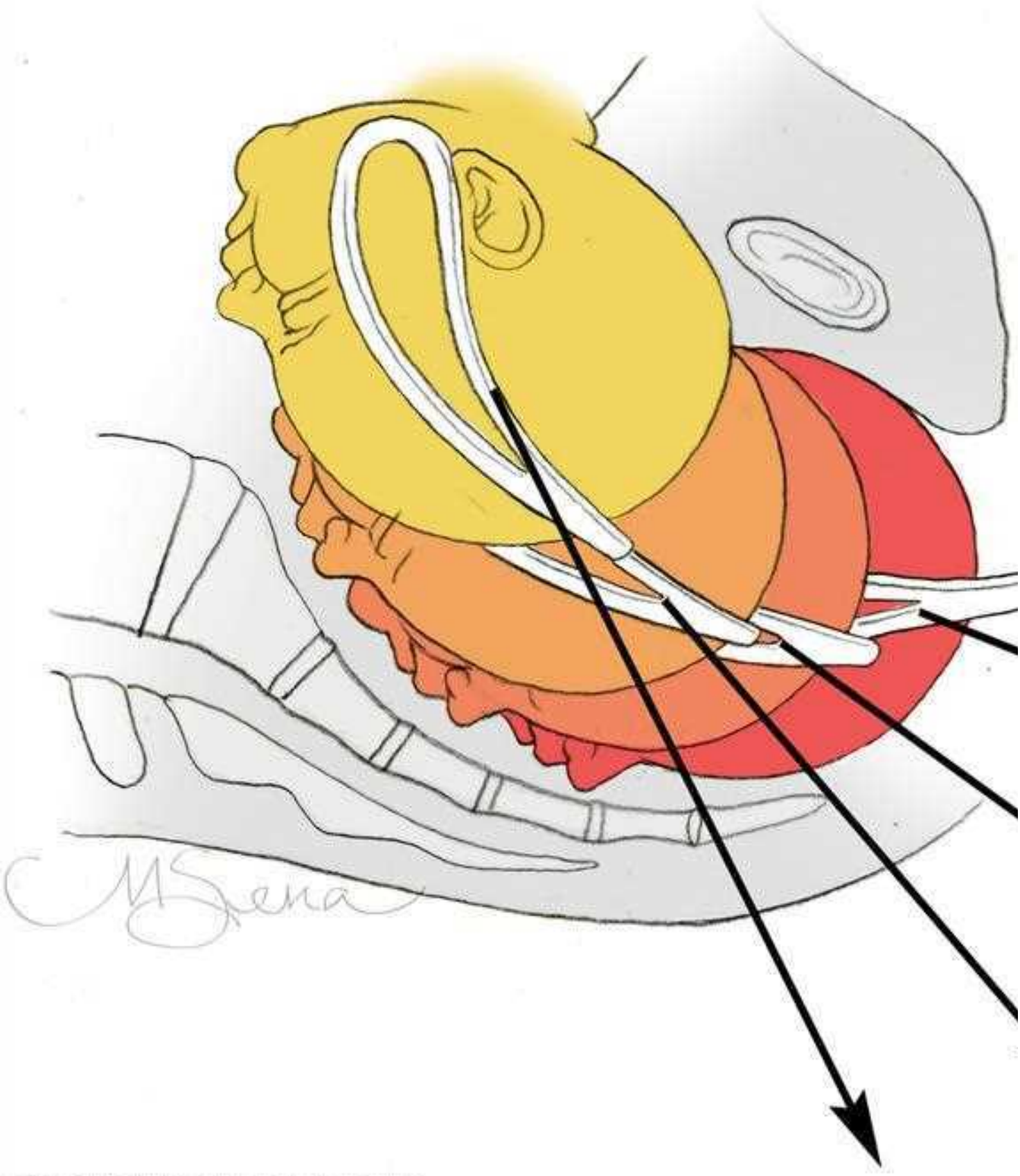
FIGURE 29-9

A. If LOA, the vertex is rotated (*arrow*) from this position to OA **(B).** (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



When it is certain that the blades are placed satisfactorily, then gentle, intermittent, downward and outward traction is exerted concurrent with maternal efforts until the perineum begins to bulge. When the head is at 0 to +2 of +5 station, the initial direction of traction is quite posterior, almost toward the floor. With head descent, the vector of forces changes continuously (Fig. 29-10). As a teaching tool for this, a *Bill axis traction device* can be attached over the finger guards of most forceps. The instrument has an arrow and indicator line. When the arrow points directly to the line, traction is along the path of least resistance. With traction, as the vulva is distended by the occiput, an episiotomy may be performed if indicated. Additional horizontal traction is applied, and the handles are then gradually elevated. As the handles are raised, the head is extended. During the birth of the head, mechanisms of spontaneous delivery should be simulated as closely as possible.

FIGURE 29-10
With low forceps, the direction of gentle traction for delivery of the head is indicated (*arrow*). The vector changes with fetal descent.

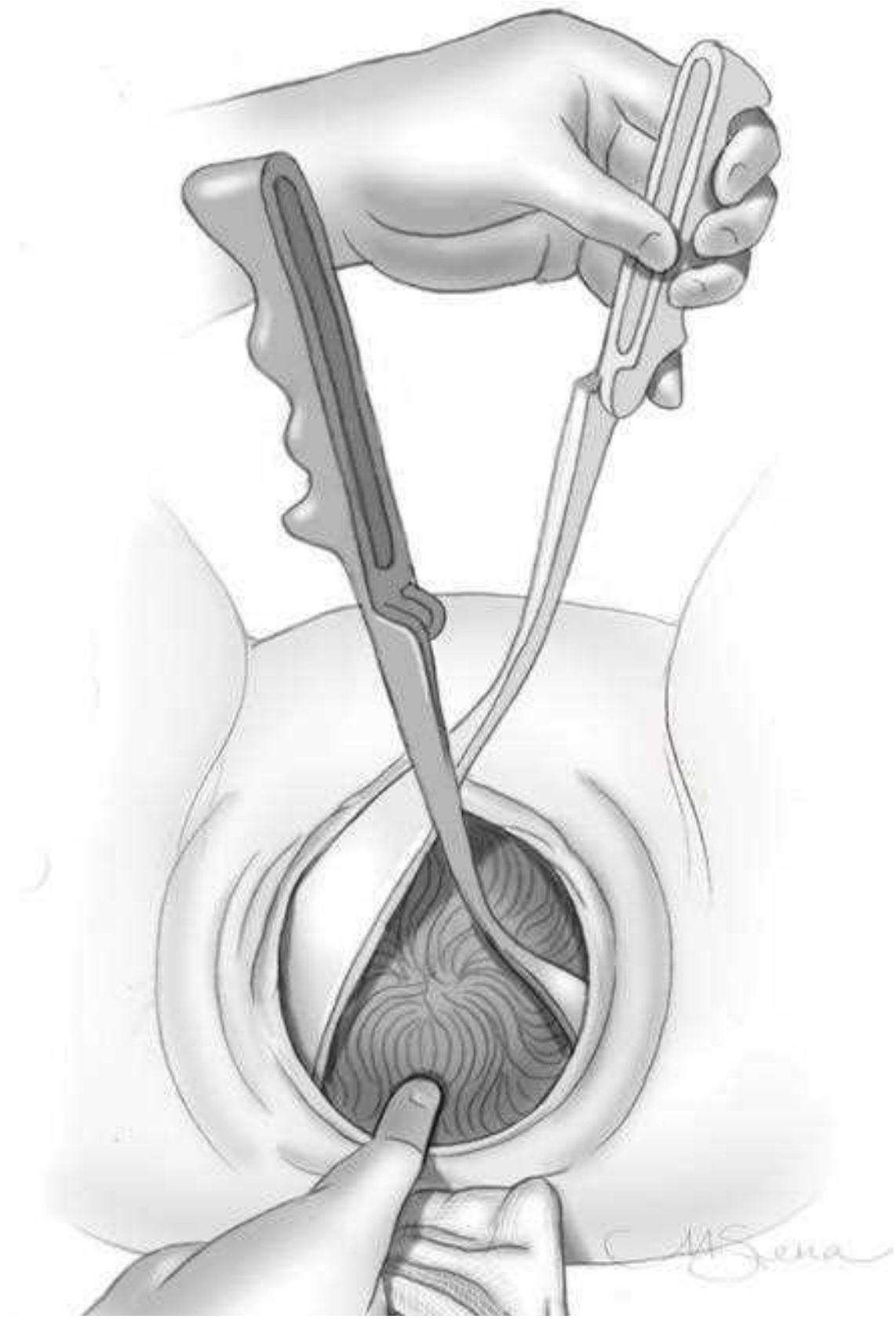


The force produced by the forceps on the fetal skull is a function of both traction and compression by the forceps, as well as friction produced by maternal tissues. It is impossible to ascertain the amount of force exerted by forceps for an individual patient. Traction should therefore be intermittent, and the head should be allowed to recede between contractions, as in spontaneous labor. Except when urgently indicated, as in severe fetal bradycardia, delivery should be sufficiently slow, deliberate, and gentle to prevent undue head compression. It is preferable to apply traction only with each uterine contraction. Maternal pushing will augment these efforts.

After the vulva has been well distended by the head, the delivery may be completed in several ways. Some clinicians keep the forceps in place to control the head. If this is done, however, the blade volume adds to vulvar distention, thus increasing the likelihood of laceration or necessitating a large episiotomy. To prevent this, the forceps may be removed, and delivery is then completed by maternal pushing (Fig. 29-11). Importantly, if blades are disarticulated and removed too early, the head may recede and lead to a prolonged delivery. Delivery in some cases may be aided by addition of the modified Ritgen maneuver.

FIGURE 29-11

Branches are removed in the opposite order from that in which they were originally placed. The fingers of the right hand, covered by a sterile towel, bolster the perineum. The thumb is placed directly on the head to prevent sudden egress. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



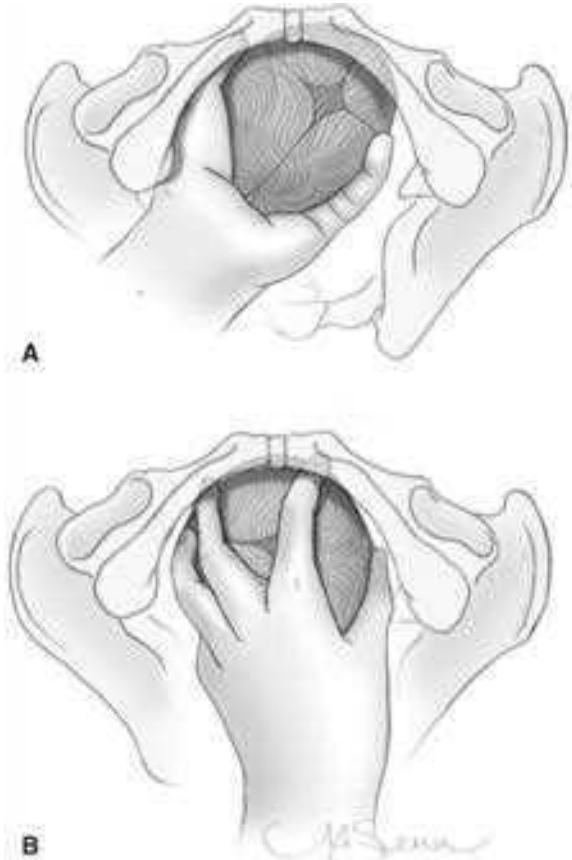
Occiput Posterior Positions

Prompt delivery may at times become necessary when the small occipital fontanel is directed toward one of the sacroiliac synchondroses. In these right OP (ROP) or left OP (LOP) positions, the fetal head is often imperfectly flexed. With OP positions, second-stage labor can be lengthened. In these cases, the head may spontaneously deliver OP, may be manually or instrumentally rotated to an OA position, or may be delivered OP by forceps or vacuum.

With manual rotation, an open hand is inserted into the vagina. The palm straddles the sagittal suture of the fetal head. The operator's fingers wrap around one side of the fetal face and thumb extends along the other side. If the occiput is ROP, rotation is clockwise to bring it to an ROA or OA position (Fig. 29-12). With LOP position, rotation is counterclockwise. Three actions are performed simultaneously between contractions. The first is fetal head flexion to provide a smaller diameter for rotation and subsequent descent. Second, slight destationing of the fetal head moves the head to a level in the maternal pelvis with sufficient room to complete the rotation. Importantly, destationing should not be confused with disengaging the fetal head, which is proscribed. Concurrently, some prefer to also place the other hand externally on the corresponding side of the maternal abdomen to pull the fetal back up toward the midline in synchrony with the internal rotation. Le Ray and colleagues (2007, 2013) reported a success rate of greater than 90 percent with manual rotation. Barth (2015) provides an excellent summary of this technique.

FIGURE 29-12

A. Manual rotation using the left hand, palm-up, to rotate from ROP. **B.** The head is flexed and destationed during clockwise rotation to reach an OA position. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)

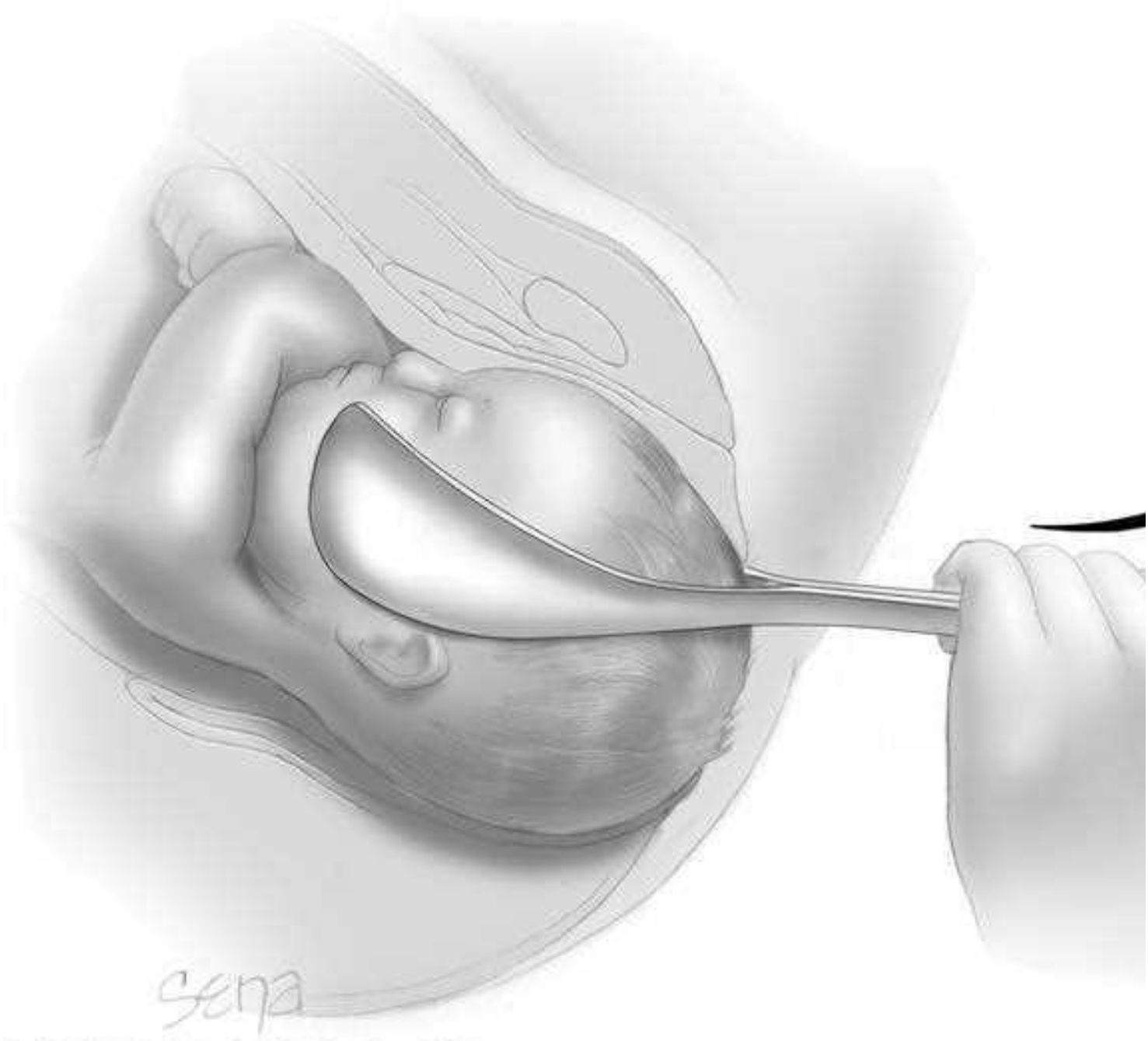


Manual rotations are most easily completed in multiparas. If manual rotation cannot be easily accomplished, application of forceps blades to the head in the posterior position and delivery from an OP position may be the safest procedure. In many cases, the cause of a persistent OP position and of the difficulty in accomplishing rotation is an anthropoid pelvis. This architecture opposes rotation and predisposes to posterior delivery (Fig. 2-17).

With forceps delivery from an OP position, downward and outward traction is applied until the base of the nose passes under the symphysis (Fig. 29-13). The handles are then slowly elevated until the occiput gradually emerges over the upper margin of the perineum. The forceps are directed downward again, and the nose, mouth, and chin successively emerge from the vulva.

FIGURE 29-13

Outlet forceps delivery from an OP position. The head should be flexed after the bregma passes under the symphysis.

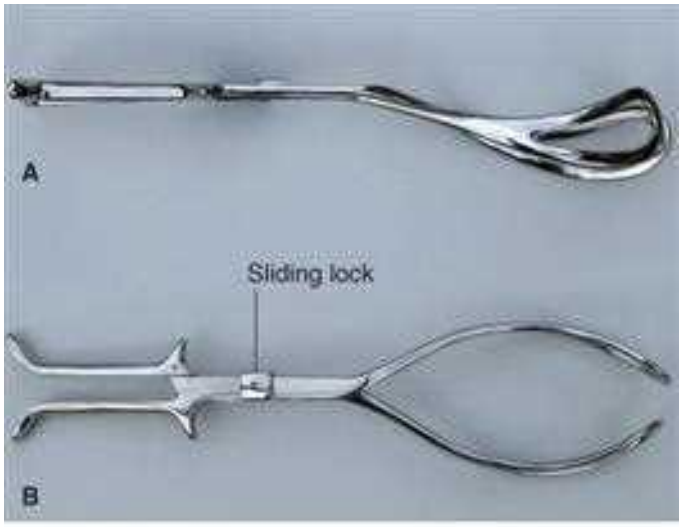


OP delivery causes greater distention of the vulva, and a large episiotomy may be needed. OP deliveries have a higher incidence of severe perineal lacerations and extensive episiotomy compared with OA positions (de Leeuw, 2008; Pearl, 1993). Also, newborns delivered from OP positions have a higher incidence of Erb and facial nerve palsies, 1 and 2 percent, respectively, than those delivered from OA positions. As expected, rotations to OA ultimately decrease perineal delivery trauma (Bradley, 2013).

Last, for forceps rotations from an OP to OA position, the Kielland instruments are preferred because they have a less pronounced pelvic curve (Fig. 29-14). *Cunningham and Gilstrap's Operative Obstetrics, 3rd edition,* offers a more detailed description of this Kielland forceps procedure (Yeomans, 2017).

FIGURE 29-14

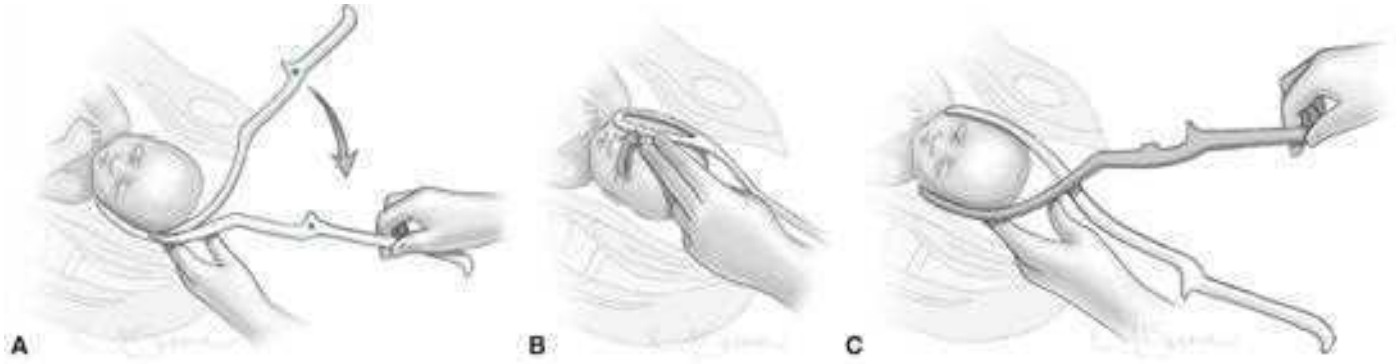
Kielland forceps. The characteristic features are minimal pelvic curvature **(A)**, sliding lock **(B)**, and light weight.



Occiput Transverse Positions

With occiput transverse (OT) positions, rotation is required for delivery. With experienced operators, high success rates with minimal maternal morbidity can be achieved (Burke, 2012; Stock, 2013). Either standard forceps, such as Simpson, or specialized forceps, such as Kielland, are employed. With Kielland forceps, each handle has a small knob, and branches are placed so that this knob faces the occiput. The station of the fetal head must be accurately determined to be at, or preferably below, the level of the ischial spines, especially in the presence of extreme molding.

FIGURE 29-15
A. Application of the right branch of the Kielland forceps to a head in LOT position. The knob on this branch (*colored blue*) will ultimately face the occiput. **B.** The right branch is wandered to its final position behind the symphysis. **C.** Insertion of the left branch of the Kielland forceps directly posterior along the hollow of the sacrum. This branch is inserted to the maternal right of the anterior branch to aid in engaging the sliding lock. (Reproduced with permission from Yeomans ER: Operative vaginal delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Kielland described two methods of applying the anterior blade. In our example, placement with a left OT (LOT) position is described. With the wandering method, the anterior blade is first introduced into the posterior pelvis (Fig. 29-15). The blade is then arched around the face to an anterior position. To permit this sweep of the blade, the handle is held close to the maternal left buttock throughout the maneuver. The second blade is introduced directly posteriorly, and the branches are locked.

After checking the application, the handles of the Kielland forceps are pulled slightly to the patient's right to increase fetal head flexion and create a smaller diameter for rotation. The first and second fingers of the left hand are placed over the finger guards with the palm against the handles. This palm faces the maternal left. Concurrently, the first two fingers of the operator's right hand are placed against the anterior lambdoid suture. The fetal head is then destationed approximately 1 cm. For rotation in a counterclockwise direction, the wrist of the left hand supinates, to direct this palm upward. Simultaneously, two fingers of the right hand press on the edge of the right parietal bone that borders the lambdoid suture. This ensures that the fetal head turns with the blades and does not slip.

The second type of blade application introduces the anterior blade with its cephalic curve directed upward to curve under the symphysis. After it has been advanced far enough toward the upper vagina, it is turned on its long axis through 180 degrees to adapt the cephalic curvature to the head.

With either application, after rotation completion, the operator may choose from two acceptable methods for delivery. In one, the operator applies traction on the Kielland forceps using a bimanual grip described previously for conventional forceps (Forceps Delivery). When the posterior fontanel has passed under the subpubic arch, the handles can be elevated to the horizontal. Raising the handles above the horizontal may cause vaginal sulcus tears because of the reverse pelvic curve (Dennen, 1955). Alternatively, the Kielland forceps can be removed after rotation and replaced with conventional forceps. With this approach, moderate traction is first employed to seat the head before switching instruments.

Face Presentations

With a mentum anterior face presentation, forceps can be used to effect vaginal delivery. The blades are applied to the sides of the head along the occipitomental diameter, with the pelvic curve directed toward the neck. Downward traction is exerted until the chin appears under the symphysis. Then, by an upward movement, the face is slowly extracted, with the nose, eyes, brow, and occiput appearing in succession over the anterior margin of the perineum. *Forceps should not be applied to the mentum posterior presentation because vaginal delivery is impossible except in very small fetuses.*

VACUUM EXTRACTION

Vacuum Extractor Design

With vacuum delivery, suction is created within a cup placed on the fetal scalp such that traction on the cup aids fetal expulsion. In the United States, *vacuum extractor* is the preferred term, whereas in Europe it is commonly called a *ventouse* (Fig. 29-16). Theoretical benefits of this tool compared with forceps include simpler requirements for precise positioning on the fetal head and avoidance of space-occupying blades within the vagina, thereby mitigating maternal trauma.

FIGURE 29-16
Vacuum delivery systems. **A.** The *Kiwi OmniCup* contains a handheld vacuum-generating pump, which is attached via flexible tubing to a rigid plastic mushroom cup. **B.** The *Mityvac Mystic II MitySoft Bell Cup* has a soft bell cup attached by a semirigid shaft to a handheld pump.

Vacuum devices contain a cup, shaft, handle, and vacuum generator. Vacuum cups may be metal or hard or soft plastic, and they may also differ in their shape, size, and reusability. In the United States, nonmetal cups are generally preferred, and there are two main types. The soft cup is a pliable bell-shaped dome, whereas the rigid type has a firm flattened mushroom-shaped cup and circular ridge around the cup rim (Table 29-2). When compared, rigid mushroom cups generate significantly more traction force (Hofmeyr, 1990; Muise, 1993). With OP positions or with asynclitism, the flatter cup also permits improved placement at the flexion point, which is typically less accessible with these head positions. The trade-off is that the flatter cups have higher scalp laceration rates. Thus, many manufacturers recommend soft bell cups for more straightforward OA deliveries.

TABLE 29-2

Vacuum Cups for Operative Vaginal Delivery

Cup Style	Manufacturer
Soft Bell Cup	
GentleVac	OB Scientific
Kiwi ProCup	Clinical Innovations
Mityvac MitySoftBell	CooperSurgical
Pearl Edge Bell Cup	CooperSurgical
Secure Cup	Utah Medical Products
Soft Touch	Utah Medical Products
Tender Touch	Utah Medical Products
Tender Touch Ultra	Utah Medical Products
Velvet Touch[a]	Utah Medical Products
Reusable vacuum delivery cup[a]	CooperSurgical
Rigid Mushroom Cup	
Flex Cup	Utah Medical Products
Mityvac M-Style	CooperSurgical
Super M-Style	CooperSurgical
Mityvac M-Select[b]	CooperSurgical
Kiwi OmniCup[b]	Clinical Innovations
Kiwi Omni-MT	Clinical Innovations
Kiwi Omni-C Cup[c]	Clinical Innovations

[a]Reusable cups.

[b]Suitable for occiput posterior positions or asynclitism.

[c]For extractions through a hysterotomy incision during cesarean delivery.

Several investigators have compared outcomes with various rigid and soft cups. Metal cups provide higher success rates but greater rates of scalp injuries, including cephalohematomas (O'Mahony, 2010). In another study, Kuit and coworkers (1993) found that the only advantage of the soft cups was a lower incidence of scalp injury. They reported a 14-percent episiotomy extension rate with both rigid and pliable cups. In a review, Vacca (2002) concluded that there were fewer scalp lacerations with the soft cup, but that the rate of cephalohematomas and subgaleal hemorrhage was similar between soft and rigid cups. Importantly, high-pressure vacuum generates large amounts of force regardless of the cup used (Duchon, 1998).

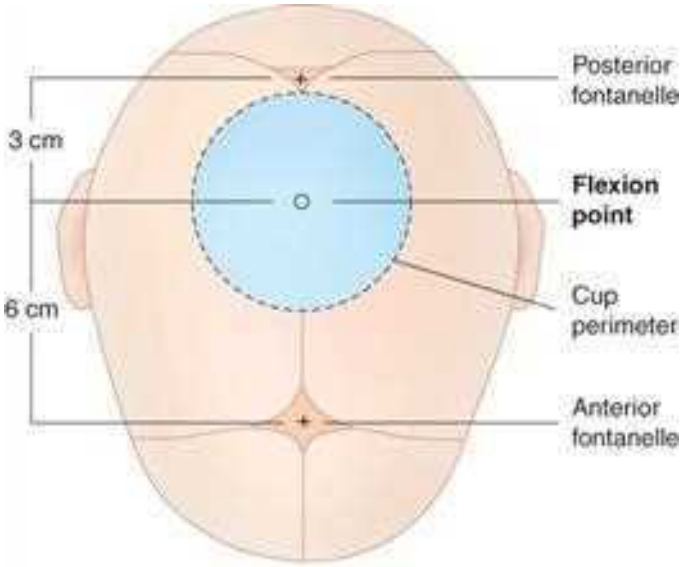
Aside from the cup, the shaft that connects the cup and handle may be flexible or semiflexible. Tubing-like flexible shafts may be preferred for OP positions or asynclitic presentation to permit better seating of the cup. Last, the vacuum generator may be handheld and actuated by the operator or may be held and operated by an assistant.

Technique

An important step in vacuum extraction is proper cup placement over the *flexion point*. This pivot point maximizes traction, minimizes cup detachment, flexes but averts twisting the fetal head, and delivers the smallest head diameter through the pelvic outlet. This improves success rates, lowers fetal scalp injury rates, and lessens perineal trauma because the smallest fetal head diameter distends the vulva (Baskett, 2008).

The flexion point is found along the sagittal suture, approximately 3 cm in front of the posterior fontanel and approximately 6 cm from the anterior fontanel. Because cup diameters range from 5 to 6 cm, when properly placed, the cup rim lies 3 cm from the anterior fontanel (Fig. 29-17). Placement of the cup more anteriorly on the fetal cranium—near the anterior fontanel—should be avoided as it leads to cervical spine extension during traction unless the fetus is small. Such placement also delivers a wider fetal head diameter through the vaginal opening. Last, asymmetrical placement relative to the sagittal suture may worsen asynclitism. For elective use, cup placement in OA positions is seldom difficult. In contrast, when the indication for delivery is failure to descend caused by occipital malposition— with or without asynclitism or deflexion—cup positioning can be difficult.

FIGURE 29-17
Drawing demonstrates correct cup placement at the flexion point. Along the sagittal suture, this spot lies 3 cm from the posterior fontanel and 6 cm from the anterior fontanel.



During cup placement, maternal soft tissue entrapment predisposes the mother to lacerations and virtually ensures cup dislodgement, colloquially called a "pop off." Thus, the entire cup circumference should be palpated both before and after the vacuum has been created and again prior to traction to exclude such entrapment. Gradual vacuum creation is advocated by some and is generated by increasing the suction in increments of 0.2 kg/cm^2 every 2 minutes until a total negative pressure of 0.8 kg/cm^2 is reached (Table 29-3). That said, other studies have shown that negative pressure can be increased to 0.8 kg/cm^2 in <2 minutes without a significant difference in efficacy or in maternal and fetal outcomes (Suwannachat, 2011, 2012).

TABLE 29-3
Vacuum Pressure Conversions

mm Hg	cm Hg	inches Hg	lb/in^2	kg/cm^2
100	10	3.9	1.9	0.13
200	20	7.9	3.9	0.27
300	30	11.8	5.8	0.41
400	40	15.7	7.7	0.54
500	50	19.7	9.7	0.68
600	60	23.6	11.6	0.82

Once suction is created, the instrument handle is grasped, and traction is initiated. Similar to forceps delivery, traction angles mirror that in Figure 29-10. Efforts are intermittent and coordinated with maternal expulsive efforts. Manual torque to the cup is avoided as it can cause cup displacement or cephalohematomas and, with metal cups, "cookie-cutter"–type scalp lacerations. Thus, OA oblique positions are corrected not by rotation, but solely by downward outward traction. During pulls, the operator should place the nondominant hand within the vagina, with the thumb on the extractor cup and one or more fingers on the fetal scalp. So positioned,

descent of the presenting part can be judged and the traction angle can be adjusted with head descent. In addition, the relationship of the cup edge to the scalp can be assessed to help detect cup separation.

Between contractions, some physicians will lower the suction levels to decrease rates of scalp injury, whereas others will maintain suction in cases with a nonreassuring fetal heart rate to aid rapid delivery. No differences in maternal or fetal outcome were noted if the level of vacuum was decreased between contractions or if an effort was made to prevent fetal loss of station (Bofill, 1997). Once the head is extracted, the vacuum pressure is relieved and the cup removed.

Vacuum extraction should be considered a trial. Without early and clear evidence of descent toward delivery, an alternative delivery approach should be considered. As a general guideline, progressive descent should accompany each traction attempt. Neither data nor consensus are available regarding the number of pulls required to effect delivery, the maximum number of cup pop-offs that can be tolerated, or optimal total duration of the procedure. Some manufacturers have recommendations regarding these in their instructional literature (Clinical Innovations, 2016; CooperSurgical, 2011).

During a vacuum extraction trial, cup dislodgement due to technical failure or less than optimal placement should not be equated with dislodgement under ideal conditions of exact cup placement and optimal vacuum maintenance. These cases may merit either additional attempts at placement or, alternatively, a trial of forceps (Ezenagu, 1999; Williams, 1991). The least desirable cases are those in which traction without progress or multiple disengagements occur following correct cup application and appropriate traction. As with forceps, clinicians should embrace a willingness to abandon attempts at vacuum extraction if satisfactory progress is not made (American College of Obstetricians and Gynecologists, 2015).

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CHAPTER 30: Cesarean Delivery and Peripartum Hysterectomy

The anterior surface of the uterus is opened longitudinally along its midline. This is best accomplished by making an incision a few centimetres long with a scalpel, and then rapidly enlarging it with the scissors to 16 or 18 centimetres. The membranes are then ruptured, the child is seized by one foot and rapidly extracted.

—J. Whitridge Williams (1903)

INTRODUCTION

From the above description, cesarean technique has evolved during the past century. For example, preference for classical hysterotomy has given way to low transverse incision. Evidence-based data now guide many surgical steps and are presented throughout this chapter.

Of definitions, *cesarean delivery* defines the birth of a fetus via laparotomy and then hysterotomy. This definition is not applied to removal of the fetus from the abdominal cavity in the case of uterine rupture or with abdominal pregnancy. Rarely, hysterotomy is performed in a woman who has just died or in whom death is expected soon—*postmortem* or *perimortem cesarean delivery* (Chap. 47, Cardiopulmonary Resuscitation).

In some instances, abdominal hysterectomy is indicated following delivery. When performed at the time of cesarean delivery, the operation is termed *cesarean hysterectomy*. If done within a short time after vaginal delivery, it is termed *postpartum hysterectomy*. *Peripartum hysterectomy* is a broader term that combines these two. In most cases, hysterectomy is total, but supracervical hysterectomy is an option. The adnexa are not usually removed. In most instances, a simple or type I hysterectomy is performed. However, for women with invasive cervical cancer, *radical hysterectomy* removes the uterus, parametrium, and proximal vagina to achieve tumor excision with negative margins. Also, for cases of placenta percreta that extend toward the pelvic sidewall, similar radical excision of the parametrium may be needed.

CESAREAN DELIVERY IN THE UNITED STATES

In the United States, the cesarean delivery rate rose from 4.5 percent in 1970 to 32.9 percent in 2009. Following this peak, the rate has trended slightly downward, and it was 32.0 percent in 2015 (Martin, 2017). Some indications for performing cesarean delivery are shown in Table 30-1. More than 85 percent of these operations are performed for four reasons—prior cesarean delivery, dystocia, fetal jeopardy, or abnormal fetal presentation. The latter three compose the main indications for primary cesarean delivery (Barber, 2011; Boyle, 2013).

TABLE 30-1

Some Indications for Cesarean Delivery

Maternal
Prior cesarean delivery
Abnormal placentation
Maternal request
Prior classical hysterotomy
Unknown uterine scar type
Uterine incision dehiscence
Prior full-thickness myomectomy
Genital tract obstructive mass
Invasive cervical cancer
Prior trachelectomy
Permanent cerclage
Prior pelvic reconstructive surgery
Prior significant perineal trauma
Pelvic deformity
HSV or HIV infection
Cardiac or pulmonary disease
Cerebral aneurysm or arteriovenous malformation
Pathology requiring concurrent intraabdominal surgery
Perimortem cesarean delivery
Maternal-Fetal
Cephalopelvic disproportion
Failed operative vaginal delivery
Placenta previa or placental abruption
Fetal
Nonreassuring fetal status
Malpresentation
Macrosomia
Congenital anomaly
Abnormal umbilical cord Doppler study
Thrombocytopenia

Prior neonatal birth trauma

HIV = human immunodeficiency virus; HSV = herpes simplex virus.

The reasons for persistently significant cesarean rates are not completely understood, but some explanations include the following:

1. Women are having fewer children, thus, a greater percentage of births are among *nulliparas,* who are at increased risk for cesarean delivery.
2. The average *maternal age* is rising, and older women, especially nulliparas, have a higher risk of cesarean delivery.
3. The use of *electronic fetal monitoring* is widespread. This practice is associated with an increased cesarean delivery rate compared with intermittent fetal heart rate auscultation. Fetal distress accounts for only a minority of all cesareans. In many more cases, concern for an abnormal or "nonreassuring" fetal heart rate tracing prompts cesarean delivery.
4. Most fetuses presenting *breech* are now delivered by cesarean.
5. The frequency of *operative vaginal delivery* has declined.
6. Rates of *labor induction* continue to rise, and induced labor, especially among nulliparas, raises the cesarean delivery rate.
7. *Obesity,* which is a cesarean delivery risk, has reached epidemic proportions.
8. Rates of cesarean delivery in women with preeclampsia have increased, whereas labor induction rates for these patients have declined.
9. The rate of *vaginal birth after cesarean—VBAC*—has decreased from a high of 28 percent in 1996 and was 11 percent in 2014 (Hamilton, 2015).
10. Elective cesarean deliveries are increasingly being performed for various indications that include *maternal request,* concern for *pelvic floor injury* associated with vaginal birth, and reduction of *fetal injury* rates.
11. *Assisted reproductive technology* is more widely used than in the past and is associated with greater cesarean delivery rates (Reddy, 2007).
12. *Malpractice litigation* related to fetal injury during spontaneous or operative vaginal delivery continues to contribute to the present cesarean delivery rate.

CESAREAN DELIVERY RISKS

To provide accurate informed consent, understanding both maternal and neonatal risks and benefits with surgery is essential. In broad terms, cesarean delivery has higher maternal surgical risks for the current and subsequent pregnancies compared with spontaneous vaginal birth. This is balanced against lower rates of perineal injury and short-term pelvic floor disorders. For the neonate, cesarean delivery offers lower rates of birth trauma and stillbirth but greater rates of initial respiratory difficulties.

Maternal Mortality and Morbidity

For the mother, death attributable solely to cesarean delivery is rare in the United States. Even so, numerous studies attest to increased mortality risks. Clark and colleagues (2008), in a review of nearly 1.5 million pregnancies, found maternal mortality rates of 2.2 per 100,000 cesarean deliveries compared with 0.2 per 100,000 vaginal births. In a metaanalysis of 203 studies, Guise and coworkers (2010) reported a maternal mortality rate of 13 per 100,000 with elective repeat cesarean delivery compared with 4 per 100,000 women undergoing a trial of labor after prior cesarean.

Similar to mortality rates, the frequencies of some maternal complications are increased with all cesarean compared with vaginal deliveries. Villar and associates (2007) reported that maternal morbidity rates increased twofold with cesarean compared with vaginal delivery. Principal among these are infection, hemorrhage, and thromboembolism. In addition, anesthetic complications, which also rarely include death, have a greater incidence with cesarean compared with vaginal delivery (Cheesman, 2009; Hawkins, 2011). Adjacent organs infrequently may be injured, which is described in detail in Urinary Tract or Bowel Injury.

Women who undergo a cesarean delivery are much more likely to be delivered by a repeat operation in subsequent pregnancies. For women undergoing subsequent cesarean, the maternal risks just described are even greater (Cahill, 2006; Marshall, 2011; Silver, 2006).

As an advantage, cesarean delivery is associated with lower rates of urinary incontinence and pelvic organ prolapse than is vaginal birth (Glazener, 2013; Gyhagen, 2013a,b; Handa, 2011; Leijonhufvud, 2011). Rates of anal incontinence appear uninfluenced by delivery route (Fritel, 2007; Nelson, 2010). Protective advantages persist to some degree over time, but cesarean delivery is not totally protective. Moreover, longitudinal studies suggest that initial pelvic floor advantages gained from cesarean delivery are lost as women age (Dolan, 2010; MacArthur, 2011, 2013; Nelson, 2010). To address this, the National Institutes of Health (2006) held a conference on cesarean delivery on maternal request. It summarized that stress urinary incontinence rates after elective cesarean delivery are lower than those following vaginal delivery. However, the duration of this protection is unclear, particularly in older and multiparous populations. This same panel considered the evidence implicating vaginal delivery in other pelvic floor disorders to be weak and not favoring either delivery route.

Neonatal Morbidity

Cesarean delivery is associated with a lower rate of fetal trauma (Linder, 2013; Moczygemba, 2010). Alexander and colleagues (2006) found that fetal injury complicated 1 percent of cesarean deliveries. Skin laceration was most common, but others included cephalohematoma, clavicular fracture, brachial plexopathy, skull fracture, and facial nerve palsy. Cesarean deliveries following a failed operative vaginal delivery attempt had the highest injury rate, whereas the lowest rate—0.5 percent—occurred in the elective cesarean delivery group. That said, Worley and colleagues (2009) noted that approximately a third of women who were delivered at Parkland Hospital entered spontaneous labor at term, and 96 percent of these delivered vaginally without adverse neonatal outcomes.

Some evidence shows higher asthma and allergy rates in those delivered by cesarean. With the hope to improve neonatal microbiota, swabbing the newborn mouth with a gauze that was incubated in the maternal vagina 1 hour before surgery is described in preliminary studies. However, the American College of Obstetricians and Gynecologists (2017e) does not encourage this practice due to few data and the potential for transmission of harmful organisms.

Cesarean Delivery on Maternal Request

Some women request elective cesarean delivery. Data regarding the true incidence of *cesarean delivery on maternal request (CDMR)* are poor. Rate estimates range from 1 to 8 percent in the United States (Barber, 2011; Declercq, 2005; Gossman, 2006; Menacker, 2006).

Reasons for the request include pelvic floor protection, convenience, fear of childbirth, and reduced risk of fetal injury. Data to address these concerns are slowly accruing. One study of more than 66,000 Chinese parturients compared outcomes of those who elected planned vaginal or primary cesarean delivery (Liu, 2015). Short-term serious maternal morbidity and neonatal mortality rates were similar. For the newborns, rates of birth trauma, infection, and hypoxic ischemic encephalopathy were low in both groups but statistically lower with cesarean delivery. Respiratory distress syndrome rates were greater in the CMDR cohort. A smaller study comparing these two routes of delivery support these findings (Larsson, 2011).

The debate surrounding CDMR includes these medical points, the concept of informed free choice by the woman, and the autonomy of the physician in offering CMDR. During the National Institutes of Health panel (2006) cited above, participants noted that most of the maternal and neonatal outcomes examined had insufficient data to permit recommendations. Despite this, the panel was able to draw a few conclusions, which are echoed by the American College of Obstetricians and Gynecologists (2017a). Namely, CMDR should not be performed before 39 weeks' gestation unless fetal lung maturity is confirmed. Cesarean delivery is ideally avoided in women desiring several children because of placental implantation abnormalities and cesarean hysterectomy risks. Finally, CMDR should not be motivated by the unavailability of effective pain management.

PATIENT PREPARATION

Delivery Availability

No nationally recognized standard of care currently dictates the acceptable time interval to begin cesarean delivery. Previously, a 30-minute decision-to-incision interval was recommended. In studying this, Bloom and coworkers (2001) found that 69 percent of 7450 cesareans performed in labor commenced more than 30 minutes after the decision to operate. In a second study, Bloom and colleagues (2006) evaluated cesarean deliveries performed for emergency indications. They reported that failure to achieve a cesarean delivery decision-to-incision time of less than 30 minutes was not associated with a negative neonatal outcome. A subsequent systematic review echoed this finding (Tolcher, 2014). Despite this, when faced with an acute, catastrophic deterioration in fetal condition, cesarean delivery usually is indicated as rapidly as possible, and thus purposeful delays are inappropriate. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that facilities giving obstetrical care should have the ability to initiate cesarean delivery in a time frame that best incorporates maternal and fetal risks and benefits.

Informed Consent

Obtaining informed consent is a process and not merely a medical document (American College of Obstetricians and Gynecologists, 2015). The conversation should enhance a woman's awareness of her diagnosis and contain a discussion of medical and surgical care alternatives, procedure goals and limitations, and surgical risks. For women with a prior cesarean delivery, the option of a trial of labor should be included for suitable candidates. Also, in those desiring permanent sterilization or intrauterine device insertion, consenting for these can be completed concurrently.

An informed patient may decline a particular recommended intervention, and a woman's decision-making autonomy must be respected. In the medical record, clinicians should document her reasons for refusal and should note that the intervention's value and the health consequences of not proceeding with it have been explained.

For Jehovah's Witnesses, informed consent discussions regarding blood products ideally begin early in pregnancy. Acceptable blood products vary widely among individual women, and a preoperative checklist of approved products allows superior preparation (Hubbard, 2015; Husarova, 2016). In general, red cells, white cells, platelets, and plasma are viewed as primary blood components and are eschewed. However, certain clotting factors or cell fractions may be acceptable (Lawson, 2015). Before and after surgery, iron, folate, and, if necessary, erythropoietin are accepted agents to help maximize hemoglobin levels. Perioperatively, phlebotomy should be limited, and pediatric collection tubes are preferable. Intraoperative options include treatment of atony to limit blood loss; topical hemostatic agents, tranexamic acid, and desmopressin to promote clot formation; red blood cell salvage or acute normovolemic hemodilution to provide autologous donation; and controlled hypotensive anesthesia, uterine artery embolization, occlusive vascular balloons, and temporary aortic compression for uncontrolled bleeding (Belfort, 2011; Mason, 2015).

Timing of Scheduled Cesarean Delivery

Adverse neonatal sequelae from neonatal immaturity with elective delivery before 39 completed weeks are appreciable (Clark, 2009; Tita, 2009). To avoid these, assurance of fetal maturity before scheduled elective surgery is essential as outlined by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) and discussed in Chapter 31 (Labor and Delivery Considerations). To assist with this and other components of cesarean delivery planning, the American College of Obstetricians and Gynecologists (2011, 2014b) has created Patient Safety Checklists to be completed before the planned surgery.

Preoperative Care

If cesarean delivery is scheduled, a sedative may be given at bedtime the night before surgery. In general, no other sedatives, narcotics, or tranquilizers are administered until after the fetus is born. In one small randomized trial, no benefits were gained from a presurgical enema (Lurie, 2012). Solid food intake is stopped at least 6 to 8 hours before the procedure. Uncomplicated patients may have moderate amounts of clear liquids up to 2 hours before surgery (American Society of Anesthesiologists, 2016). This comports with Enhanced Recovery After Surgery (ERAS) protocols that strive to maintain anabolic homeostasis and advocate clear carbohydrate drinks up to 2 hours before scheduled surgery and early postoperative feeding (Ljungqvist, 2017). Although evidence supports an ERAS approach for many procedures, data specifically addressing this for cesarean delivery are scarce (Wrench, 2015).

The woman scheduled for repeat cesarean delivery typically is admitted the day of surgery and evaluated by the obstetrical and anesthesia teams. Recently performed hematocrit and indirect Coombs test are reviewed. If the latter is positive, then availability of compatible blood must be ensured.

As discussed in Chapter 25 (Neuraxial Analgesia), regional analgesia is preferred for cesarean delivery. An antacid is given shortly before regional analgesia or induction of general anesthesia. One example is Bicitra, 30 mL orally in a single dose. This minimizes the lung injury risk from gastric acid aspiration. Once the woman is supine, a wedge beneath the right hip and lower back creates a left lateral tilt to aid venous return and avoid hypotension. Data are insufficient to determine the value of fetal monitoring before scheduled cesarean delivery in women without risk factors. Our practice is to obtain a 5-minute tracing prior to elective cases. At minimum, fetal heart sounds should be documented in the operating room prior to surgery.

Of further preparations, hair removal at the surgical site does not lower surgical site infection (SSI) rates (Kowalski, 2016). However, if hair is obscuring, it is removed the day of surgery by clipping, which is associated with fewer SSIs than shaving (Tanner, 2011). Chemical depilation the night before surgery compared with clipping has similar SSI rates (Lefebvre, 2015). An electrosurgical grounding pad is placed near the surgical incision and typically on the lateral thigh. An indwelling bladder catheter is typically placed at Parkland Hospital to collapse the bladder away from the hysterotomy incision, to avert urinary retention secondary to regional analgesia, and to allow accurate postoperative urine measurement. Small studies show that catheterization may be withheld in hemodynamically stable women to minimize urinary infections (Abdel-Aleem, 2014; Li, 2011; Nasr, 2009).

The risk of venous thromboembolism is increased with pregnancy and almost doubled in those undergoing cesarean delivery (James, 2006). Accordingly, for all women not already receiving thromboprophylaxis, the American College of Obstetricians and Gynecologists (2017d) recommends initiation of pneumatic compression hose before cesarean delivery. These are usually discontinued once the woman ambulates. Recommendations between organizations vary, and the American College of Chest Physicians suggests only early ambulation for women without risk factors who are undergoing cesarean delivery (Bates, 2012). For women already receiving prophylaxis or those with increased risk factors, they support escalation of prophylaxis. Last, the Royal College of Obstetricians and Gynaecologists (2015) are the most conservative and suggest pharmacological prophylaxis for the largest proportion of patients. These various methods and recommendations are discussed in Chapter 52 and are shown in Table 52-6.

Some women scheduled for cesarean delivery have concurrent comorbidity that requires specific management in anticipation of surgery. Among others, these include insulin-requiring or gestational diabetes, coagulopathy or thrombophilia, chronic corticosteroid use, and significant reactive airway disease. Surgical preparations are discussed in the respective chapters covering these topics.

Infection Prevention

Antibiotic Prophylaxis

Cesarean delivery is considered a clean contaminated case, and postoperative febrile morbidity is common. Numerous good-quality trials show that a single dose of an antibiotic given at the time of cesarean delivery significantly decreases infectious morbidity (Smaill, 2014). Although more obvious for women undergoing unscheduled cesarean delivery, this practice also pertains to women undergoing elective surgery (American College of Obstetricians and Gynecologists, 2016). Depending on drug allergies, most recommend a single intravenous dose of a β-lactam antibiotic—either a cephalosporin or extended-spectrum penicillin. A 1-g dose of cefazolin (Ancef) is an efficacious and cost-effective choice. Additional doses are considered in cases with blood loss >1500 mL or with duration longer than 3 hours. Recommendations for the best dose in obese parturients are conflicting (Ahmadzia, 2015; Maggio, 2015; Swank, 2015; Young, 2015). One recent pharmacokinetic analysis showed sufficient tissue levels with a 2-g dose for cesarean deliveries lasting 1.5 hours. Authors recommended consideration for redosing in obese women if surgeries were longer (Grupper, 2017).

A growing body of evidence supports extending the antibiotic spectrum (Andrews, 2003; Tita, 2008). One large randomized trial added azithromycin, 500 mg intravenously, to standard prophylaxis prior to cesarean delivery for women in labor or with ruptured membranes (Tita, 2016). Rates of wound infection and endometritis were significantly lower in the extended-spectrum group compared with those in the standard prophylaxis cohort.

In pregnant women with a history of infection with methicillin-resistant *Staphylococcus aureus* (MRSA), a single dose of vancomycin added to the standard prophylaxis for cesarean deliveries can be elected. Decolonization plays a limited role but may be considered prior to a planned cesarean delivery in women with known MRSA colonization (American College of Obstetricians and Gynecologists, 2016).

Significant penicillin or cephalosporin allergy, which manifests by anaphylaxis, angioedema, respiratory distress, or urticaria, merits prophylaxis with a single 600-mg intravenous dose of clindamycin combined with a weight-based dose of an aminoglycoside as an alternative. A 900-mg clindamycin dose is used for obese patients.

Antibiotic administration before surgical incision lowers postoperative infection rates without adverse neonatal effects compared with drug administration after umbilical cord clamping (Mackeen, 2014b; Sullivan, 2007; Witt, 2011). Prophylaxis is ideally administered within the 60 minutes prior to the start of planned cesarean delivery. For emergent delivery, antibiotics are given as soon as feasible.

Preoperative preparation of the abdominal wall skin is effective to prevent wound infection. Either chlorhexidine or povidone-iodine solutions are suitable (Hadiati, 2014; Ngai, 2015; Springel, 2017). In studies that found a difference, chlorhexidine was favored, and this is our practice (Menderes, 2012; Tuuli, 2016a). In addition, preoperative vaginal cleansing with a povidone-iodine scrub has been evaluated in small randomized trials (Haas, 2014; Caissutti, 2017). Some showed lower rates of metritis, especially for those with ruptured membranes or active labor, but not lower rates of wound infection (Haas, 2010; Memon, 2011; Yildirim, 2012). Some recommend preoperative vaginal cleansing, but we do not do this at Parkland Hospital.

Antibiotic prophylaxis against infective endocarditis is not recommended for most cardiac conditions—exceptions are women with cyanotic heart disease, prosthetic valves, or both (American College of Obstetricians and Gynecologists, 2016). Regimens selected for routine cesarean infection prophylaxis will also serve as appropriate endocarditis coverage (Chap. 49, Infective Endocarditis).

Other Preventions

Glycemic control in diabetics lowers wound infection rates and is emphasized in Chapter 57 (First Trimester). Smoking is another modifiable risk, and its mitigation is especially helpful for morbidly obese women (Alanis, 2010; Avila, 2012; Shree, 2016). Intraoperative normothermia lowers wound infection rates in general surgery and is a Surgical Care Improvement Project measure (Kurz, 1996; The Joint Commission, 2016). This tenet might logically be extrapolated to cesarean delivery, although definitive studies are lacking (Carpenter, 2012). Perioperative supplementation with high-concentration inspired oxygen does not lower wound infection rates (Duggal, 2013; Klingel, 2013).

Surgical Safety

The Joint Commission (2013) established a protocol to prevent surgical errors. For cesarean delivery, all relevant documents are verified immediately before surgery, and a “time out” is completed. The “time out” requires attention of the entire team to confirm that the patient, site, and procedure are correct. Important discussions also include introduction of the patient-care team members, verification of prophylactic antibiotics, estimation of procedure length, and communication of anticipated complications. Additionally, requests for special instrumentation should be addressed preoperatively to prevent potential patient compromise and intraoperative delays.

An instrument, sponge, and needle count before and after surgery is crucial to surgical safety. If counts are not reconciled, radiographic imaging for retained foreign objects is obtained (American College of Obstetricians and Gynecologists, 2014a).

CESAREAN DELIVERY TECHNIQUE

With minor variations, surgical performance of cesarean delivery is comparable worldwide. Most steps are founded on evidence-based data, and these have been reviewed by Dahlke and associates (2013). As with all surgery, a clear understanding of relevant anatomy is essential, and this is described and illustrated in Chapter 2 (Anterior Abdominal Wall).

Laparotomy

In obstetrics, a suprapubic transverse incision or a midline vertical one is chosen for laparotomy. Transverse abdominal entry is by either Pfannenstiel or Maylard incisions. Of all these, the Pfannenstiel incision is selected most frequently for cesarean delivery.

Transverse incisions follow Langer lines of skin tension. Thus, compared with vertical ones, Pfannenstiel incisions offer superior cosmesis and lower incisional hernia rates. Use of the Pfannenstiel incision, however, is often discouraged for cases in which a large operating space is essential or in which access to the upper abdomen may be needed. With transverse incisions, because of the layers created during incision of the internal and external oblique aponeuroses, purulent fluid can collect between these. Therefore, some favor a midline vertical incision for cases with high infection risks. Emergent entry is typically faster with vertical incision during primary and repeat cesarean delivery (Wylie, 2010). Last, neurovascular structures, which include the ilioinguinal and iliohypogastric nerves and superficial and inferior epigastric vessels, are often encountered with transverse incisions. Logically, bleeding, wound hematoma, and neurological disruption may more frequently complicate these incisions compared with vertical ones. The best incision for the morbidly obese parturient is unclear (Smid, 2016). As discussed in Chapter 48 (Bariatric Surgery), our preference with very obese women is a periumbilical midline vertical incision.

The Maylard incision differs mainly from the Pfannenstiel in that the bellies of the rectus abdominis muscle are transected horizontally to widen the operating space. It is technically more difficult due to its required muscle cutting and isolation and ligation of the inferior epigastric arteries, which lie laterally to these muscle bellies.

Once access is gained, metal handheld retractors provide exposure for hysterotomy. A few small randomized studies have evaluated postcesarean wound infection rates with a disposable plastic barrier retractor (Alexis-O). Results showing benefit are contradictory (Hinkson, 2016; Scolari Childress, 2016; Theodoridis, 2011).

Transverse Incisions

With the Pfannenstiel incision, the skin and subcutaneous tissue are incised using a low, transverse, slightly curvilinear incision. This is made at the level of the pubic hairline, which is typically 3 cm above the superior border of the symphysis pubis. The incision is extended laterally sufficiently to accommodate delivery—12 to 15 cm is typical.

Sharp dissection is continued through the subcutaneous layer to the fascia. The superficial epigastric vessels can usually be identified halfway between the skin and fascia, several centimeters from the midline, and are coagulated. If lacerated, these may be suture ligated with 3–0 plain gut suture or coagulated with an electrosurgical blade.

The fascia is then incised sharply at the midline. The anterior abdominal fascia is typically composed of two visible layers, the aponeurosis from the external oblique muscle and a fused layer containing aponeuroses of the internal oblique and transverse abdominis muscles. Ideally, the two layers are individually incised during lateral extension of the fascial incision. The inferior epigastric vessels usually lie outside the lateral border of the rectus abdominis muscle and beneath the fused aponeuroses of the internal oblique and transverse abdominis muscles. Thus, although infrequently required, extension of the fascial incision further laterally may cut these vessels. With extension, these vessels are best identified and coagulated or ligated to prevent bleeding and vessel retraction.

Once the fascia is incised, the inferior fascial edge is grasped with Kocher clamps and elevated by an assistant as the operator separates the fascial sheath from the underlying rectus abdominis muscle either bluntly or sharply until the superior border of the symphysis pubis is reached. Next, the superior fascial edge is grasped and again, separation of fascia from the rectus muscle is completed. Blood vessels coursing between the sheath and muscles are clamped, cut, and ligated, or they are coagulated with an electrosurgery blade. Meticulous hemostasis is imperative to lower rates of incisional hematoma and infection. The fascial separation progresses cephalad and laterally to create a semicircular area above the transverse incision with a radius of approximately 8 cm. This will vary depending on fetal size. The rectus abdominis and pyramidalis muscles are then separated in the midline, first superiorly and then inferiorly, by sharp and blunt dissection to expose the transversalis fascia and peritoneum.

The transversalis fascia and preperitoneal fat are bluntly dissected away to reach the underlying peritoneum. The peritoneum near the upper end of the incision is opened carefully, either bluntly or by elevating it with two hemostats placed approximately 2 cm apart. This upper site lowers cystotomy risks. The tented fold of peritoneum between the clamps is examined and palpated to ensure that omentum, bowel, or bladder is not adjacent. The peritoneum is then incised. The peritoneal incision is extended superiorly to the upper pole of the fascial dissection and downward to just above the peritoneal reflection over the bladder. Importantly, in women with prior intraabdominal surgery, including cesarean delivery, omentum or bowel may be adhered to the undersurface of the peritoneum. In women with obstructed labor, the bladder may be pushed cephalad almost to the level of the umbilicus.

Midline Vertical Incision

This incision begins 2 to 3 cm above the superior margin of the symphysis. It should sufficiently long to allow fetal delivery, and 12 to 15 cm is typical. Sharp or electrosurgical blade dissection through the subcutaneous layers ultimately exposes the anterior rectus sheath. A small opening is made sharply with scalpel in the upper half of the linea alba. Placement here helps avoid potential cystotomy. Index and middle fingers are placed beneath the fascia to elevate it, and the fascial incision is extended first superiorly and then inferiorly with scissors. Midline separation of the rectus muscles and pyramidalis muscles and peritoneal entry are similar to those with the Pfannenstiel incision.

Hysterotomy

Most often, the lower uterine segment is incised transversely as described by Kerr in 1921. Occasionally, vertical incision confined solely to the lower uterine segment may be elected (Krönig, 1912). In contrast, a classical incision begins as a low-vertical incision, which is then extended cephalad into the active portion of the uterine corpus. Last, a fundal or even posterior incision may be selected for cases with placental accrete syndromes.

Low Transverse Cesarean Incision

For most cesarean deliveries, this incision is preferred. Compared with a classical incision, it is easier to repair, causes less incision-site bleeding, and promotes less bowel or omentum adherence to the myometrial incision. Located in the inactive segment, it also is less likely to rupture during a subsequent pregnancy.

Before any hysterotomy, the surgeon palpates the fundus to identify degrees of uterine rotation. The uterus may be rotated so that one round ligament is more anterior and closer to the midline. In such cases, the uterus can be manually reoriented and held to permit centering of the incision. This avoids incision extension into and laceration of the adjacent uterine artery. A moist sponge may be used to pack protruding bowel away from the operative field.

The reflection of peritoneum at the upper margin of the bladder and overlying the lower uterine segment is grasped in the midline with forceps and incised transversely with scissors (Fig. 30-1). Following this initial incision, scissors are inserted between peritoneum and lower uterine segment. Open scissors are pushed laterally from the midline on each side. This transverse peritoneal incision extends almost the full length of the lower uterine segment. As the lateral margin on each side is approached, the scissors are directed slightly cephalad (Fig. 30-2). The lower edge of peritoneum is elevated, and the bladder is gently separated from the underlying lower uterine segment with blunt or sharp dissection within this vesicouterine space (Fig. 30-3). This bladder flap creation effectively moves the bladder away from the planned hysterotomy site. It also helps prevent bladder laceration if an unintended inferior hysterotomy extension occurs during fetal delivery.

FIGURE 30-1
The loose peritoneum above the bladder reflection is grasped with forceps and incised with Metzenbaum scissors.

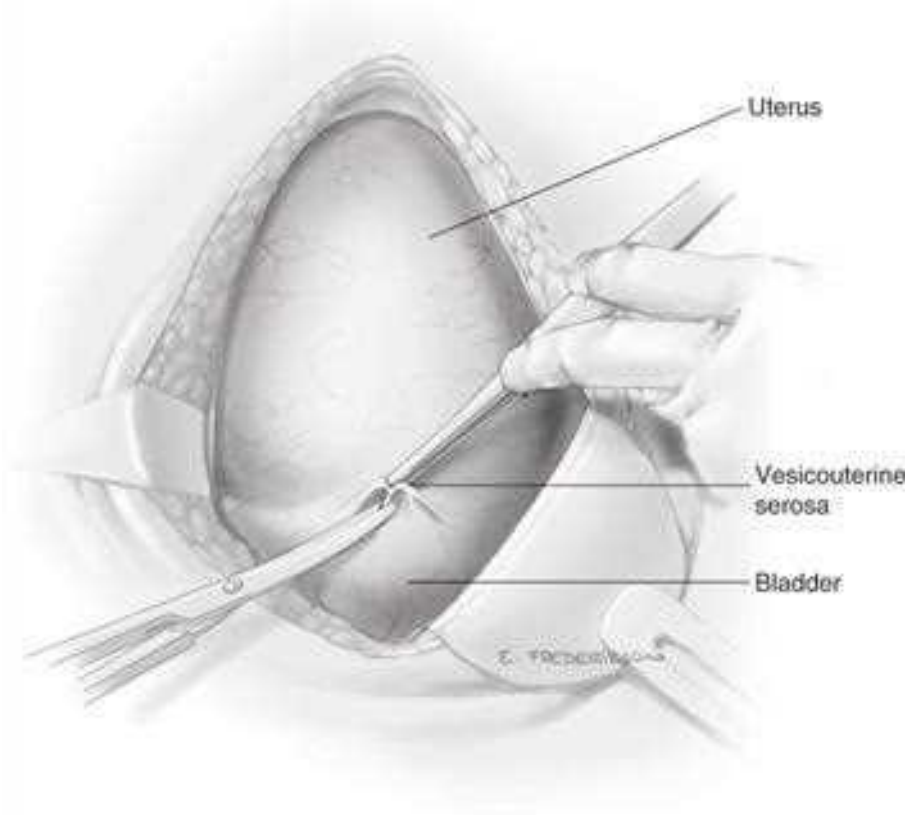


FIGURE 30-2

This peritoneal edge is elevated and incised laterally.

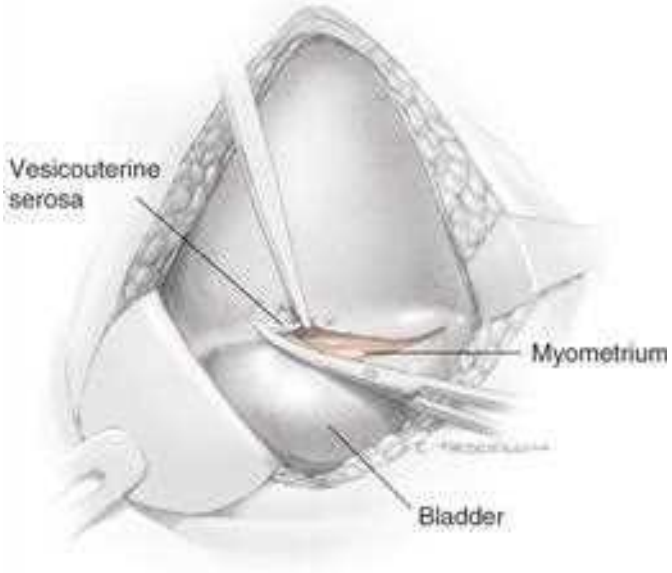
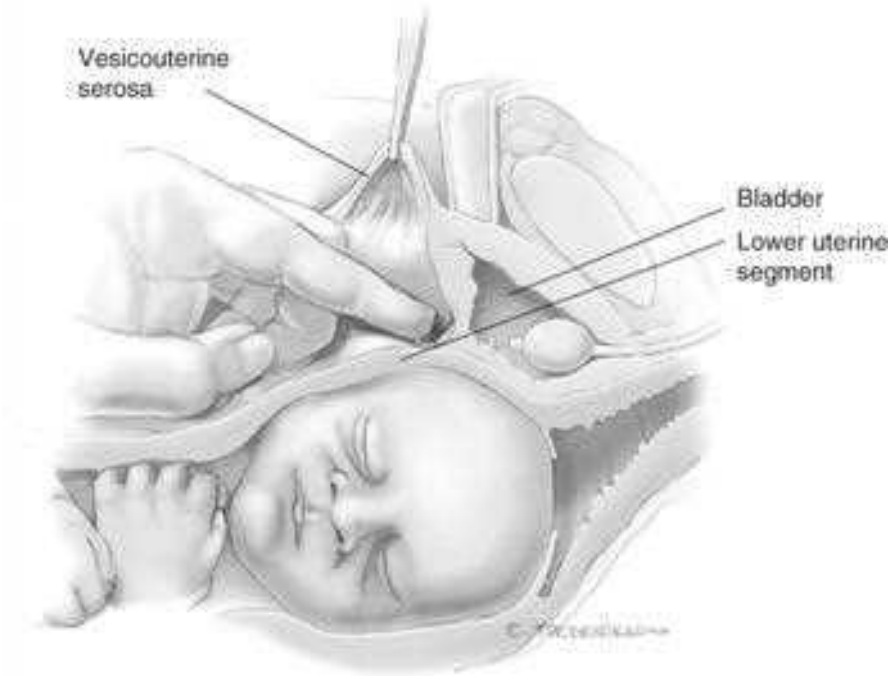


FIGURE 30-3

Cross section shows blunt dissection of the bladder off the uterus to expose the lower uterine segment.



In general, this caudad separation of bladder does not exceed 5 cm and usually is less. However, in instances in which cesarean hysterectomy is planned or anticipated, extended caudad dissection is recommended to aid total hysterectomy and decrease the risk of cystotomy.

Some surgeons do not create a bladder flap. The main advantage is a shorter skin incision-to-delivery time. However, data supporting this practice are limited (O'Neill, 2014; Tuuli, 2012).

Uterine Incision

The uterus is entered through the lower uterine segment. Digital palpation to find the physiological border between firmer upper segment myometrium and the more flexible lower segment can guide placement. The bladder flap incision can also serve as a guide, and a hysterotomy site near this line is often selected.

For women with advanced or complete cervical dilatation, the hysterotomy is placed relatively higher. Failure to adjust increases the risk of lateral extension of the incision into the uterine arteries. It may also lead to incision of the cervix or vagina rather than the lower uterine segment. Such incisions into the cervix can distort postoperative cervical anatomy.

The uterus can be incised by various techniques. Each is initiated by using a scalpel to transversely incise the exposed lower uterine segment for 1 to 2 cm in the midline (Fig. 30-4). Repetitive shallow strokes avoid fetal laceration. As the myometrium thins, a fingertip can then bluntly enter the uterine cavity. Once the uterus is opened, the hysterotomy is lengthened by simply spreading the incision, using lateral and slightly upward pressure applied with each index finger (Fig. 30-5). Some evidence also supports widening the lower-uterine-segment incision instead with fingers pulling in opposition in a cephalocaudad direction (Cromi, 2008; Xodo, 2016).

FIGURE 30-4

The myometrium is incised with shallow strokes to avoid cutting the fetal head.

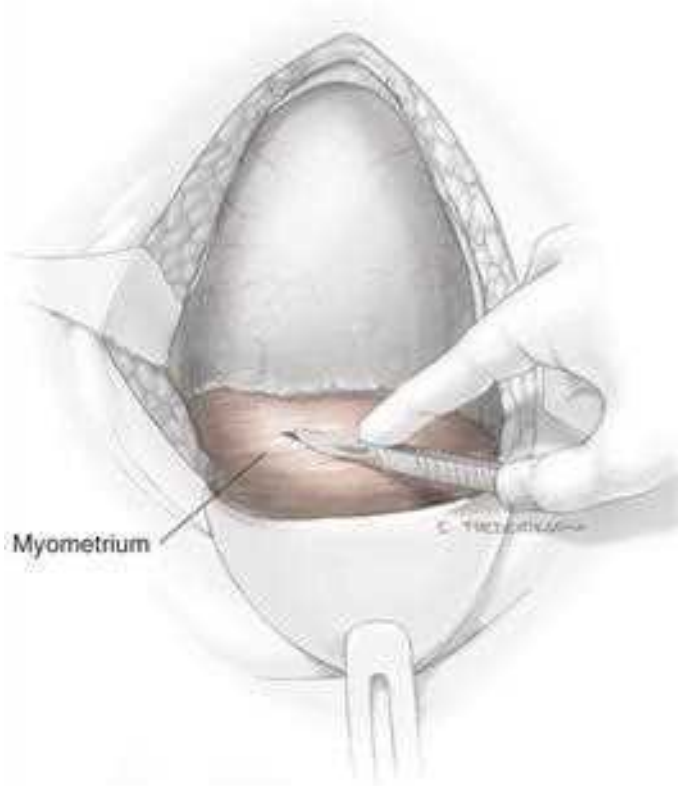
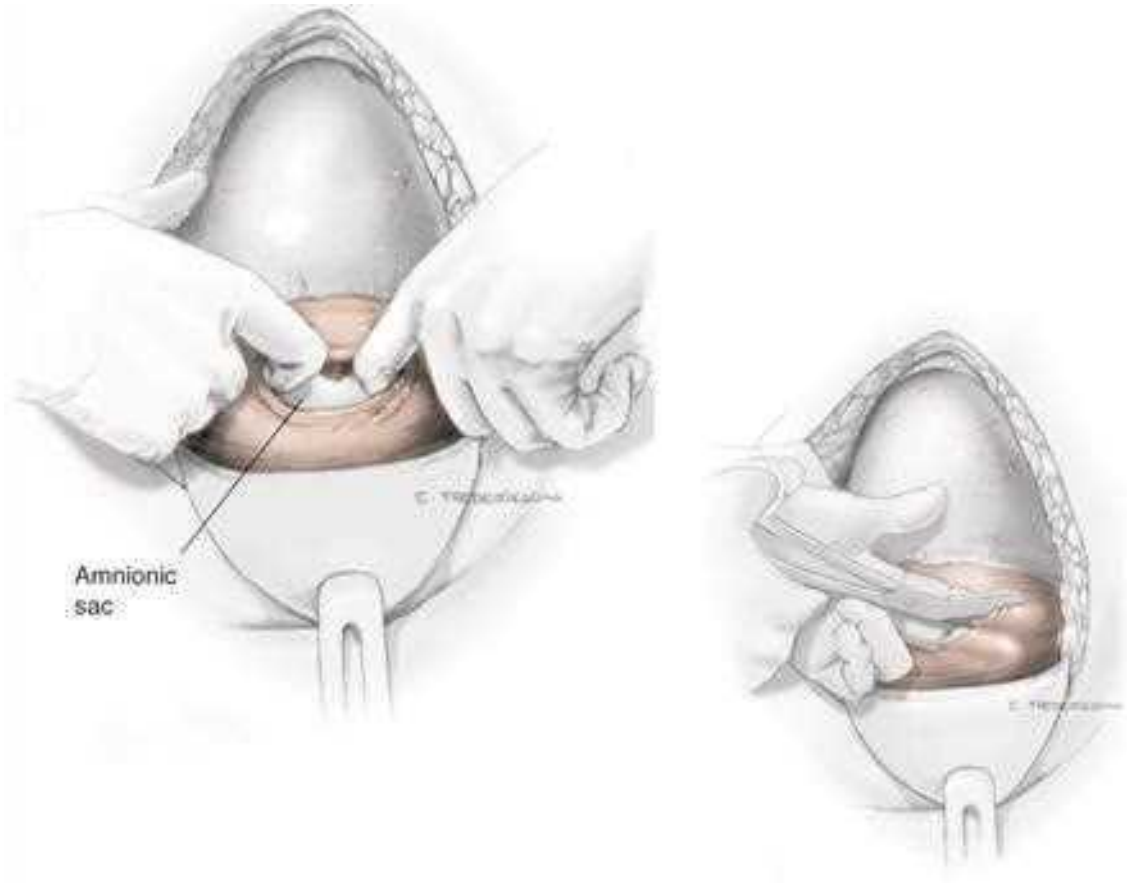


FIGURE 30-5

After entering the uterine cavity, the incision is extended laterally with fingers or with bandage scissors (*inset*).



Alternatively, if the lower uterine segment is thick and unyielding, cutting laterally and then slightly upward with bandage scissors will lengthen the incision. Importantly, when scissors are used, the index and midline fingers of the nondominant hand should be insinuated beneath the myometrium and above fetal parts to

prevent fetal laceration. Comparing blunt and sharp expansion of the initial uterine incision, blunt stretch is associated with fewer unintended incision extensions, shorter operative time, and less blood loss. However, the rates of infection and need for transfusion do not differ (Asıcıoglu, 2014; Saad, 2014).

The uterine incision is made large enough to allow delivery of the fetus without tearing into the uterine vessels that course along the lateral uterine margins. If the placenta is encountered in the incision line, it must be either detached or incised. Placental function is thereby compromised, and thus delivery is performed expeditiously.

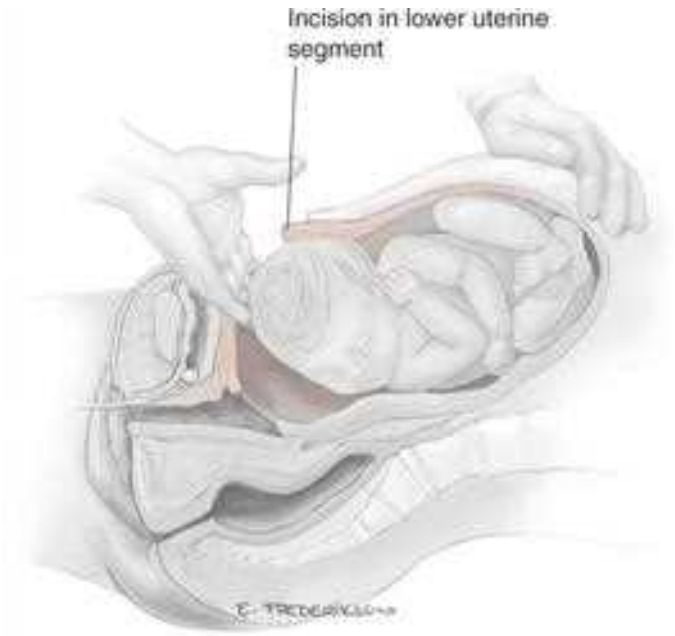
At times, a low transverse hysterotomy is selected but provides inadequate room for delivery. In such instances, one corner of the hysterotomy incision is extended cephalad into the contractile portion of the myometrium—a *J incision*. If this is completed bilaterally, a *U incision* is formed. Last, some prefer instead to extend in the midline—a *T incision*. As expected, each has higher intraoperative blood loss (Boyle, 1996; Patterson, 2002). Moreover, as these extend into the contractile portion, a trial of labor is more likely to be complicated by uterine rupture in future pregnancies.

Delivery of the Fetus

In a cephalic presentation, a hand is slipped into the uterine cavity between the symphysis and fetal head. The head is elevated gently with the fingers and palm through the incision. Once the head enters the incision, delivery may be aided by modest transabdominal fundal pressure (Fig. 30-6).

FIGURE 30-6

Delivery of the fetal head.



After a long labor with cephalopelvic disproportion, the fetal head may be tightly wedged in the birth canal. Release of an impacted fetal head raises the risk of hysterotomy extension, of associated blood loss, and of fetal skull fracture. In this situation, there are three considerations for delivery. First, a “push” method may be used. With this, upward pressure exerted by a hand in the vagina by an assistant will help to dislodge the head and allow its delivery above the symphysis. If this is anticipated, a patient in frog-leg position may allow easier vaginal access.

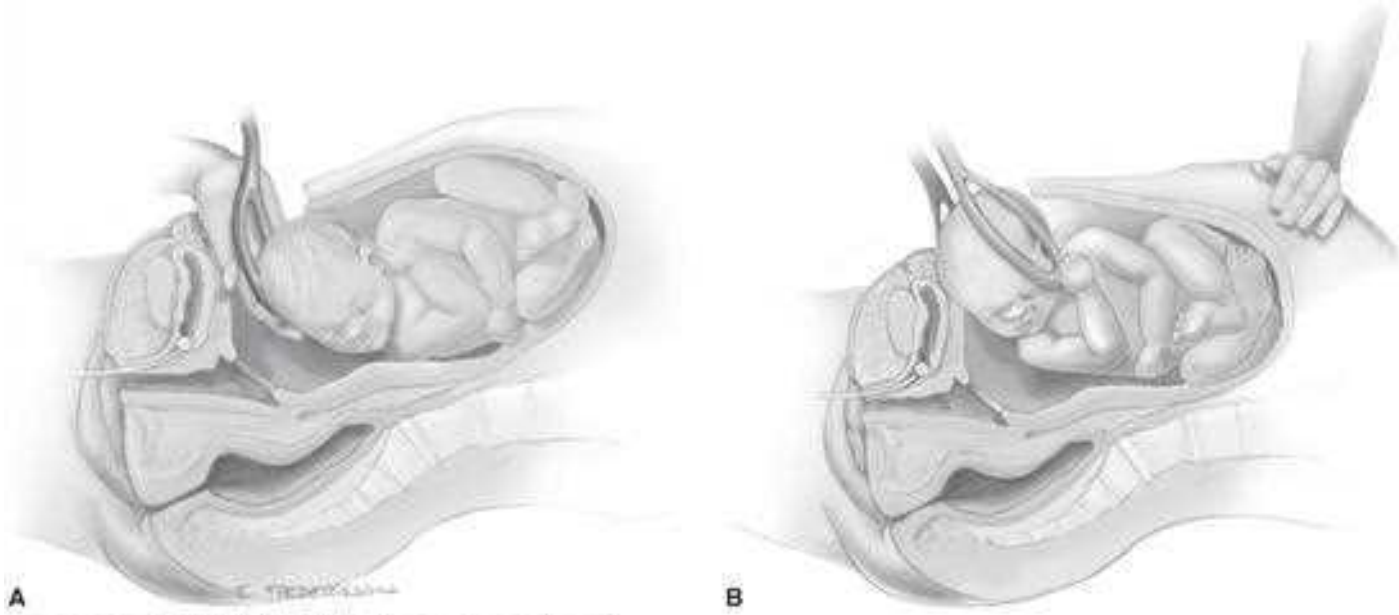
Second, as an alternative, a “pull” method grasps the fetal legs to bring them through the hysterotomy. The fetus is then delivered by traction as one would complete a breech extraction. Support for this latter approach comes only from small randomized trials and retrospective cohort studies (Berhan, 2014; Jeve, 2016; Nooh, 2017). A low vertical hysterotomy incision, which will give more room for the “pull” technique, may be selected. If a low transverse incision has already been made, then this can be extended to a J-, U-, or T-incision as previously discussed.

The third method is use of the “fetal pillow,” which is a distensible intravaginal balloon that when inflated, elevates the fetal head. The device is available outside the United States, but evidence for its efficacy is limited (Safa, 2016; Seal, 2016).

Conversely, in women without labor, the fetal head may be unmolded and without a leading cephalic point. The round head may be difficult to lift through the uterine incision in a relatively thick lower segment that is unattenuated by labor. In such instances, either forceps or a vacuum device may be used to deliver the fetal head (Fig. 30-7).

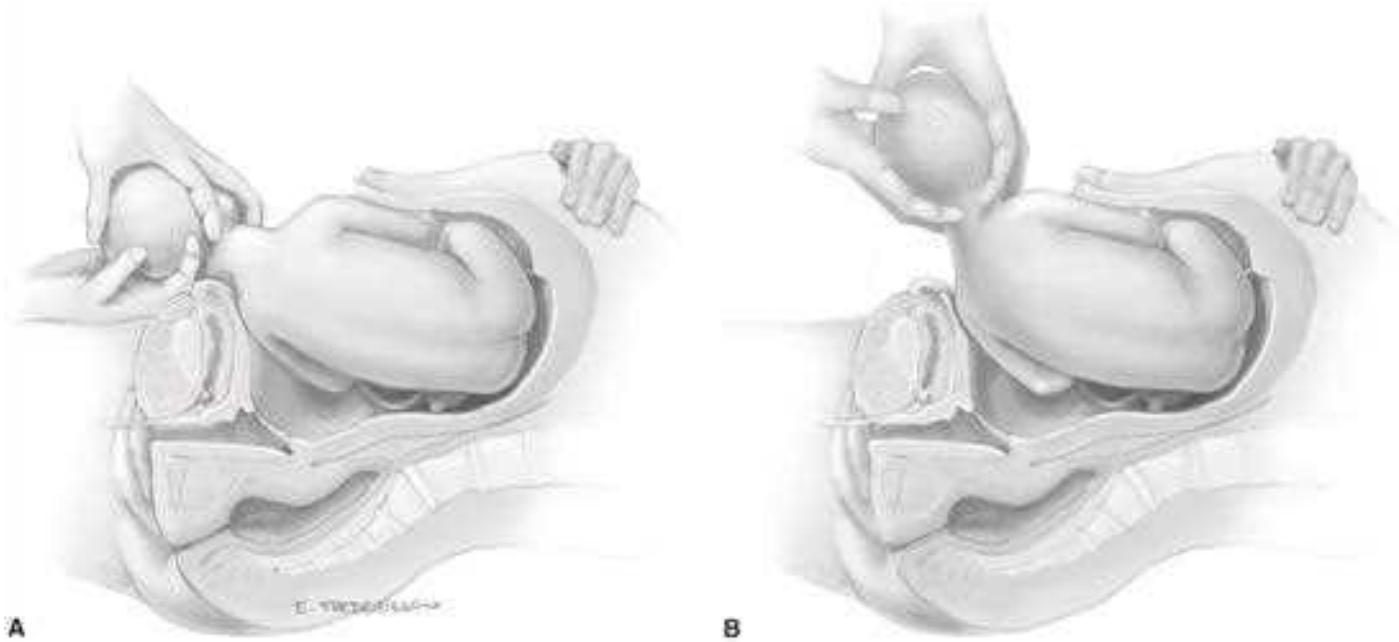
FIGURE 30-7

A. The first cesarean forceps blade is placed. **B.** Slight upward and outward traction is used to lift the head through the incision.



After head delivery, a finger should be passed across the fetal neck to determine whether it is encircled by one or more umbilical cord loops. If present, these are slipped over the head. The head is rotated to an occiput transverse position, which aligns the fetal bisacromial diameter vertically. The sides of the head are grasped with two hands, and gentle downward traction is applied until the anterior shoulder enters the hysterotomy incision (Fig. 30-8). Next, by upward movement, the posterior shoulder is delivered. During delivery, abrupt or powerful force is avoided to avert brachial plexus injury. With steady outward traction, the rest of the body then readily follows. Gentle fundal pressure may aid this.

FIGURE 30-8
The anterior **(A)** and then the posterior **(B)** shoulder are delivered.



With some exceptions, current American Heart Association neonatal resuscitation recommendations eschew suctioning immediately following birth, even with meconium present (Wyckoff, 2015). A fuller discussion of this and delayed umbilical cord clamping is found in Chapter 27 (Delivery of the Shoulders). The umbilical cord is clamped, and the newborn is given to the team member who will conduct resuscitative efforts as needed.

Comparing elective cesarean under neuraxial anesthesia and spontaneous vaginal deliveries, studies show that the need for neonatal resuscitation is not practically significant between the two (Atherton, 2006; Gordon, 2005; Jacob, 1997). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that “a qualified person who is skilled in neonatal resuscitation should be in the delivery room.” At Parkland Hospital, pediatric nurse practitioners attend uncomplicated, scheduled cesarean deliveries. Notably, as anticipated neonatal risks rise, so too should the resuscitative skills of the attendants (Wyckoff, 2015).

To promote breastfeeding, the American College of Obstetricians and Gynecologists (2017b) recommends skin-to-skin contact between newborn and mother in the delivery room. Although most randomized trials focus on vaginal birth, several small studies support such contact following cesarean delivery, and this our practice (Moore, 2016; Stevens, 2014).

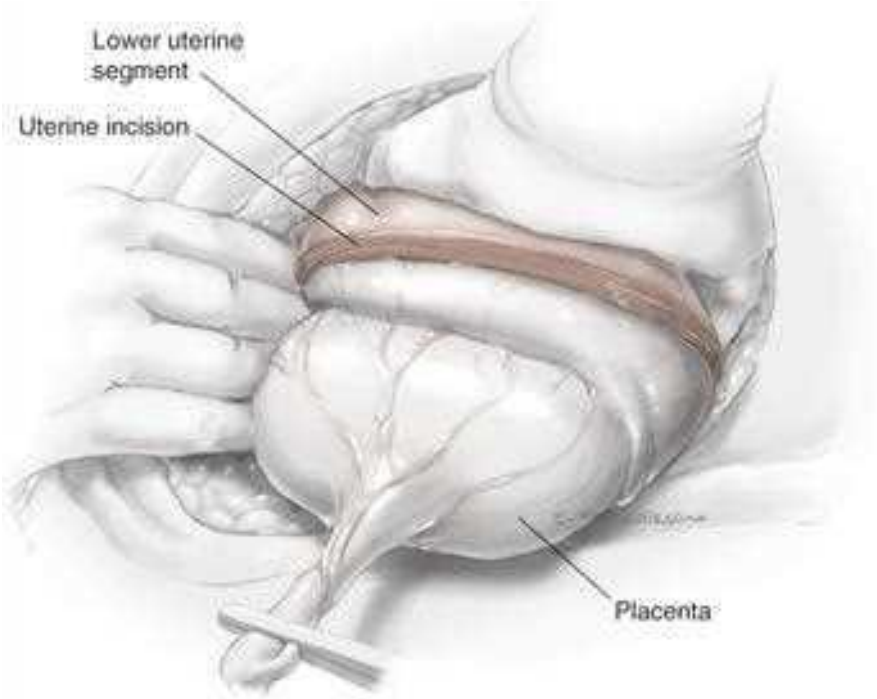
After birth, an intravenous infusion containing two ampules or 20 units of oxytocin per liter of crystalloid is infused at 10 mL/min. Some prefer higher infusion dosages, however, nondilute boluses are avoided because of associated hypotension (Roach, 2013). Once the uterus contracts satisfactorily, the rate can be reduced. An alternative is *carbetocin*—a longer-acting oxytocin derivative that is not available in the United States—that provides suitable, albeit more expensive, hemorrhage prophylaxis (Jin, 2016). Ergot-alkaloids are second-tier agents and carry hypertensive side effects. Carboprost, a 15-methyl derivative of prostaglandin $F_{2\alpha}$, is another second-tier agent used to treat uterine atony. Some but certainly not all studies indicate that misoprostol appears to perform similarly to oxytocin (Chaudhuri, 2014; Conde-Agudelo, 2013). Finally, some recommend the use of tranexamic acid added to a standard oxytocin infusion to decrease blood loss (Simonazzi, 2016; Wang, 2015). Its antifibrinolytic action and effects on thromboembolism rates in pregnant surgical patients are unclear. Larger trials are needed before widespread use. Additional discussions of all these agents are found in Chapter 41 (Risk Factors).

Delivery of the Placenta

The uterine incision is observed for any vigorously bleeding sites. These should be quickly clamped with Pennington or ring forceps. Although some surgeons may prefer manual removal of the placenta, spontaneous delivery prompted by some cord traction may reduce the risk of operative blood loss and infection (Anorlu, 2008; Baksu, 2005). Fundal massage may begin as soon as the fetus is delivered to hasten placental separation and delivery (Fig. 30-9).

FIGURE 30-9

Placenta bulging through the uterine incision as the uterus contracts. A hand gently massages the fundus to help aid spontaneous placental separation.



Immediately after delivery and quick gross inspection of the placenta, the uterine cavity is suctioned and wiped out with a gauze sponge to remove avulsed membranes, vernix, and clots. In the past, double-gloved fingers or ring forceps placed through the hysterotomy incision were used to dilate an ostensibly closed cervix. This practice does not reduce infection rates from potential hematometra and is not recommended (Kirscht, 2017; Liabsuetrakul, 2011).

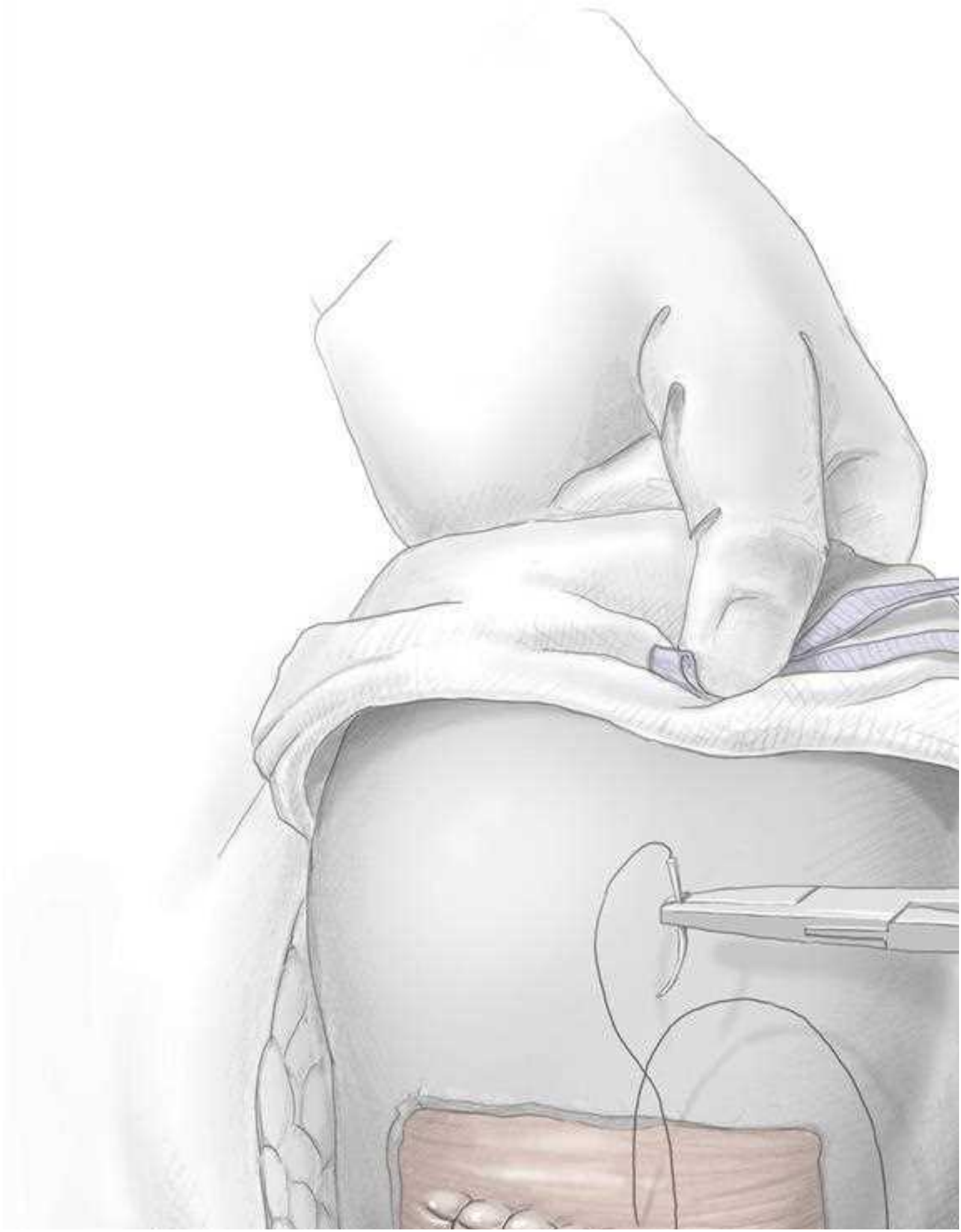
Uterine Repair

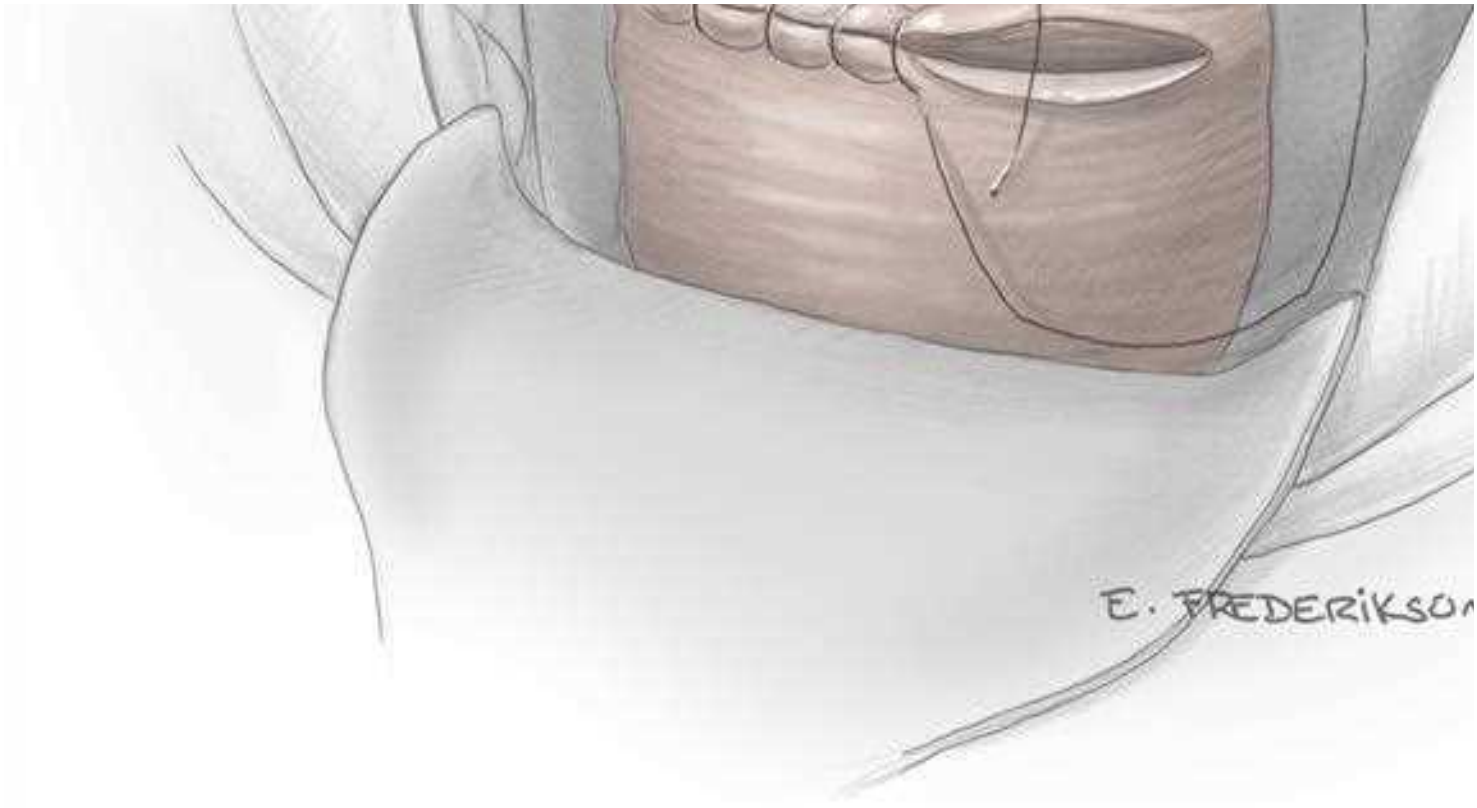
After placental delivery, the uterus is lifted through the incision and onto the draped abdominal wall, and the fundus is covered with a moistened laparotomy sponge. We favor this and believe a relaxed, atonic uterus can be recognized quickly and massage applied. Incision and bleeding points are more easily visualized and repaired, especially if there have been extensions. Adnexal exposure is superior, and thus, tubal sterilization is easier. Instead, some clinicians prefer to close the hysterotomy with the uterus in situ. Comparing these two approaches, febrile morbidity, pain, and blood loss are not significantly different (Walsh, 2009; Zaphiratos, 2015).

Before hysterotomy closure, previously clamped large vessels may be ligated separately or incorporated within the running incision closure. IUD insertion, if planned, is completed prior to hysterotomy closure (Chap. 38, Progestin Implants). One angle of the uterine incision is grasped to stabilize and maneuver the incision. The uterine incision is then closed with one or two layers of continuous 0- or no. 1 absorbable suture (Fig. 30-10). Chromic catgut suture is used by many, but some prefer synthetic delayed-absorbable polyglactin 910 (Vicryl). In subsequent pregnancy, neither suture type has been shown superior by mitigating against greater rates of adverse pregnancy outcomes such as uterine incision rupture (CORONIS Collaborative Group, 2016). Single-layer closure is typically faster and is not associated with higher rates of infection or transfusion (CAESAR Study Collaborative Group, 2010; Dodd, 2014; Roberge, 2014). Moreover, most studies observed that the number of layers does not significantly affect complication rates in the next pregnancy (Chapman, 1997; CORONIS Collaborative Group, 2016; Durnwald, 2003; Roberge, 2011).

FIGURE 30-10

The cut edges of the uterine incision are approximated with a running, locking suture.





At Parkland Hospital, we use a one-layer uterine closure with chromic catgut. The initial suture is placed just beyond one angle of the uterine incision. A continuous, locking suture line for hemostasis is then performed, with each suture penetrating the full thickness of the myometrium. The suture line then extends to a point just beyond the opposite incision angle. If approximation is not satisfactory after a single layer or if bleeding sites persist, then more sutures are required. Either another layer of running suture is placed to achieve approximation and hemostasis, or individual bleeding sites can be secured with targeted figure-of-eight or mattress stitches.

Traditionally, the peritoneum in the anterior cul-de-sac is approximated with a continuous 2–0 chromic catgut suture line. Multiple randomized trials suggest that omission of this step causes no postoperative complications (Grundsell, 1998; Irion, 1996; Nagele, 1996). If tubal sterilization is to be performed, it is completed as described in Chapter 39 (Puerperal Tubal Sterilization).

Adhesions

Following cesarean delivery, adhesions commonly form within the vesicouterine space or between the anterior abdominal wall and uterus. And, with each successive pregnancy, the percentage of affected women and adhesion severity rise (Morales, 2007; Tulandi, 2009). Adhesions can significantly lengthen incision-to-delivery time and total operative time (Rossouw, 2013; Sikirica, 2012). Although occurring infrequently, rates of cystotomy and bowel injury are also increased because of adhesive disease (Rahman, 2009; Silver, 2006).

Intuitively, scarring can be reduced by handling tissues delicately, achieving hemostasis, and minimizing tissue ischemia, infection, and foreign-body reaction. Most recent data on short- and long-term outcomes show no benefit to peritoneal closure (CAESAR Study Collaborative Group, 2010; CORONIS Collaborative Group, 2013, 2016; Kapustian, 2012). Similarly, most studies show no benefit from placement of an adhesion barrier at the hysterotomy site (Edwards, 2014; Kiefer, 2016).

Abdominal Closure

Any laparotomy sponges are removed, and the paracolic gutters and cul-de-sac are gently suctioned of blood and amnionic fluid. Some surgeons irrigate the gutters and cul-de-sac, especially in the presence of infection or meconium. Routine irrigation in low-risk women, however, leads to greater intraoperative nausea but not to lower postoperative infection rates (Eke, 2016; Viney, 2012).

Prior to abdominal closure, correct sponge and instrument counts are verified. The rectus abdominis muscle bellies are allowed to fall into place. With significant diastasis, the rectus muscles may be approximated with one or two figure-of-eight sutures of 0 or no. 1 chromic gut suture. The overlying rectus fascia is closed by a continuous, nonlocking technique with a delayed-absorbable suture. In patients with a higher risk for infection, there may be theoretical value in selecting a monofilament suture here rather than braided material.

The subcutaneous tissue usually need not be closed if it is less than 2 cm thick. With thicker layers, however, closure is recommended to minimize seroma and hematoma formation, which can lead to wound infection and/or disruption (Bohman, 1992; Chelmow, 2004). One recent metaanalysis found lower rates of seroma formation and of developing any wound complication with closure, but hematoma and wound infection rates were unaffected (Pergialiotis, 2017). Addition of a subcutaneous drain does not prevent significant wound complications (Hellums, 2007; Ramsey, 2005).

Skin is closed with a running subcuticular stitch of 4–0 delayed-absorbable suture, with adhesive glue, or with staples. In comparison, final cosmetic results and infection rates appear similar, skin suturing takes longer, but wound separation rates are higher with metal staples (Basha, 2010; Figueroa, 2013; Mackeen, 2014a, 2015). Poliglecaprone 25 (Monocryl) or polyglactin 910 (Vicryl) are both suitable (Tuuli, 2016b). Outcomes with 2-octyl cyanoacrylate adhesive (Dermabond) were equivalent to sutures for Pfannenstiel incisions (Daykan, 2017; Siddiqui, 2013). A sterile thin abdominal wound dressing is sufficient. In morbidly obese women, application of a prophylactic negative-pressure device atop the closed skin incision to prevent seroma and subsequent infection does not appear to lower wound complication rates (Hussamy, 2018; Smid, 2017).

Joel-Cohen and Misgav Ladach Techniques

The Pfannenstiel-Kerr technique just described has been used for decades. More recently, Joel-Cohen and Misgav Ladach techniques have been added (Holmgren, 1999). These differ from traditional Pfannenstiel-Kerr entry mainly by their initial incision placement and greater use of blunt dissection.

The Joel-Cohen technique creates a straight 10-cm transverse skin incision 3 cm below the level of the anterior superior iliac spines (Oloffson, 2015). The subcutaneous tissue layer is opened sharply 2 to 3 cm in the midline. This is carried down, without lateral extension, to the fascia. A small transverse incision is made in the fascia, and curved Mayo scissors are pushed laterally on each side and beneath intact subcutaneous fat to incise the fascia. With this incision completed, an index finger from each hand is inserted between the rectus abdominis muscle bellies and beneath the fascia. One finger is moved cranially and the other caudally, in opposition, to separate the bellies and further open the fascial incision. Then, a finger from each hand hooks under each belly to stretch the muscles laterally. The peritoneum is entered sharply, and this incision is sharply extended cephalocaudad. Entry with the Misgav Ladach technique differs in that the peritoneum is entered bluntly (Holmgren, 1999).

Modifications to the Joel-Cohen method abound. For emergency delivery, we begin along a line somewhat lower on the abdomen. For speed, we extend the fascial incision bluntly by hooking index fingers in the fascial incision's lateral angles and pulling laterally (Hofmeyr, 2009; Oloffson, 2015). Index fingers insinuated between the rectus bellies then move cephalocaudad in opposition to stretch the incision. Blunt index-finger dissection enters the peritoneum, and again, cranial and caudad opposing stretch opens this layer. Last, all the layers of the abdominal wall are grasped manually and pulled laterally in opposition to further open the operating space.

These techniques have been associated with shorter operative times and with lower rates of intraoperative blood loss and postoperative pain (Mathai, 2013). They may, however, prove difficult for women with anterior rectus fibrosis and peritoneal adhesions (Bolze, 2013).

Classical Cesarean Incision

Indications

This incision is usually avoided because it encompasses the active upper uterine segment and thus is prone to rupture with subsequent pregnancies. Some indications stem from difficulty in exposing or safely entering the lower uterine segment. For example, a densely adhered bladder from previous surgery is encountered; a *leiomyoma* occupies the lower uterine segment; the cervix has been invaded by cancer; or massive maternal obesity precludes safe access to the lower uterine segment. A classical incision is also preferred for placenta previa with anterior implantation, especially those complicated by placenta accrete syndromes. In extreme cases of this, the typical classical hysterotomy may be placed even higher in the uterine body or posteriorly to avoid the placenta. As such, fetuses with cephalic presentation are then delivered in a manner similar to total breech extraction (Chap. 28, Total Breech Extraction).

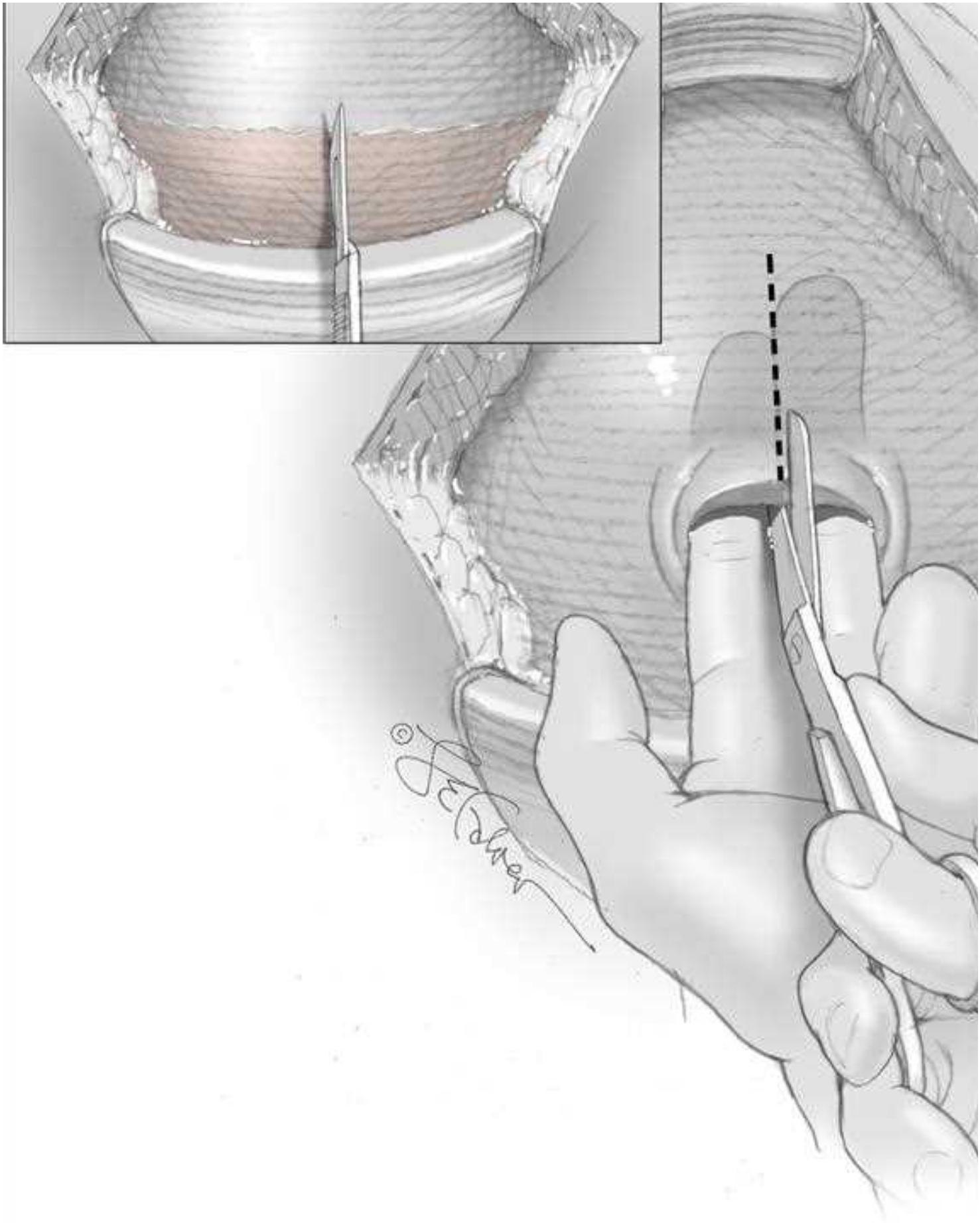
In other instances, fetal indications dictate the need. *Transverse lie of a large fetus*, especially if the membranes are ruptured and the shoulder is impacted in the birth canal, usually necessitates a classical incision. A fetus presenting as a back-down transverse lie is particularly difficult to deliver through a transverse uterine incision. In instances when the fetus is very small and breech, a classical incision may be preferable (Osmundson, 2013). In such cases, the poorly developed lower uterine segment provides inadequate space for the manipulations required for breech delivery. Or, less commonly, the small fetal head may become entrapped by a contracting uterine fundus following membrane rupture. Last, with multiple fetuses, a classical incision again may provide suitable room for extraction of fetuses that may be malpositioned or preterm (Osmundson, 2015).

Uterine Incision and Repair

A vertical uterine incision is initiated with a scalpel beginning as low as possible and preferably within the lower uterine segment (Fig. 30-11). If adhesions, insufficient exposure, a tumor, or placenta percreta preclude development of a bladder flap, then the incision is made above the level of the bladder. Once the uterus is entered with a scalpel, the incision is extended cephalad with bandage scissors until it is long enough to permit delivery of the fetus. With scissor use, the fingers of the nondominant hand are insinuated between the myometrium and fetus to prevent fetal laceration. As the incision is opened, numerous large vessels that bleed profusely are commonly encountered within the myometrium. The remainder of fetal and placental delivery mirrors that with a low transverse hysterotomy.

FIGURE 30-11

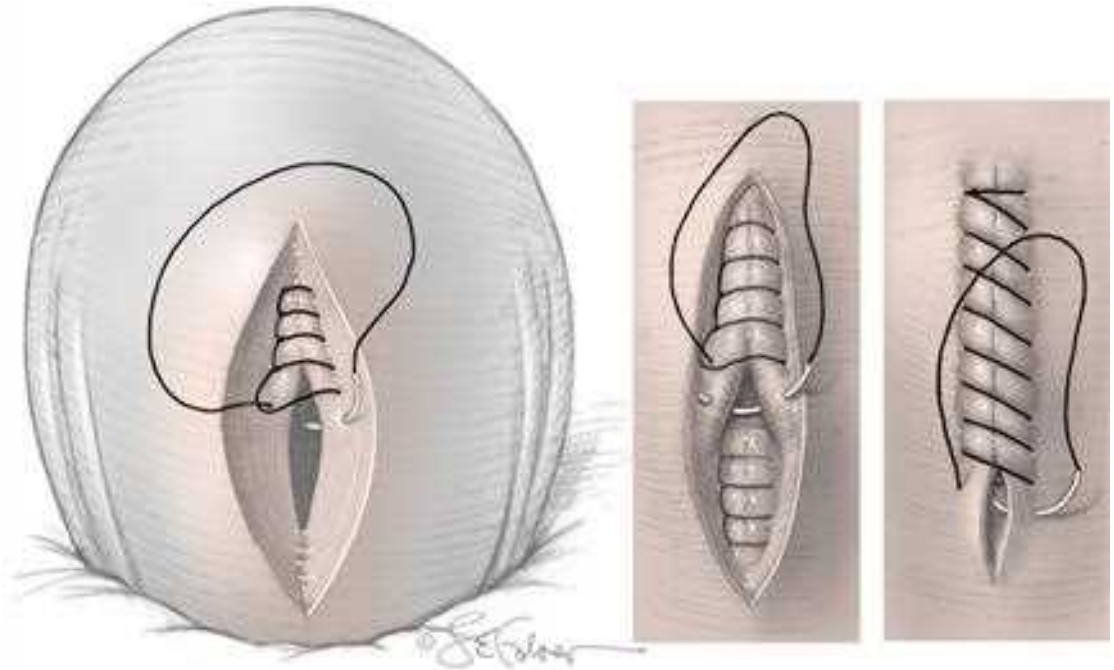
An initial small vertical hysterotomy incision is made in the lower uterine segment. Fingers are insinuated between the myometrium and fetus to avoid fetal laceration. Scissors extend the incision cephalad as needed for delivery. (Reproduced with permission from Johnson DD: Cesarean delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

For incision closure, one method employs a layer of 0- or no. 1 chromic catgut with a running stitch to approximate the deeper length of the incision (Fig. 30-12). The outer layer of myometrium is then closed along its length with similar suture and with a running suture line. To achieve good approximation and to prevent the suture from tearing through the myometrium, it is helpful to have an assistant compress the uterus on each side of the wound toward the midline as each stitch is placed.

FIGURE 30-12
Classical incision closure. The deeper half (*left*) and superficial half (*middle*) of the incision are closed in a running fashion. The serosa is then closed (*right*). (Reproduced with permission from Johnson DD: Cesarean delivery. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



PERIPARTUM HYSTERECTOMY

Indications

Hysterectomy is most commonly performed to arrest or prevent hemorrhage from intractable uterine atony or abnormal placentation (Bateman, 2012; Hernandez, 2012; Owolabi, 2013). It is more often completed during or after cesarean delivery but may be needed following vaginal birth. If all deliveries are considered, the peripartum hysterectomy rate in the United States approximates 1 per 1000 births and has risen significantly during the past few decades (Bateman, 2012; Govindappagari, 2016). During a 25-year period, the rate of peripartum hysterectomy at Parkland Hospital was 1.7 per 1000 births (Hernandez, 2012). Most of this rise is attributed to the increasing rates of cesarean delivery and its associated complications in subsequent pregnancy (Bateman, 2012; Bodelon, 2009; Flood, 2009; Orbach, 2011). Of hysterectomies, approximately one half to two thirds are total, whereas the remaining cases are supracervical (Rossi, 2010; Shellhaas, 2009).

Major complications of peripartum hysterectomy include greater blood loss and risk of urinary tract damage. Blood loss is usually appreciable because hysterectomy is being performed for hemorrhage that frequently is torrential, and the procedure itself is associated with substantial bleeding. Although many cases with hemorrhage cannot be anticipated, those with abnormal implantation are often identified antepartum. Preoperative preparations for placenta accreta are discussed in Chapter 41 (Management) and have also been outlined by the Society for Maternal-Fetal Medicine (2010) and American College of Obstetricians and Gynecologists (2017c).

An important factor affecting the cesarean hysterectomy complication rate is whether the operation is performed electively or emergently. With anticipated or planned cesarean hysterectomy, rates of blood loss, blood transfusion, and urinary tract complications are lower that with emergent procedures (Briery, 2007; Glaze, 2008).

Hysterectomy Technique

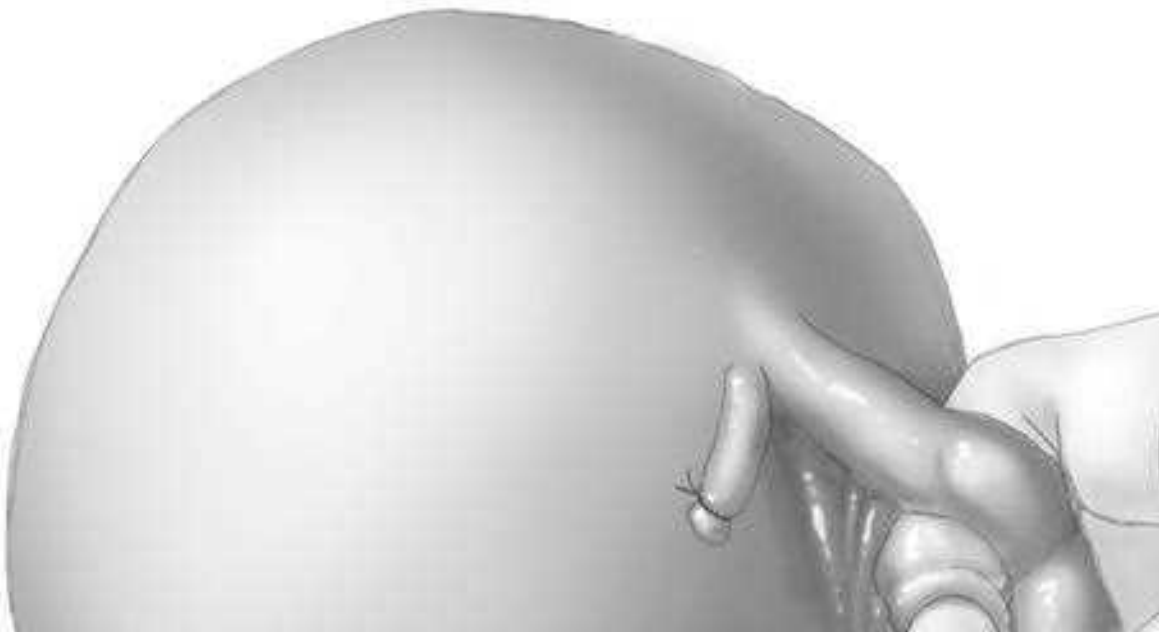
Total or supracervical hysterectomy is performed using standard operative techniques. Adequate exposure is essential, but initially, placement of a self-retaining retractor such as a Balfour is not necessary. Rather, satisfactory exposure is obtained with cephalad traction on the uterus by an assistant, along with handheld Richardson or Deaver retractors. The bladder flap is deflected downward to the level of the cervix if possible to permit total hysterectomy. In cases in which cesarean hysterectomy is planned or strongly suspected, extended bladder flap dissection is ideally completed before initial hysterotomy. Later attempts at bladder dissection may be obscured by bleeding, or excess blood may be lost while this dissection is performed.

After cesarean delivery, the placenta is typically removed. In cases of placenta accrete syndrome for which hysterectomy is already planned, the placenta is usually left undisturbed in situ. In either situation, if the hysterotomy incision is bleeding appreciably, it can be sutured or Pennington or sponge forceps can be applied for hemostasis. If bleeding is minimal, neither maneuver is necessary.

The round ligament is divided close to the uterus between clamps, and each pedicle is ligated (Fig. 30-13). Either 0 or no. 1 suture can be used in either chromic gut or delayed-absorbable material. The anterior leaf of the broad ligament is incised downward to meet the former bladder flap incision. The posterior leaf of the broad ligament adjacent to the uterus is bluntly or sharply perforated just beneath the fallopian tube, uteroovarian ligament, and ovarian vessels (Fig. 30-14). These structures together are then divided between sturdy clamps placed close to the uterus (Fig. 30-15). The lateral pedicle is doubly ligated. The medial clamp remains and is removed later with the entire uterine specimen. The posterior leaf of the broad ligament is incised toward the uterosacral ligaments (Fig. 30-16). Next, the bladder and attached peritoneal flap are further deflected and dissected as needed. If the bladder flap is unusually adhered, as it may be after previous hysterotomy incisions, careful sharp dissection may be necessary (Fig. 30-17).

FIGURE 30-13
The round ligaments are clamped, doubly ligated, and transected bilaterally.

FIGURE 30-14
The posterior leaf of the broad ligament adjacent to the uterus is perforated just beneath the fallopian tube, uteroovarian ligaments, and ovarian vessels.



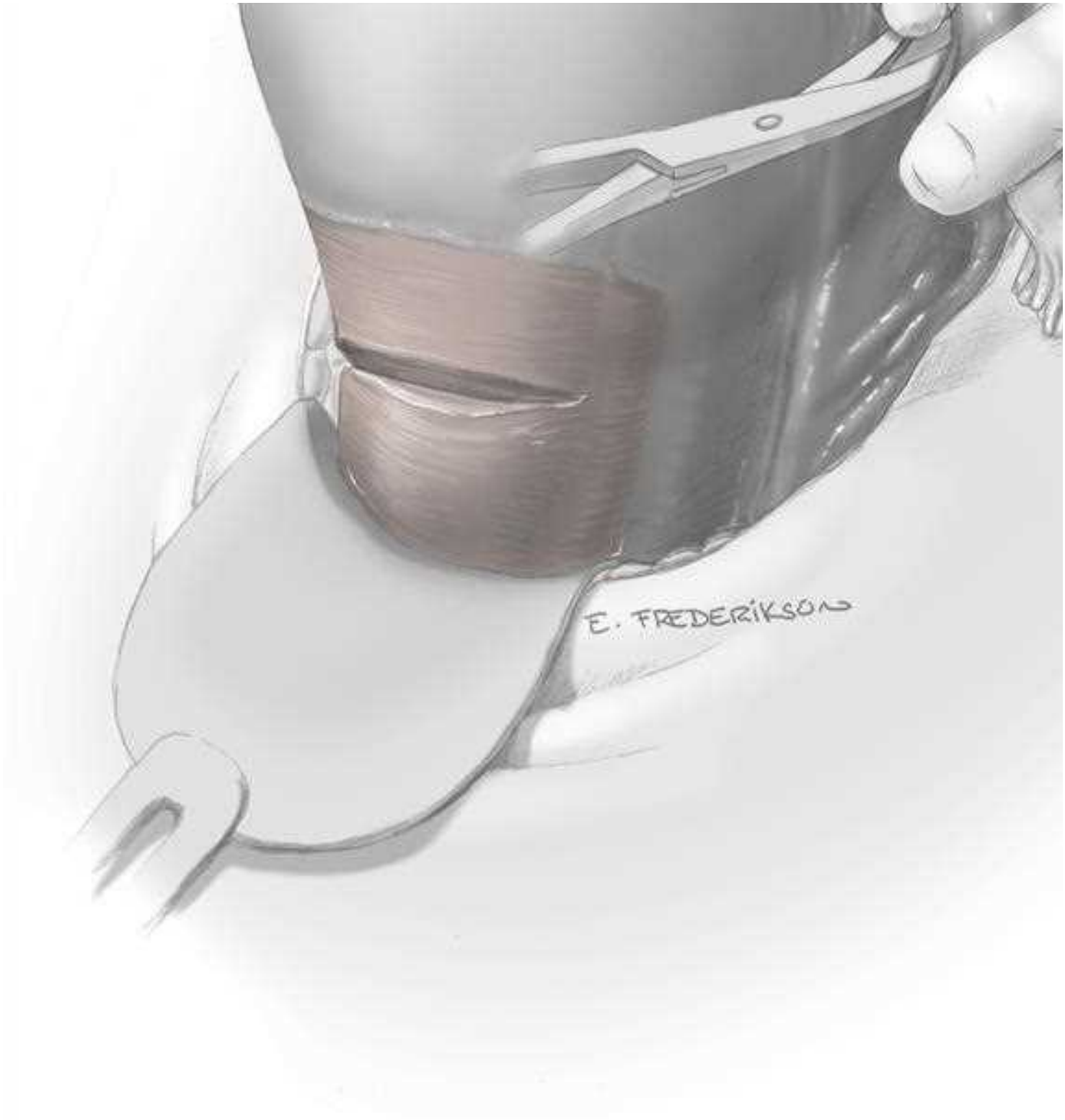


FIGURE 30-15

The uteroovarian ligament and fallopian tube are clamped and cut. The lateral pedicle is doubly ligated.

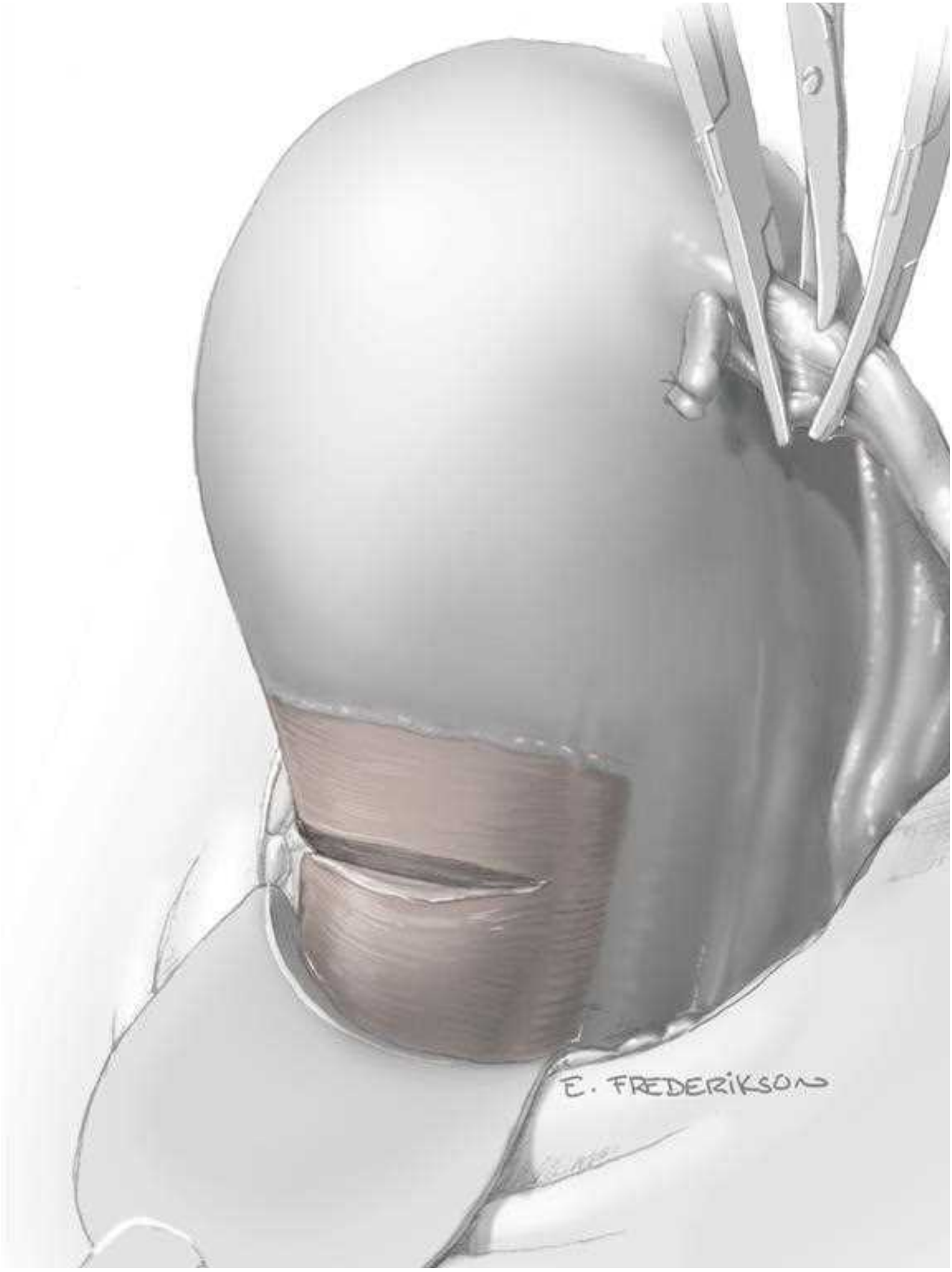

E. FREDERIKSON

FIGURE 30-16

The posterior leaf of the broad ligament is divided inferiorly toward the uterosacral ligament.

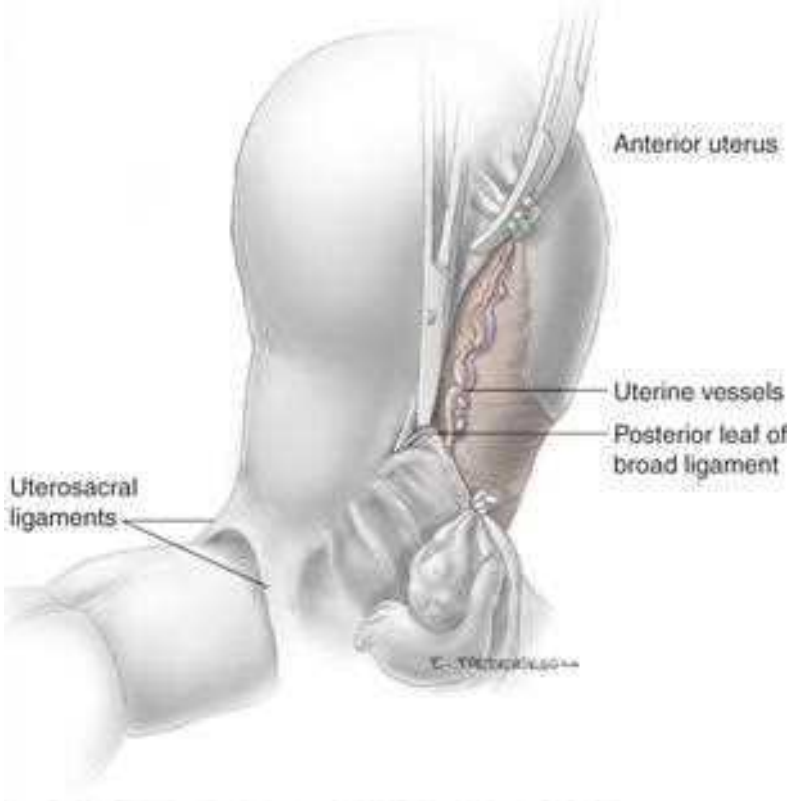
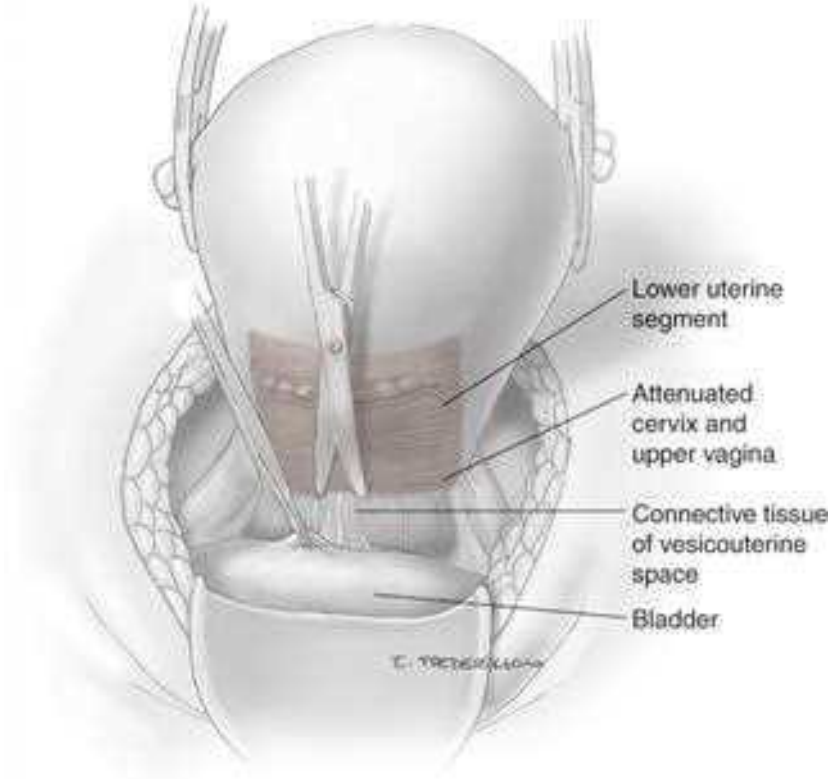


FIGURE 30-17

The bladder is dissected sharply from the lower uterine segment.



Special care is required from this point on to avoid injury to the ureters, which pass beneath the uterine arteries. To help accomplish this, an assistant places constant traction to pull the uterus in the direction away from the side on which the uterine vessels are being ligated. The ascending uterine artery and veins on either side are identified. These vessels are then clamped adjacent to the uterus. For security, some may prefer two lateral clamps as shown in Figure 30-18. The most medial clamp helps prevents back bleeding from the uterus and remains for later removal with the specimen. The uterine vessels are divided, and the lateral tissue pedicle is doubly suture ligated. After securing the uterine vessels on one side, the round ligament, adnexal pedicle, and uterine vessels are then addressed on the contralateral side.

FIGURE 30-18

The uterine vessels are clamped, and a third medial clamp helps prevent “back bleeding.” Once divided, the lateral vascular pedicle is doubly ligated to ensure hemostasis.

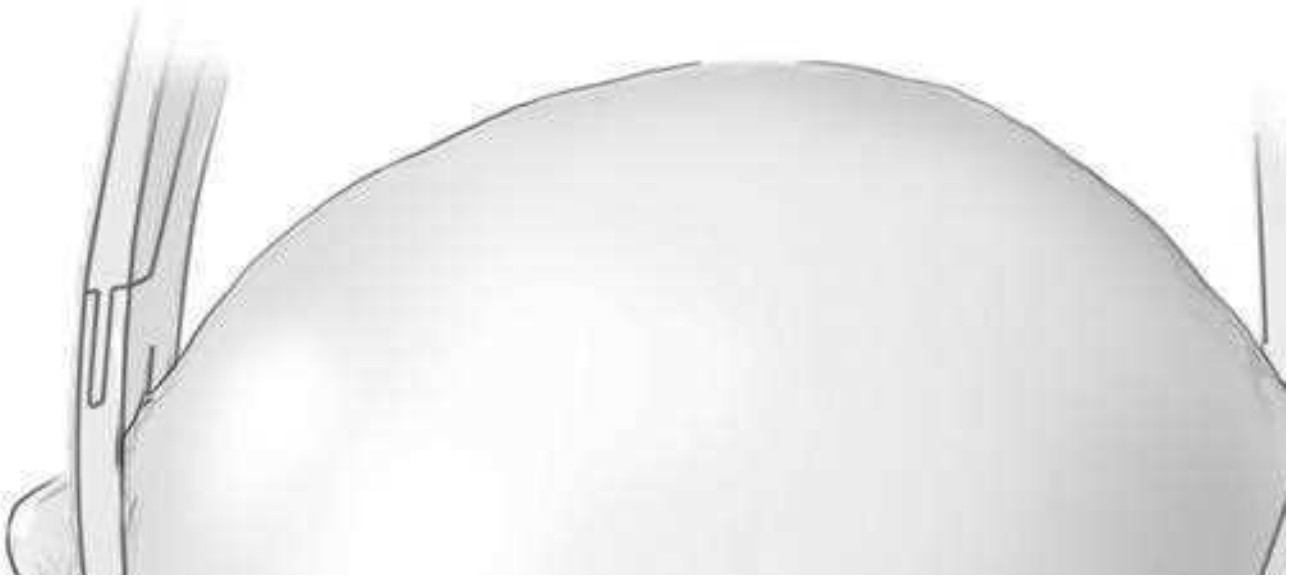
With cesarean hysterectomy, it may be more advantageous in cases of profuse hemorrhage to rapidly double clamp and divide all of the vascular pedicles between clamps to gain hemostasis. The surgical team can then return to ligate all of the pedicles.

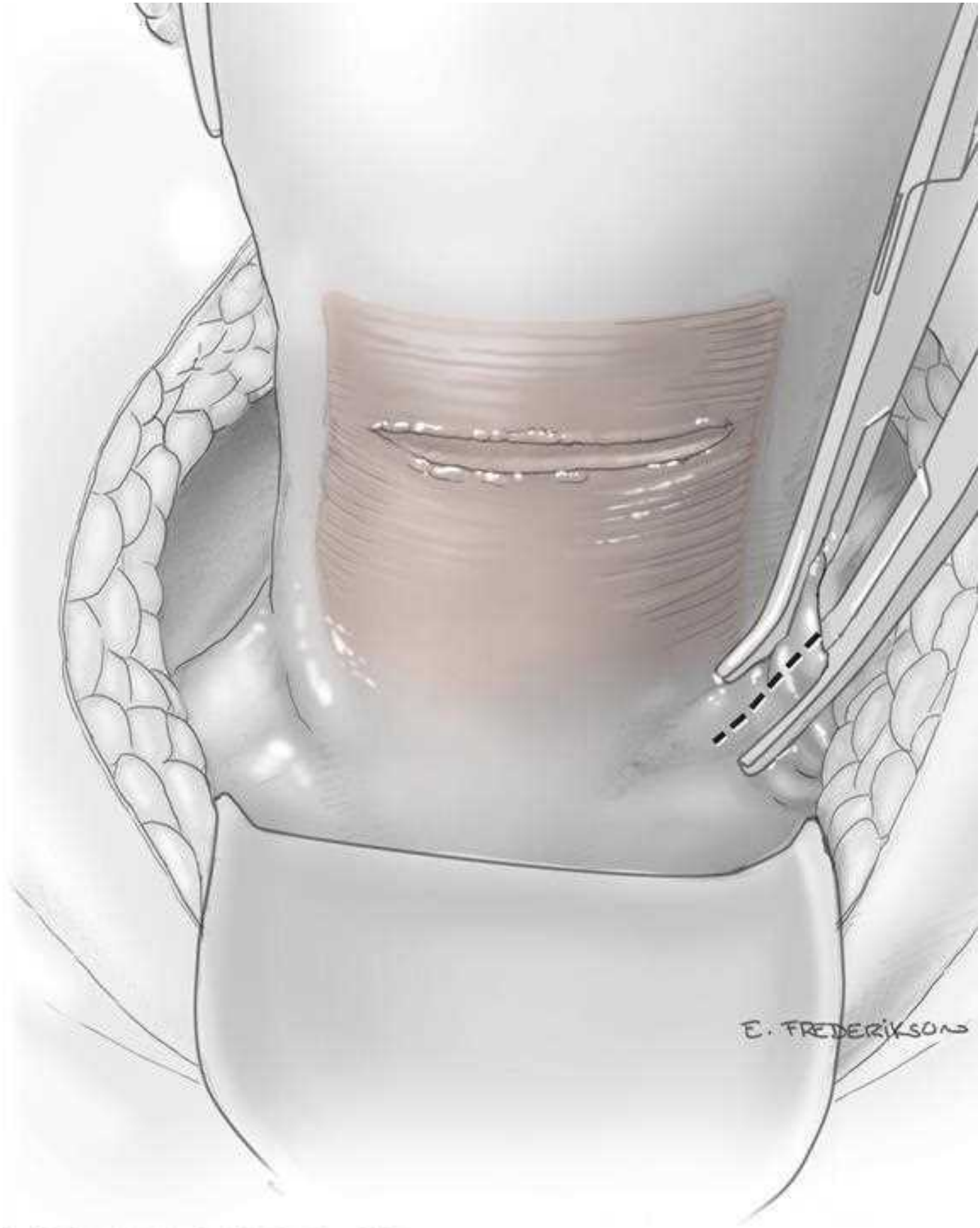
Total Hysterectomy

Even if total hysterectomy is planned, we find it technically easier in many cases to finish the operation after amputating the uterine fundus and placing Ochsner or Kocher clamps on the cervical stump for traction and hemostasis. Self-retaining retractors also may be placed at this time. To remove the cervix, the bladder is mobilized further if needed. This carries the ureters caudad as the bladder is retracted beneath the symphysis and will prevent laceration or suturing of the bladder during cervical excision and vaginal cuff closure.

The cardinal ligament, the uterosacral ligaments, and the many large vessels these ligaments contain are clamped systematically with sturdy Heaney-type curved or straight clamps (Fig. 30-19). The clamps are placed as close to the cervix as possible, taking care not to include excessive tissue in each clamp. The tissue between the pair of clamps is incised, and the lateral pedicle is suture ligated. These steps are repeated caudally and bilaterally until the level of the lateral vaginal fornix is reached on each side. In this way, the descending branches of the uterine vessels are clamped, cut, and ligated as the cervix is separated from the cardinal ligaments.

FIGURE 30-19
The cardinal ligaments are clamped, incised, and ligated.



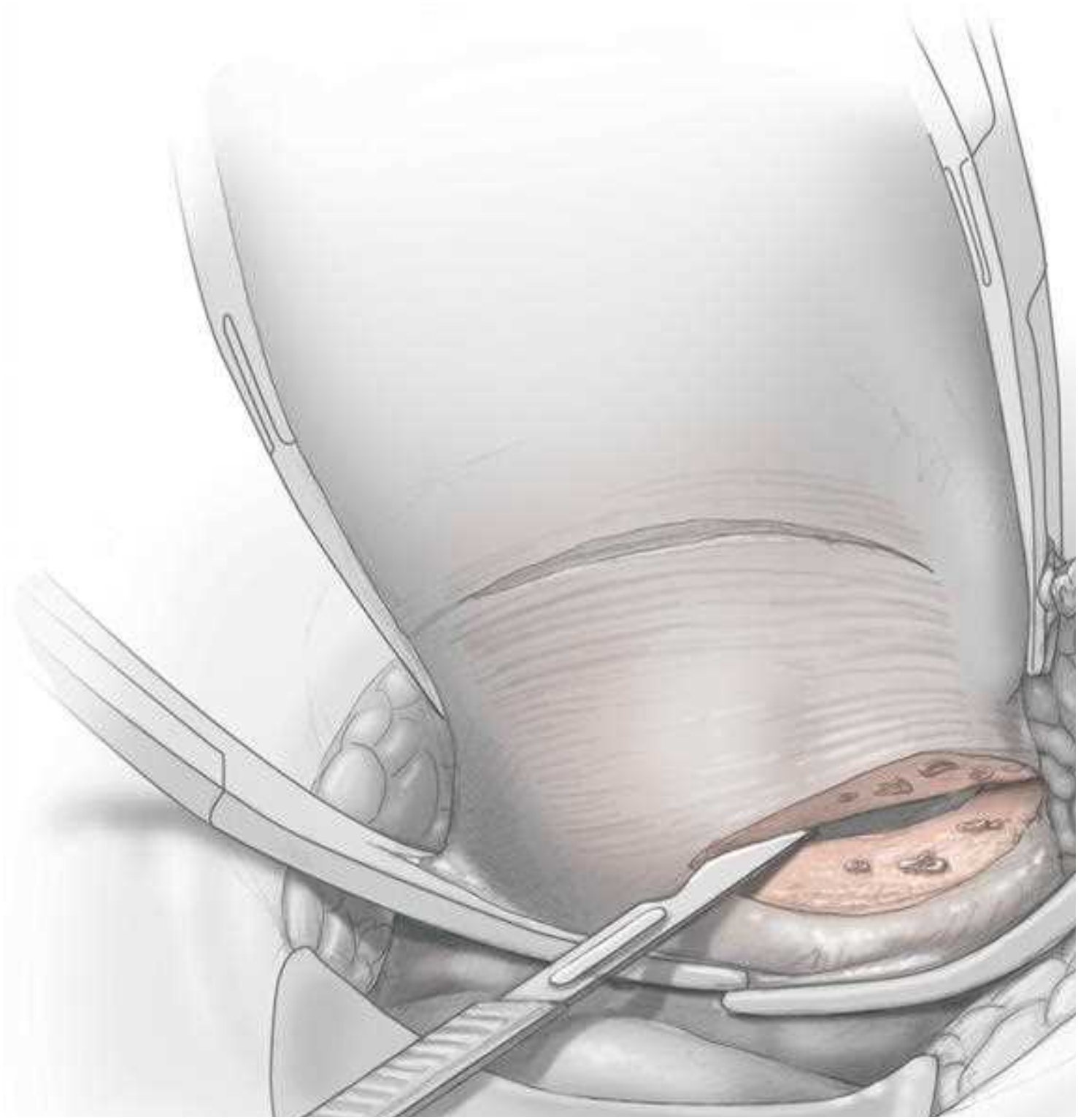


Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

If the cervix is effaced and dilated considerably, its softness may obscure palpable identification of the cervicovaginal junction. The junction location can be ascertained through a vertical uterine incision made anteriorly in the midline, either through the open hysterotomy incision or through an incision created at the level of the ligated uterine vessels. A finger is directed inferiorly through the incision to identify the free margin of the dilated, effaced cervix. The contaminated glove is replaced. Another useful method to identify the cervical margins in cases of planned hysterectomy is to transvaginally place four metal skin clips or brightly colored sutures at 12, 3, 6, and 9 o'clock positions on the cervical edges.

Immediately below the level of the cervix, a curved clamp is placed across the lateral vaginal fornix on each side, and the vagina is incised above the clamp (Fig. 30-20). The cervix is inspected to ensure that it has been completely removed. A transfixing suture is used for vaginal cuff closure as each clamp is removed. Interrupted stitches may be added to approximate the middle portion of the cuff. Each lateral vaginal fornix is secured to the uterosacral ligaments to mitigate later vaginal prolapse. For cuff closure, some surgeons instead prefer to close the vagina by apposing the anterior and posterior vaginal walls with interrupted figure-of-eight sutures or running suture line (Fig. 30-21).

FIGURE 30-20
A curved clamp is placed across the lateral vaginal fornix below the level of the cervix, and the tissue incised medially to the point of the clamp.



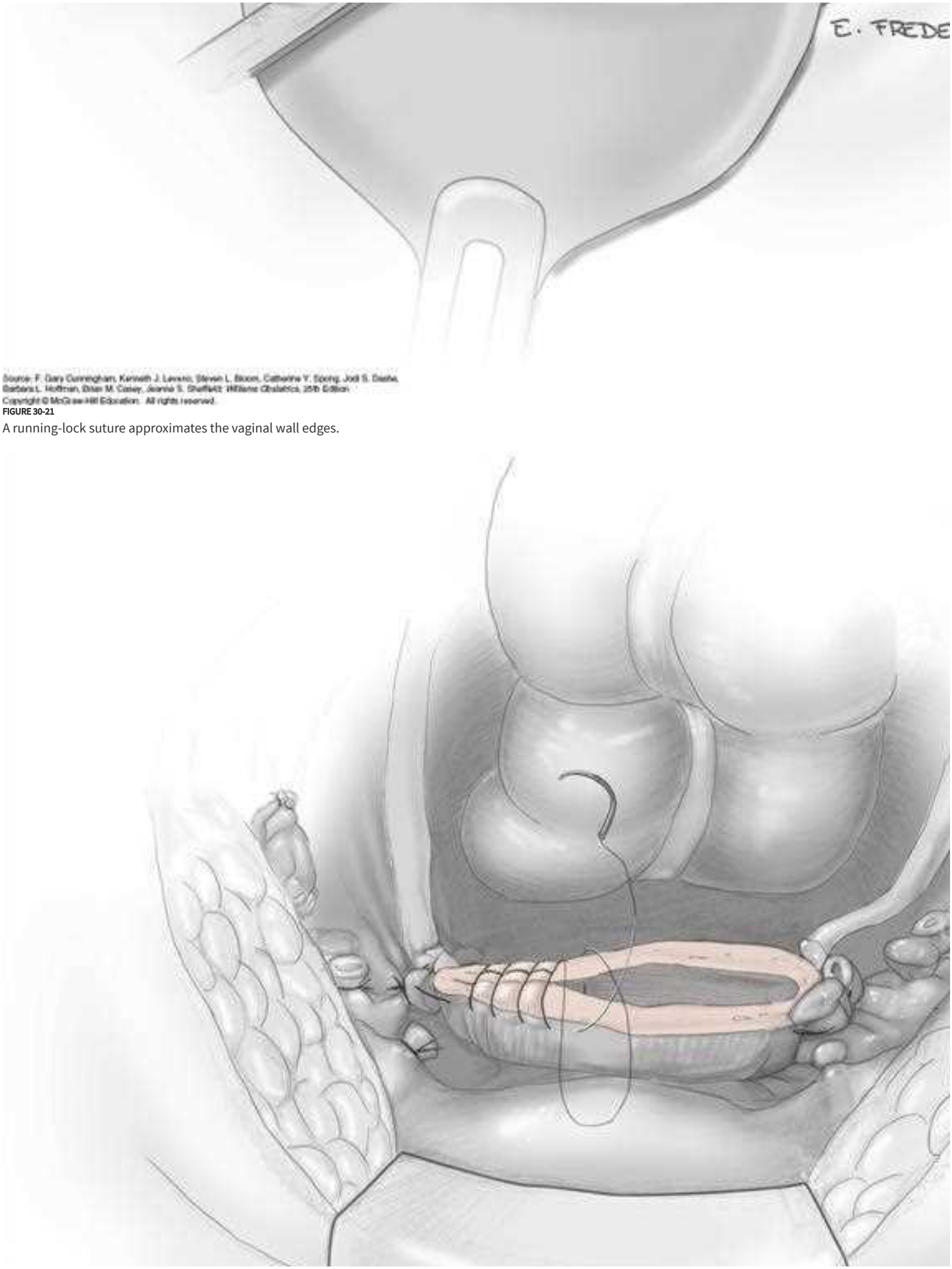


FIGURE 30-21

A running-lock suture approximates the vaginal wall edges.

All sites are examined carefully for bleeding. One technique is to perform a systematic bilateral survey from the fallopian tube and ovarian ligament pedicles to the vaginal vault and bladder flap. Bleeding sites are ligated with care to avoid the ureters. The abdominal wall normally is closed in layers, as previously described for cesarean delivery (Adhesions).

Supracervical Hysterectomy

To perform a subtotal hysterectomy, the uterine body is amputated immediately above the level of uterine artery ligation. The cervical stump may be closed with continuous or interrupted chromic catgut suture. Subtotal hysterectomy is often all that is necessary to stop hemorrhage. It may be preferred for women who would benefit from a shorter surgery or for those with extensive adhesions that threaten significant urinary tract injury.

Salpingo-oophorectomy

Because of the large adnexal vessels and their close proximity to the uterus, it may be necessary to remove one or both adnexa to obtain hemostasis. Briery and colleagues (2007) reported unilateral or bilateral oophorectomy in a fourth of cases. Preoperative counseling for anticipated hysterectomy should include this possibility.

Urinary Tract or Bowel Injury

These injuries are rare during cesarean delivery. The bladder laceration rate approximates 2 per 1000 cesarean deliveries, whereas that for ureteral trauma nears 0.3 per 1000 cases (Güngördük, 2010; Oliphant, 2014; Rajasekar, 1997). Bowel is damaged in about 1 in 1000 cesarean deliveries (Silver, 2006).

Cystotomy

Bladder laceration most commonly occurs during blunt or sharp dissection in the vesicouterine space to create the bladder flap, during peritoneal cavity entry, and during hysterotomy (Phipps, 2005; Rahman, 2009). Risks are prior cesarean delivery; emergency cesarean delivery; comorbid adhesive disease; cesarean hysterectomy, especially cases with morbidly adherent placenta; and surgery in second-stage labor compared with first-stage (Alexander, 2007; Silver, 2006; Yossepowitch, 2004).

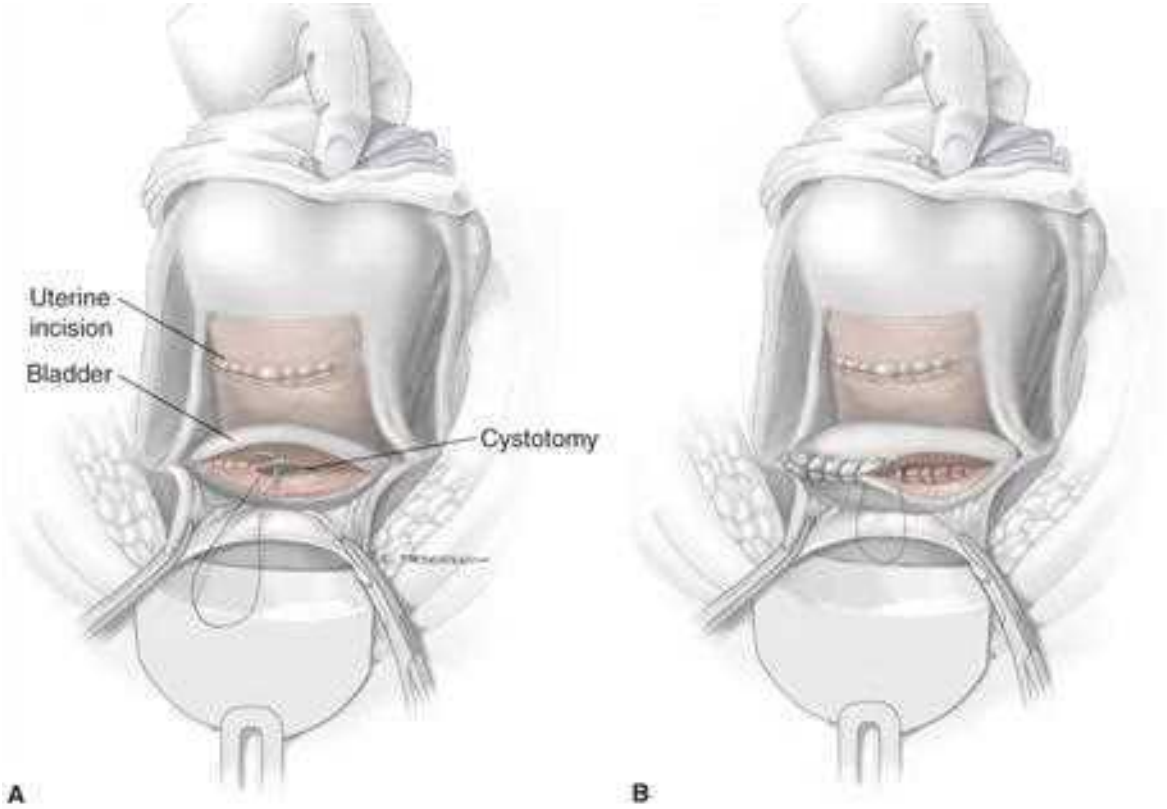
Bladder injury is typically identified intraoperatively, and initially, a clear-fluid gush or the Foley bulb may be seen. If cystotomy is suspected, it can be confirmed with retrograde instillation of infant formula or methylene-blue-stained saline through a Foley catheter into the bladder. Leakage of opaque milk or methylene blue aids in identification of the laceration as well as delineation of its borders. The dome is lacerated in 95 percent of cases, and injuries at the trigone form the remainder (Phipps, 2005).

Prior to cystotomy repair, ureters are examined, and surveillance for urine jets from each orifice follows. This can be done directly through the cystotomy, if at the dome, or through a separate diagnostic extraperitoneal or retropubic cystotomy, if injury nears the trigone. Jet visualization can be assisted by 50 mg of methylene blue administered intravenously.

Once ureteral patency is confirmed, the bladder may be closed with a two- or three-layer running closure using a 3–0 absorbable or delayed-absorbable suture (Fig. 30-22). The first layer inverts the mucosa into the bladder. The bladder is then filled with a marker fluid to demonstrate integrity of the repair. Leaking defects can be closed with interrupted reinforcing stitches. Subsequent layers reapproximate the bladder muscularis. Postoperative care requires continuous bladder drainage for 7 to 14 days to permit healing and minimize the risk of fistula formation. Uropathogen prophylaxis during this drainage is not required. Also, cystourethrography need not be routinely performed prior to catheter removal for a simple, single laceration (Davis, 1999).

FIGURE 30-22

Cystotomy repair. **A.** The primary layer inverts the bladder mucosa with running or interrupted sutures of 3–0 delayed-absorbable or absorbable suture. **B.** Second and possibly a third layer approximate the bladder muscularis to reinforce the incision closure.



Larger lacerations in or near the trigone require careful attention. Specialists may be consulted, and in preparation, ureteral stents can be assembled. In these cases, ureteral orifices are directly inspected to document jets from both. If not seen, then stents may be passed through the cystotomy and into each orifice to confirm patency. Once this is confirmed, repair should not disrupt the ureteral orifices, and stents may remain to ensure ureteral patency.

Unrepaired cystotomy can manifest as hematuria, oliguria, abdominal pain, ileus, ascites, peritonitis, fever, urinoma, or fistula. For diagnosis, retrograde cystography or abdominal computed tomography (CT) with cystography can be used (Tarney, 2013). Cystoscopy is also an option but may require an operating room. Once identified, prompt repair is indicated (Balgobin, 2017).

Ureteral Injury

These injuries occur most often during repair of hysterotomy extensions into the broad ligament or vagina (Eisenkop, 1982). If ureteral injury is suspected, methylene blue is administered. The pelvis is directly inspected for dye extravasation, which suggests ureteral transection. Next, brisk dye-stained urine jets are sought from each orifice to exclude ureteral kinking or ligation. Orifice viewing may be via cystoscopy, if available; through a comorbid traumatic cystotomy; or through a diagnostic cystotomy. With sluggish or absent jets, consultation with a specialist is typically requested. A ureteral catheter is first threaded to identify a potential obstruction site and guide ureterolysis. Kinked or ligated ureters can be relieved by release of ensnaring sutures. Crush injuries are inspected to ensure vital tissue. In these cases, stents are left to avert ureteral stricture. A Foley catheter remains for 7 to 10 days, and the ureteral catheters are removed via cystoscopy after 14 days. Intravenous pyelography (IVP) is usually not necessary before removal of the stent if it was placed as a precautionary measure after relatively minor injury (Davis, 1999).

Crush injuries with devascularization, thermal injury, or transection require more extensive repair. If a healthy-appearing ureter can be reimplanted into the bladder without undue tension, then ureteroneocystostomy is preferable. For more proximal injuries, ureteroureterostomy, psoas hitch, or Boari flap creation may be needed. An explanation of these more extensive procedures is found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Balgobin, 2017).

Unrecognized ureteral injury can mimic those of cystotomy with the addition of possible costovertebral angle tenderness. CT urography is a preferred initial diagnostic tool (Sharp, 2016). The duration of time from injury to identification directs repair. Those identified early are often suitable for immediate repair.

Bowel Injury

Serosal tears represent weak points in the small bowel. If obstruction develops postoperatively, these weak spots may perforate, leading to peritonitis. If serosal tears are few in number, they can be oversewn with either a fine absorbable or nonabsorbable suture (Davis, 1999). More significant lacerations are often repaired in consultation with a general surgeon or gynecologic oncologist.

POSTOPERATIVE CARE

Euvolemia Evaluation

During and after cesarean delivery, requirements for intravenous fluids can vary considerably. Administered fluids consist of either lactated Ringer solution or a similar crystalloid solution with 5-percent dextrose. Typically, at least 2 L is infused during surgery. Blood loss with uncomplicated cesarean delivery approximates 1000 mL. The average-sized woman with a hematocrit of 30 percent or more and with a normally expanded blood and extracellular fluid volume most often will tolerate blood loss up to 2000 mL without difficulty. Unappreciated bleeding through the vagina during the procedure, bleeding concealed in the uterus after its closure, or both commonly lead to underestimation.

Blood loss averages 1500 mL with elective cesarean hysterectomy, although this is variable (Pritchard, 1965). Most peripartum hysterectomies are unscheduled, and blood loss in these cases is correspondingly greater. Thus, in addition to close monitoring of vital signs and urine output, the hematocrit should be determined intra- or postoperatively as indicated.

Recovery Suite

The amount of vaginal bleeding is closely monitored for at least an hour in the immediate postoperative period. The uterine fundus is also identified frequently by palpation to ensure that the uterus remains firmly contracted. Unfortunately, as conduction analgesia fades or the woman awakens from general anesthesia, abdominal palpation is likely to produce pain. A patient-controlled analgesia (PCA) pump can be effective. Once regional analgesia begins to fade or the woman becomes fully awake following general anesthesia, criteria for transfer to the postpartum ward include minimal bleeding, stable vital signs, and adequate urine output.

Hospital Care until Discharge

Analgesia, Vital Signs, Intravenous Fluids

Several schemes are suitable for postoperative pain control. One PCA regimen uses intravenous morphine given as needed as a 1-mg dose with a 6-minute lockout interval and maximum dose of 30 mg in 4 hours. An additional 2-mg booster dose is permitted for a maximum of 2 doses. Alternatively, intramuscular (IM) meperidine, 50 to 75 mg every 3 to 4 hours, or IM morphine, 10 to 15 mg every 3 to 4 hours, is suitable. In a trial using these options, Yost and associates (2004) found that morphine provided superior pain relief to meperidine and was associated with significantly higher rates of breastfeeding and continuation of newborn rooming in. Breastfeeding can be initiated the day of surgery. If the mother elects not to breastfeed, a binder that supports the breasts without marked compression usually will minimize discomfort.

After transfer to her room, the woman is assessed at least hourly for 4 hours, and thereafter at intervals of 4 hours. Deep breathing and coughing are encouraged to prevent atelectasis. Vital signs, uterine tone, urine output, and bleeding are evaluated. The hematocrit is routinely measured the morning after surgery. It is checked sooner if there was unusual blood loss or if there is hypotension, tachycardia, oliguria, or other evidence to suggest hypovolemia. If the hematocrit is decreased significantly from the preoperative level, the measurement is repeated and a search is instituted to identify the cause. If the hematocrit stabilizes, the mother can be allowed to ambulate, and if there is little likelihood of further blood loss, iron therapy is preferred to transfusion.

Postpartum, the patient begins to mobilize and excrete her physiologically expanded extravascular volume. Thus, maintenance intravenous fluid proves adequate after surgery until consistent oral intake is reestablished. If urine output falls below 30 mL/hr, however, the woman should be reevaluated promptly. The cause of the oliguria can range from unrecognized blood loss to an antidiuretic effect from infused oxytocin.

Women undergoing unscheduled cesarean delivery may have pathological retention or constriction of the extracellular fluid compartment caused by severe preeclampsia, sepsis syndrome, vomiting, prolonged labor without adequate fluid intake, or increased blood loss. Women with these complications are generally observed in the recovery room until stabilization is assured.

Bladder and Bowel Function

The Foley catheter most often can be removed by 12 hours postoperatively, or more conveniently, the morning after surgery. The prevalence of urinary retention following cesarean delivery approximates 3 to 7 percent (Chap. 36, Perineal Care). Failure to progress in labor and postoperative narcotic analgesia are identified risks (Chai, 2008; Kandadai, 2014; Liang, 2007).

In uncomplicated cases, liquids or solid food may be offered within hours of surgery and advanced as tolerated (Guo, 2015). Some degree of adynamic ileus follows virtually every abdominal operation, but in most cases of cesarean delivery, it is negligible. Postoperative ileus symptoms include abdominal distention, gas pains, and an inability to pass flatus or stool. With persistent nausea and vomiting or with prolonged bowel function delay, radiological imaging may aid exclusion of bowel obstruction. A plain abdominal radiograph is a frequent first choice. However, in the general population, this study is diagnostic in only 50 to 60 percent of small bowel obstruction cases (Maglinte, 1997). Thus, a radiograph may best serve as a triage tool in cases in which ileus is the suspected diagnosis. Notably, an enlarged postpartum uterus can compress the rectosigmoid and prevent it from filling with gas. Thus, findings suggesting a distal colonic obstruction may confuse true cases

of transient ileus (Kammen, 2000). In comparison, CT with intravenous contrast provides greater accuracy for small bowel obstruction. Oral contrast is concurrently given when SBO is a consideration (Katz, 2013). Last, although uncommon, an unrecognized bowel injury may be responsible for otherwise unexplained fever and poor bowel function. Here, CT may be most diagnostic of potential etiologies.

As treatment of ileus, intravenous fluids compensate for poor oral intake and losses from emesis. Electrolyte imbalances are corrected to improve smooth muscle activity and avoid bowel edema. Nasogastric decompression is necessary only with persistent vomiting or severe distention.

For prevention, intraoperative goals strive to minimize bowel manipulation, avoid excess intravenous fluids or profound hypovolemia, and limit surgery length (Bragg, 2015). Postoperatively, gum chewing enhances early bowel function recovery by nearly 7 hours after cesarean delivery (Zhu, 2014). Among studies, chewing was initiated immediately or up to 12 hours later, lasted 15 to 60 minutes, and was repeated in at least three sessions daily (Pereira Gomes Morais, 2016).

Ambulation and Wound Care

As discussed earlier, women undergoing cesarean delivery have an increased risk of venous thromboembolism compared with those delivering vaginally. Early ambulation lowers the thromboembolism risk. Walking to the bathroom begins, initially with assistance. Brief walks are encouraged, and ambulation can be timed so that a recently administered analgesic will minimize discomfort.

Although not evidence based, we remove the surgical dressing after 24 hours and inspect the incision daily. One small randomized trial showed no wound healing differences if removed at 6 hours (Peleg, 2016). By the third postpartum day, showering is not harmful to the incision. Prior to this, a plastic cover can maintain dryness during showers. If used, staples often are removed on the fourth day. Once removed, dressing strips (Steri-Strips) can be placed as needed for 1 week to reinforce skin edge integrity. If there is concern for superficial wound separation, staples remain in place for 7 to 10 days.

Hospital Discharge

For uncomplicated cesarean delivery, the average hospitalization length is three to four days (Buie, 2010). Data from studies suggest that earlier discharge is feasible for properly selected women and newborns (Bayoumi, 2016; Tan, 2012). Protocols ideally include earlier reevaluation for neonatal jaundice.

Activities during the first week should be restricted to self-care and newborn care with assistance. Driving can be resumed when pain does not limit the ability to brake quickly and when narcotic medications are not in use. In women with cesarean delivery, intercourse was resumed in 44 percent by 6 weeks postpartum, in 81 percent by 3 months, and 97 percent at 1 year (McDonald, 2013). After the puerperium, the quality of sexual functioning does not differ between those undergoing spontaneous vaginal delivery or cesarean (Chang, 2015; Fehniger, 2013; Rogers, 2014). Return to work is variable. Six weeks is commonly cited, although many women use the Family and Medical Leave Act to allow up to 12 weeks for recovery and newborn bonding.

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CHAPTER 31: Prior Cesarean Delivery

> *The occurrence of pregnancy after a Caesarean section, however, is not always devoid of danger, cases have been reported in which the uterine cicatrix ruptured in the latter part of a subsequent gestation. It is also stated that the adhesions that sometimes form between the uterus and the abdominal wall occasionally exert a deleterious influence in subsequent pregnancies.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

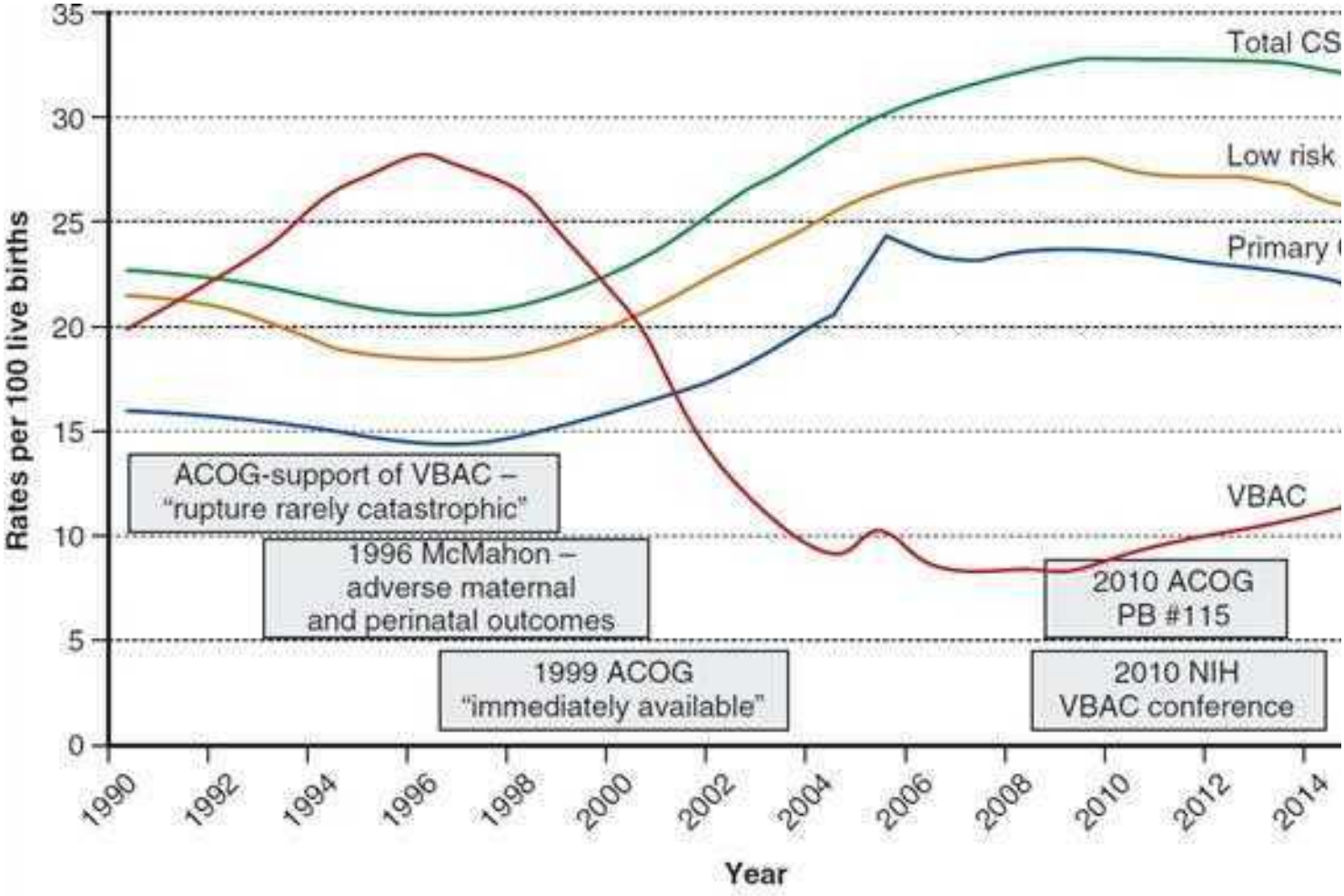
From the above, there was an early appreciation for some of the major problems encountered in women with a prior cesarean delivery. Few issues in modern obstetrics have been as controversial as the management of these women. Indeed, the dangers associated with uterine rupture led to the oft-quoted remark by Cragin in 1916: “Once a cesarean, always a cesarean.” As we reach the 100-year mark of Cragin’s pronouncement, the issue remains largely unsettled.

100 YEARS OF CONTROVERSY

By the beginning of the 20th century, cesarean delivery had become relatively safe. But, as women survived the first operation and conceived again, they were now at risk for rupture of the uterine scar. Still, the specter of rupture did not did not result in strict adherence to repeat cesarean delivery. Indeed, Eastman (1950) described a 30-percent postcesarean vaginal delivery rate at Johns Hopkins Hospital. The uterine rupture incidence was 2 percent and associated with a 10-percent maternal mortality rate. During the 1960s, observational studies suggested that vaginal delivery was a reasonable option (Pauerstein, 1966, Pauerstein, 1969). Germane to this is that through the 1960s, the overall cesarean delivery rate approximated only 5 percent. Since then, as the primary cesarean rate escalated, the rate for repeat cesarean delivery followed (Rosenstein, 2013).

During the 1980s, a National Institutes of Health (NIH) Consensus Development Conference (1981) was convened, and it questioned the necessity of routine repeat cesarean delivery. With support and encouragement from the American College of Obstetricians and Gynecologists (1988, 1994), enthusiastic attempts were begun to increase the use of *vaginal birth after cesarean—VBAC*. These attempts were highly successful, and VBAC rates increased from 3.4 percent in 1980 to a peak of 28.3 percent in 1996. These rates, along with a concomitant decline in total cesarean delivery rates for the United States, are shown in Figure 31-1.

FIGURE 31-1
Total, primary, and low-risk cesarean delivery (CS) rates and vaginal birth after previous cesarean (VBAC) rates in the United States, 1989–2015. Epochs denoted within rectangles represent contemporaneous ongoing events related to these rates. ACOG = American College of Obstetricians and Gynecologists; NIH = National Institutes of Health; PB = practice bulletin. (Data from Hamilton, 2015, 2016; National Institutes of Health: NIH Consensus Development Conference, 2010.)

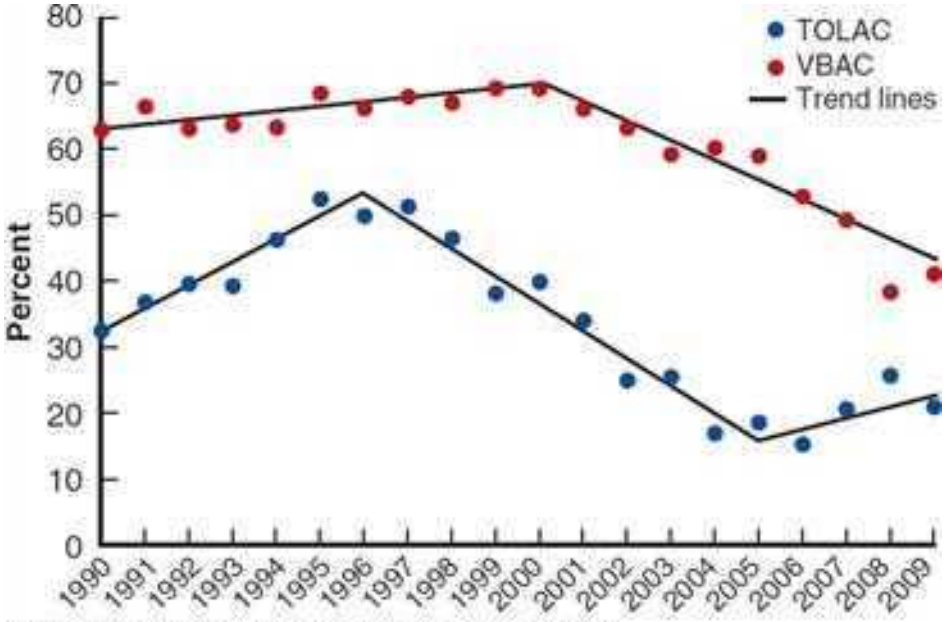


As the vaginal delivery rate increased, so did reports of uterine rupture-related maternal and perinatal morbidity and mortality (McMahon, 1996; Sachs, 1999). These complications dampened prevailing enthusiasm for a *trial of labor after cesarean section (TOLAC)* and stimulated the American College of Obstetricians and Gynecologists (1998) to caution that such trials should be attempted only in appropriately equipped institutions with physicians *readily available* to provide emergency care. Less than a year later, the College (1999) recommended that physicians should be *immediately available*. Many believe that this change of one word — from *readily* to *immediately* available—was in large part responsible for the decade-long decline in national VBAC rates illustrated in Figure 31-1 (Cheng, 2014; Leeman, 2013).

Uddin and colleagues (2013) reported the proportion of women with a prior cesarean delivery who underwent TOLAC. This number peaked in 1995, when slightly more than half of all of these women chose this option. Since that time, the proportion of women attempting TOLAC declined to a nadir in 2006 of about 16 percent and has subsequently increased to 20 to 25 percent through 2009. These investigators further reported that the percentage of VBACs reached its peak in 2000 with approximately 70 percent of women being successful, but this has subsequently declined to a nadir of 38 percent in 2008 (Fig. 31-2).

FIGURE 31-2

Percentage of births with trial of labor among all deliveries with a prior cesarean delivery and percentage of successful trials of labor among all trials of labor after caesarean delivery in the United States, 1990–2009. TOLAC = trial of labor after cesarean delivery; VBAC = vaginal birth after cesarean delivery. (Data from Uddin SFG, Simon AE: Rates and success rates of trial of labor after cesarean delivery in the United States, 1990–2009. Matern Child Health J 17:1309, 2013.)



In reality, several other interrelated factors—both medical and nonmedical—have undoubtedly contributed to declining VBAC rates. Because of their complexity and importance, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the Office of Medical Applications of Research (OMAR) convened an NIH Consensus Development Conference Panel (2010) to study the issues of VBAC. The panel report included a contemporaneous summary concerning the risks and benefits of repeat cesarean versus vaginal delivery. These findings are subsequently described along with summaries of current recommendations by various professional organizations. Importantly, data from California indicate that VBAC rates have not perceptibly increased since the 2010 NIH Consensus Conference (Barger, 2013).

INFLUENCING FACTORS

For the woman who has had a previous cesarean delivery, planning for future pregnancies and the delivery route should begin with preconceptional counseling and be addressed once again early in prenatal care. Importantly, any decision is subject to continuing revisions as dictated by exigencies that arise during pregnancy. Assuming no mitigating circumstances, there are two basic choices. First, a *TOLAC* offers the goal of achieving *VBAC*. If cesarean delivery becomes necessary during the trial, then it is termed a “failed trial of labor.” A second choice is *elective repeat cesarean delivery (ERCD)*. This includes scheduled cesarean delivery as well as unscheduled but planned cesarean delivery for spontaneous labor or another indication.

The ultimate decision should weigh clinical factors known to influence TOLAC success as well as benefits and risks. As expected, these rates vary between institutions and providers. Factors that influence a successful TOLAC are listed in Table 31-1. Finally, economic, staffing, and medicolegal factors may shape the decision to offer TOLAC.

TABLE 31-1

Some Factors That Influence a Successful Trial of Labor in a Woman with Prior Cesarean Delivery

Low-Risk	Favors Success	Increased Failure Rate	High-Risk[a]
Transverse incision Prior vaginal delivery Appropriate counseling Sufficient personnel and equipment	Teaching hospital White race Spontaneous labor Prior fetal malpresentation 1 or 2 prior transverse incisions Nonrecurrent indication Current preterm pregnancy	Single mother Increased maternal age Macrosomic fetus Obesity Breech Multifetal pregnancy Preeclampsia EGA >40 weeks Low-vertical incision Unknown incision Labor induction Medical disease Multiple prior cesarean deliveries Education <12 years Short interdelivery interval Liability concerns	Classical or T incision Prior rupture Patient refusal Transfundal surgery Obstetrical contraindication, e.g., previa Inadequate facilities

[a]Most consider these absolute contraindications.

EGA = estimated gestational age.

DELIVERY ROUTE RISKS

As evidence mounted that the risk of uterine rupture might be greater than expected, the American College of Obstetricians and Gynecologists (1988, 1998, 1999, 2017a) issued updated Practice Bulletins supporting labor trials but also urging a more cautious approach. It is problematic that both options have risks and benefits to mother and fetus but that these are not always congruent.

Maternal Risks

Rates of uterine rupture and associated complications clearly are increased with TOLAC. Uterine rupture typically is classified as either (1) *complete*, when all layers of the uterine wall are separated, or (2) *incomplete*, when the uterine muscle is separated but the visceral peritoneum is intact. Incomplete rupture is also commonly referred to as *uterine dehiscence*. It is these risks that underpin most of the angst in attempting TOLAC. Despite this, some have argued that these factors should weigh only minimally in the decision because their absolute risk is low. One systematic review by Guise and colleagues (2010) concluded that the risk of uterine rupture was significantly elevated in women undergoing TOLAC—absolute risk of 0.47 percent and relative risk of 20.7—compared with those choosing ERCD.

TABLE 31-2

Complications in Women with a Prior Cesarean Delivery Enrolled in the NICHD Maternal-Fetal Medicine Units Network, 1999–2002

Complication	Trial of Labor Group n = 17,898 No. (%)	Elective Repeat Cesarean Group n = 15,801 No. (%)	Odds Ratio (95% CI)	*p* value
Uterine rupture	124 (0.7)	0	NA	<.001
Uterine dehiscence	119 (0.7)	76 (0.5)	1.38 (1.04–1.85)	.03
Hysterectomy	41 (0.2)	47 (0.3)	0.77 (0.51–1.17)	.22
Thromboembolic disease	7 (0.04)	10 (0.1)	0.62 (0.24–1.62)	.32
Transfusion	304 (1.7)	158 (1.0)	1.71 (1.41–2.08)	<.001
Uterine infection	517 (2.9)	285 (1.8)	1.62 (1.40–1.87)	<.001
Maternal death	3 (0.02)	7 (0.04)	0.38 (0.10–1.46)	.21
Antepartum stillbirth[a]				
37–38 weeks	18 (0.4)	8 (0.1)	2.93 (1.27–6.75)	.008
≥39 weeks	16 (0.2)	5 (0.1)	2.70 (0.99–7.38)	.07
Intrapartum stillbirth[a]	2	0	NA	NS
Term HIE[a]	12 (0.08)	0	NA	<.001
Term neonatal death[a]	13 (0.08)	7 (0.05)	1.82 (0.73–4.57)	.19

[a]Denominator is 15,338 for the trial of labor group and 15,014 for the elective repeat cesarean delivery group.

CI = confidence interval; HIE = hypoxic ischemic encephalopathy; NA = not applicable; NICHD = National Institute of Child Health and Human Development; NS = not significant.

Adapted from Landon, 2004.

The Maternal-Fetal Medicine Units Network conducted a prospective study at 19 academic centers (Landon, 2004). The outcomes of nearly 18,000 women attempting TOLAC were compared with more than 15,000 gravidas undergoing ERCD. The absolute risk of uterine rupture was 0.7 percent compared with no reported uterine ruptures in the ERCD cohort (Table 31-2). Most studies suggest that the maternal *mortality* rate does not differ significantly between these two groups (Landon, 2004; Mozurkewich, 2000). But, the aforementioned systematic review by Guise (2010) found the risk of maternal death to be significantly reduced for women undergoing TOLAC compared with ERCD. In a retrospective Canadian cohort study, the maternal death rate for women undergoing ERCD was 5.6 per 100,000 cases compared with 1.6 per 100,000 for those attempting TOLAC (Wen, 2005).

Estimates of maternal *morbidity* are also conflicting. The review by Guise (2010) observed no significant differences in the risk of hysterectomy or transfusion. But, another metaanalysis reported that women undergoing TOLAC were approximately half as likely to require a blood transfusion or hysterectomy compared with those undergoing ERCD (Mozurkewich, 2000). Conversely, in the Network study, investigators observed that the risks of transfusion and infection were significantly greater for women attempting TOLAC (Landon, 2004). This disparity is also found among other studies. Notably, compared with a successful TOLAC, the risk of these major complications was fivefold greater with an attempted vaginal delivery that failed (Babbar, 2013; Rossi, 2008).

Fetal and Neonatal Risks

TOLAC is associated with significantly higher *perinatal mortality* rates compared with ERCD. The perinatal rate with TOLAC is 0.13 compared with 0.05 percent for ERCD, and the neonatal mortality rates are 0.11 versus 0.06 percent, respectively (Guise, 2010). In another study of nearly 25,000 women with a prior cesarean delivery, the vaginal-delivery-related perinatal death risk was 1.3 per 1000 among 15,515 women electing TOLAC. Although this absolute risk is small, it is *11 times greater* than the risk found in 9014 women with ERCD (Smith, 2002).

TOLAC also appears to be associated with a higher risk of *hypoxic ischemic encephalopathy (HIE)* than ERCD. The Network study reported the incidence of HIE at term to be 46 per 100,000 TOLACs compared with zero cases in women undergoing ERCD (Landon, 2004).

In the systematic review, the absolute risk of *transient tachypnea of the newborn* was slightly higher with ERCD compared with TOLAC—4.2 versus 3.6 percent (Guise, 2010). But, neonatal bag and mask ventilation were used more often in newborns delivered following TOLAC than in those delivered by ERCD—5.4 versus 2.5 percent.

Finally, there are no significant differences in 5-minute Apgar scores or neonatal intensive care unit admission rates for newborns delivered by TOLAC compared with those delivered by ERCD. Birth trauma from lacerations is more commonly seen in neonates born by ERCD.

CANDIDATES FOR TRIAL OF LABOR

Few high-quality data are available to guide selection of TOLAC candidates. In a population-based cohort study of 41,450 women delivering in California hospitals, Gregory and colleagues (2008) reported a TOLAC success rate of 74 percent when no maternal, fetal, or placental complications were present. Several algorithms and nomograms have been developed to aid prediction, but none has demonstrated reasonable prognostic value (Grobman, 2007b, 2008, 2009; Macones, 2006; Metz, 2013; Srinivas, 2007). A predictive model for failed trial of labor, however, was found to be somewhat predictive of uterine rupture or dehiscence (Stanhope, 2013). Despite these limitations for precision, several points are pertinent to candidate evaluation and are described in the next sections. Current recommendations of the American College of Obstetricians and Gynecologists (2017a) are that most women with one previous low-transverse hysterotomy are candidates, and if appropriate, they should be counseled regarding TOLAC and ERCD options. Although not our practice, those with two prior low-transverse incisions may be considered.

Prior Uterine Incision

Prior Incision Type

The type and number of prior cesarean deliveries are overriding factors in recommending TOLAC. Women with one prior low-transverse hysterotomy have the lowest risk of symptomatic scar separation (Table 31-3). The highest risks are with prior vertical incisions extending into the fundus, such as that shown in Figure 31-3. Importantly, in some women, a classical scar will rupture before labor onset, and this can happen several weeks before term. In a review of 157 women with prior classical cesarean delivery, one woman had a complete uterine rupture before labor onset, whereas 9 percent had a uterine dehiscence (Chauhan, 2002).

TABLE 31-3

Types of Prior Uterine Incisions and Estimated Risks for Uterine Rupture

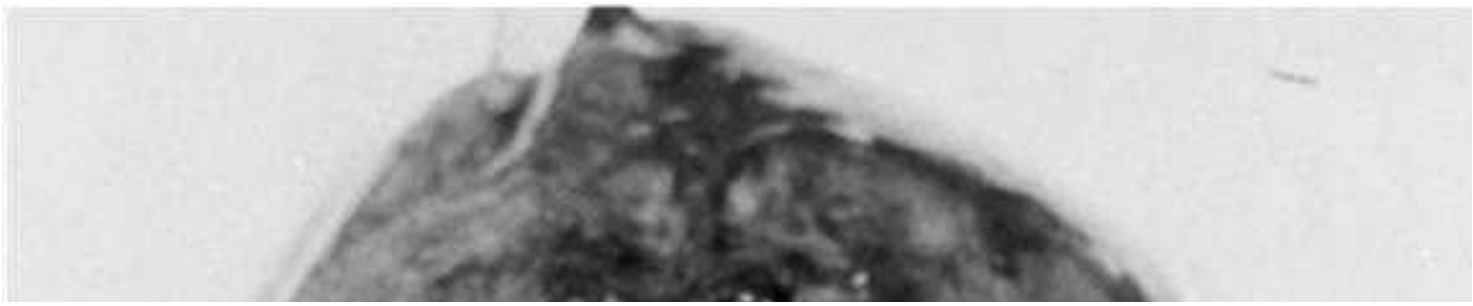
Prior Incision	Estimated Rupture Rate (%)
Classical	2–9
T-shaped	4–9
Low-vertical[a]	1–7
One low-transverse	0.2–0.9
Multiple low-transverse	0.9–1.8
Prior preterm cesarean delivery	“increased”
Prior uterine rupture	
Lower segment	2–6
Upper uterus	9–32

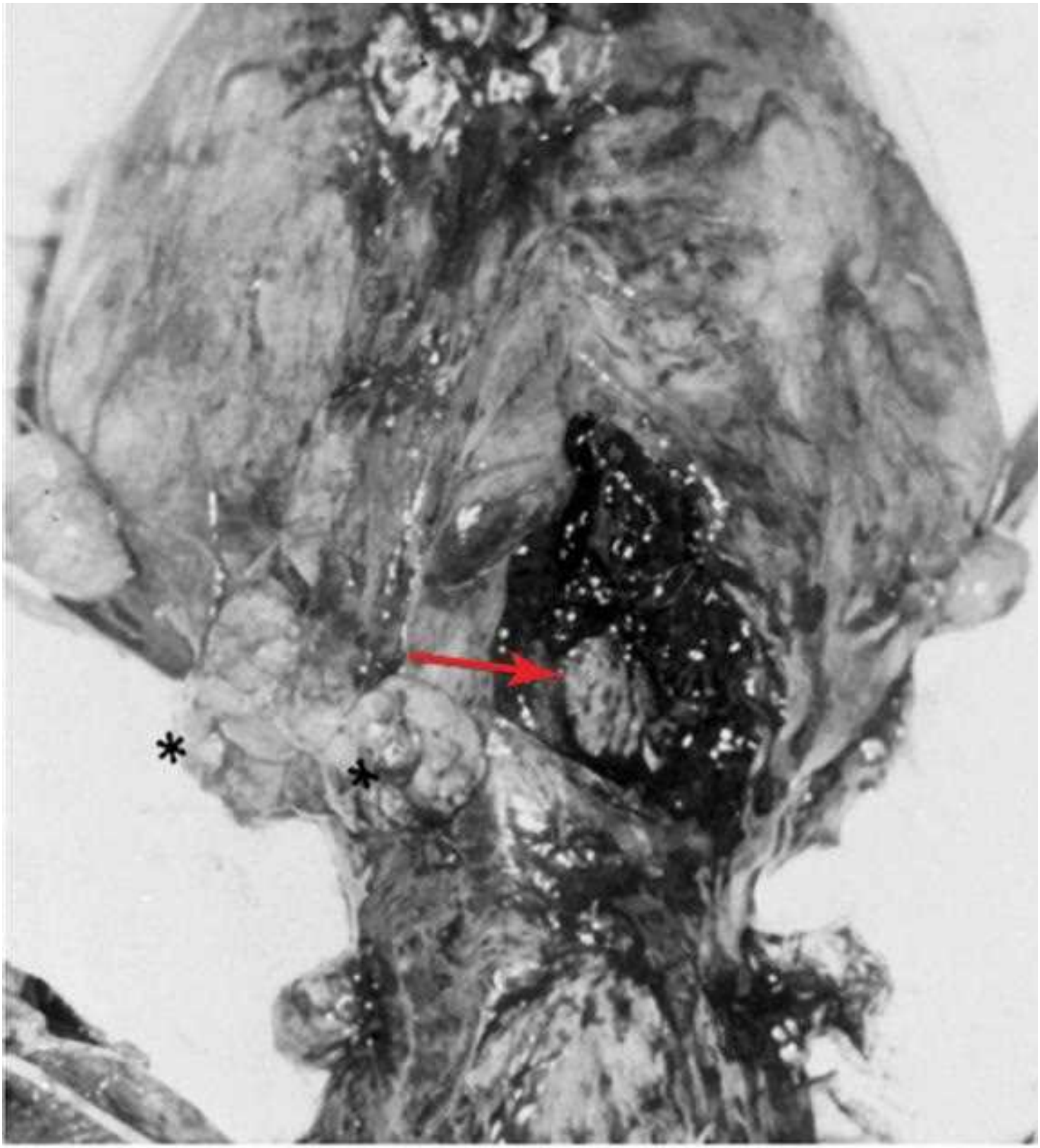
[a]See text for definition.

Data from the American College of Obstetricians and Gynecologists, 2017a; Cahill, 2010b; Chauhan, 2002; Landon, 2006; Macones, 2005a,b; Martin, 1997; Miller, 1994; Sciscione, 2008; Society for Maternal-Fetal Medicine, 2012; Tahseen, 2010.

FIGURE 31-3

Ruptured vertical cesarean delivery scar (*arrow*) identified at time of repeat cesarean delivery early in labor. The two black asterisks to the left indicate some sites of densely adhered omentum.





The risk of uterine rupture in women with a prior vertical incision that did not extend into the fundus is unclear. Martin (1997) and Shipp (1999) and their coworkers reported that these low-vertical uterine incisions did not have an increased risk for rupture compared with low-transverse incisions. The American College of Obstetricians and Gynecologists (2017a) concluded that although evidence is limited, women with a prior vertical incision in the lower uterine segment without fundal extension may be candidates for TOLAC. This is in contrast to prior classical or T-shaped uterine incisions, which are considered by most as contraindications to labor.

Although there are few indications for a primary classical incision, 53 percent of women undergoing cesarean delivery between $24^{0/7}$ weeks and $25^{6/7}$ weeks have such an incision (Osmundson, 2013). By 28 weeks' gestation, the risk drops to 35 percent and declines to <10 percent by 32 weeks. The likelihood of classical uterine

incision is also increased by noncephalic presentations. In those instances—for example, preterm breech fetus with an undeveloped lower segment—the "low vertical" incision almost invariably extends into the active segment. Prior preterm cesarean delivery may result in a twofold increased risk for rupture (Sciscione, 2008). This may be in part explained by the greater likelihood with a preterm fetus of upward uterine incision extension. Lannon and coworkers (2015) compared 456 women with a prior periviable cesarean delivery with more than 10,000 women whose prior cesarean delivery occurred at term. They observed uterine rupture in 1.8 percent in the prior periviable group versus 0.4 percent in the prior term group. Of the uterine ruptures in the periviable group, half were in women whose prior uterine incision was described as low transverse. Harper and associates (2009) did not confirm these findings.

There are also special considerations for women with uterine malformations who have undergone cesarean delivery. Earlier reports suggested that the uterine rupture risk in a subsequent pregnancy was greater than the risk in those with a prior low-transverse hysterotomy and normally formed uterus (Ravasia, 1999). But, in a study of 103 women with müllerian duct anomalies, there were no cases of uterine rupture (Erez, 2007). Given the wide range of risk for uterine rupture associated with the various uterine incision types, it is not surprising that most fellows of the American College of Obstetricians and Gynecologists consider the type of prior incision to be the most important factor when considering a TOLAC (Coleman, 2005).

Prior Incision Closure

As discussed in Chapter 30 (Uterine Repair), the low-transverse hysterotomy incision can be sutured in either one or two layers. A metaanalysis by Roberge and colleagues (2014) compared single- versus double-layer closure and locking versus unlocking suture for uterine closure. They reported that rates for uterine dehiscence or uterine rupture for these closures did not differ significantly. Single-layer closure and locked first layer, however, was associated with a reduced myometrial thickness during subsequent sonographic measurement. In contrast, Bennich and coworkers (2016) reported that a double-layer closure did not increase the residual myometrial thickness when saline contrast sonography was done several months postpartum. At Parkland Hospital, we routinely close the lower-segment incision with one running, locking suture line.

Number of Prior Cesarean Incisions

At least three studies report a doubling or tripling of the rupture rate in women with two compared with one prior transverse hysterotomy (Macones, 2005a; Miller, 1994; Tahseen, 2010). In contrast, analysis of the Network database by Landon and associates (2006) did not confirm this. Instead, they reported an insignificant difference in the uterine rupture rate in 975 women with multiple prior cesarean deliveries compared with 16,915 women with a single prior operation—0.9 versus 0.7 percent, respectively. As discussed in Multiple Repeat Cesarean Deliveries, other serious maternal morbidity increases along with the number of prior cesarean deliveries (Marshall, 2011).

Imaging of Prior Incision

Sonographic measurement of a prior hysterotomy incision has been used to predict the likelihood of rupture. Large defects in a nonpregnant uterus forecast a greater risk for subsequent rupture (Osser, 2011). Naji and coworkers (2013a,b) found that the *residual myometrial thickness* decreased as pregnancy progressed and that rupture correlated with a thinner scar. In a systematic review, women with a prior low-transverse cesarean incision underwent third-trimester sonographic evaluation (Jastrow, 2010a). Investigators concluded that the thickness of the lower uterine segment was a strong predictor for a uterine scar defect in women with prior cesarean delivery. They defined this segment as the smallest measurement between urine in the maternal bladder and amnionic fluid. That said, they could not find an ideal threshold value to recommend TOLAC. This same group subsequently recruited 1856 women contemplating vaginal birth after a single low-transverse incision, and they sonographically measured lower uterine segment thickness by between 34 weeks and 39 weeks (Jastrow, 2016). They grouped women into three risk categories for uterine rupture during TOLAC based on the measured segment value: high risk <2.0 mm; intermediate risk 2.0–2.4 mm; and low risk ≥2.5 mm. The TOLAC rates were 9, 42, and 61 percent in the three categories, respectively. Of the 984 TOLACs, there were no symptomatic uterine ruptures. Overall, data are limited, and this evaluation is currently not part of our routine practice.

Prior Uterine Rupture

Women who have previously sustained a uterine rupture are at greater risk for recurrence. As shown in Table 31-3, those with a previous low-segment rupture have up to a 6-percent recurrence risk, whereas prior upper segment uterine rupture confers a 9- to 32-percent risk (Reyes-Ceja, 1969; Ritchie, 1971). Fox and associates (2014) reported 14 women with prior uterine rupture and 30 women with prior uterine dehiscence. In 60 subsequent pregnancies, they reported no uterine ruptures or severe complications if women were managed in a standardized manner with cesarean delivery prior to labor onset.

Interdelivery Interval

Magnetic resonance imaging studies of myometrial healing suggest that complete uterine involution and restoration of anatomy may require at least 6 months (Dicle, 1997). To explore this further, Shipp and coworkers (2001) examined the relationship between interdelivery interval and uterine rupture in 2409 women with one prior cesarean delivery. There were 29 women with a uterine rupture—1.4 percent. Interdelivery intervals ≤18 months were associated with a threefold greater risk of symptomatic rupture during a subsequent TOLAC compared with intervals >18 months. Similarly, Stamilio and associates (2007) noted a threefold augmented risk of uterine rupture in women with an interpregnancy interval <6 months compared with one ≥6 months.

Prior Vaginal Delivery

Prior vaginal delivery, either before or after a cesarean birth, improves the prognosis for a subsequent vaginal delivery with either spontaneous or induced labor (Aviram, 2017; Grinstead, 2004; Hendler, 2004; Mercer, 2008). Prior vaginal delivery also lowers the risk of subsequent uterine rupture and other morbidities (Cahill, 2006; Hochler, 2014; Zelop, 1999).

Prior Cesarean Delivery Indication

Women with a nonrecurring indication—for example, breech presentation—have the highest VBAC rate of nearly 90 percent (Wing, 1999). Those with a prior cesarean delivery for fetal compromise have an approximately 80-percent VBAC rate, and for those done for labor arrest, VBAC rates approximate 60 percent (Bujold, 2001; Peaceman, 2006). Prior second-stage cesarean delivery can be associated with second-stage uterine rupture in a subsequent pregnancy (Jastrow, 2013).

Fetal Size and Lie

Most studies show that increasing fetal size is inversely related to VBAC rates. The risk for uterine rupture is less robustly linked. Zelop and associates (2001) studied outcomes of almost 2750 women undergoing TOLAC, and the rate of uterine rupture increased—albeit not significantly—with rising fetal weight. The rate was 1.0 percent for fetal weight <4000 g, 1.6 percent for >4000 g, and 2.4 percent for >4250 g. Similarly, Jastrow and colleagues (2010b) in a retrospective report of 2586 women with a prior low-transverse uterine incision, observed an elevated risk for a failed trial of labor, uterine rupture, shoulder dystocia, and perineal laceration associated with rising birthweights. Conversely, Baron and coworkers (2013) did not find higher uterine rupture rates with birthweights >4000 g. With a preterm fetus, women who attempt a TOLAC have higher VBAC rates and lower rupture rates (Durnwald, 2006; Quiñones, 2005).

Data supporting external cephalic version (ECV) for breech presentation are limited and are derived from small studies (Burgos, 2014; Weill, 2017). From these, ECV success and adverse event rates appear comparable to women without prior cesarean. The American College of Obstetricians and Gynecologists (2016) acknowledges this lack of robust data. At Parkland Hospital, we do not attempt ECV in those with a prior cesarean delivery.

Multifetal Gestation

Twin pregnancy does not appear to increase the risk of uterine rupture. Ford and associates (2006) analyzed 1850 women with twins and reported a 45-percent successful VBAC rate and a rupture rate of 0.9 percent. Similar studies by Cahill (2005) and Varner (2007) and their colleagues reported rupture rates of 0.7 to 1.1 percent and VBAC rates of 75 to 85 percent. According to the American College of Obstetricians and Gynecologists (2017a), women with twins and a prior low-transverse hysterotomy can safely undergo TOLAC.

Maternal Obesity

Multiple studies have reported an inverse relationship between prepregnancy body mass index (BMI) and VBAC rates. Hibbard and coworkers (2006) reported the following rates: 85 percent with a normal BMI, 78 percent with a BMI between 25 and 30, 70 percent with a BMI between 30 and 40, and 61 percent with a BMI ≥40. Similar findings were reported by Juhasz and associates (2005).

Fetal Death

Most women with a prior cesarean delivery and fetal death in the current pregnancy would prefer a vaginal delivery. Although fetal concerns are obviated, available data suggest that maternal risks are increased. Nearly 46,000 women with a prior cesarean delivery in the Network database had a total of 209 fetal deaths at an average gestational age of 32.8 weeks (Ramirez, 2010). There were 158 women who elected TOLAC, with a VBAC rate of 87 percent. In the entire TOLAC group, the uterine rupture rate was 2.4 percent. Of the 116 women who underwent an induction of labor, there were five uterine ruptures (3.4 percent).

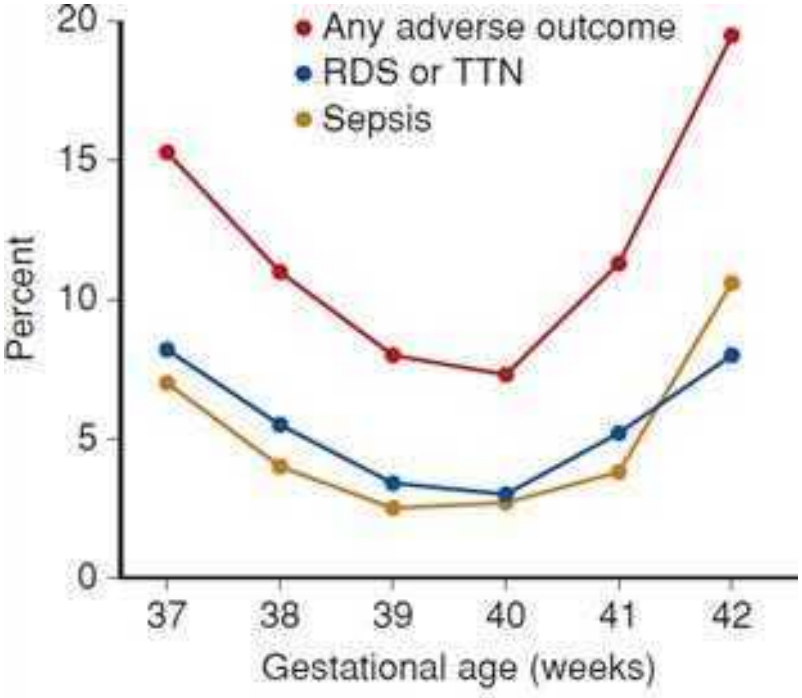
LABOR AND DELIVERY CONSIDERATIONS

Timing

The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2017b) recommend delaying nonmedically indicated deliveries until 39 completed weeks of gestation or beyond. As shown in Figure 31-4, significant and appreciable adverse neonatal morbidity has been reported with elective delivery before 39 completed weeks (Chiossi, 2013; Clark, 2009). Thus, if ERCD is planned, it is essential that the fetus be mature.

FIGURE 31-4

Neonatal morbidity rates seen with 13,258 elective repeat cesarean deliveries. Any adverse outcome includes death. Sepsis includes suspected and proven. RDS = respiratory distress syndrome; TTN = transient tachypnea of the newborn. (Data from Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med 360(2):111, 2009.)



The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have established the following guidelines for timing an elective cesarean delivery, and accurate gestational dating is suitable using any of these criteria.

1. Sonographic measurements taken before 20 weeks' gestation support a gestational age ≥39 weeks.
2. Fetal heart sounds have been documented for 30 weeks by Doppler ultrasound.
3. A positive serum or urine β-human chorionic gonadotropin (hCG) test result has been documented for ≥36 weeks.

Intrapartum Care

Because of uterine rupture risks for women undergoing TOLAC, the American Academy of Pediatricians and the American College of Obstetricians and Gynecologists (2017) recommend that such trials be undertaken only in facilities with staff immediately available to provide emergency care. Moreover, these centers should have a plan and resources for managing uterine rupture. Some argue that these provisions deny women full access to choices. For example, in an earlier survey of Ohio hospitals, 15 percent of Level I, 63 percent of Level II, and 100 percent of Level III institutions met these requirements (Lavin, 2002). Moreover, an obstetrical anesthesia workforce survey reported that due to staffing limitations, TOLAC was allowed in only 88 percent of hospitals with ≥1500 annual deliveries, in 59 percent of those with 500 to 1499 deliveries, and in 43 percent of those with <500 deliveries (Traynor, 2016). In some cases, women choose to attempt TOLAC at a birthing center or at home (Shields, 2017).

Cervical Ripening and Labor Stimulation

Labor induction is associated with a higher failure rate during TOLAC. The risks for uterine rupture, however, are less clear with induction or augmentation, with the exception of prostaglandin E_1—misoprostol—which is contraindicated (American College of Obstetricians and Gynecologists, 2017a). Although most institutions are not so conservative, we do not induce or augment labor pharmacologically in women electing TOLAC at Parkland Hospital. Instead, we attempt induction only by amniotomy. Other considerations are to avoid induction or augmentation in women with an unknown prior incision type, an unfavorable cervix, or pregnancy >40 weeks.

Oxytocin

Induction or augmentation of labor with oxytocin has been *implicated* in increased rates of uterine rupture in women undergoing TOLAC (Zelop, 1999). In the Network study reported by Landon and colleagues (2004), uterine rupture was more frequent in women induced with oxytocin alone—1.1 percent—than in those in spontaneous labor—0.4 percent. Augmentation of labor was associated with uterine rupture in 0.9 percent. Among women in this trial without a prior vaginal delivery, the uterine rupture risk associated with oxytocin induction was 1.8 percent—a fourfold greater risk compared with spontaneous labor (Grobman, 2007a). In contrast, in one case-control study, induction was not associated with a higher risk for rupture (Harper, 2012a). Cahill (2008) and Goetzl (2001) and their coworkers reported a dose-related risk of rupture with oxytocin.

Prostaglandins

Various prostaglandin preparations commonly employed for cervical ripening or labor induction are discussed in Chapter 26 (Pharmacological Techniques). As a group, their safe use in women with a prior cesarean delivery is unclear because of conflicting data.

With misoprostol (PGE_1), Wing and colleagues (1998) compared it versus oxytocin for labor induction in women with a prior cesarean delivery. They terminated their trial after two of the first 17 women assigned to misoprostol developed a uterine rupture. Other studies confirmed this, and most consider misoprostol to be contraindicated (American College of Obstetricians and Gynecologists, 2017a).

Of other prostaglandins, studies to evaluate their use for induction are contradictory. Ravasia and coworkers (2000) compared uterine rupture in 172 women given PGE_2 gel with 1544 women in spontaneous labor. The rupture rate was significantly greater in women treated with PGE_2 gel—2.9 percent compared with 0.9 percent in those with spontaneous labor. Lydon-Rochelle and associates (2001) found similar results. However, in the Network study cited previously, the uterine rupture rate was 1.4 percent when any prostaglandin was used in combination with oxytocin (Landon, 2004). But, in the subgroup of 227 women in whom labor was induced with a prostaglandin alone, there were no ruptures. Similar findings were reported with intravaginal prostaglandins, which were not associated with a greater uterine rupture risk (Macones, 2005b). These latter investigators, along with Kayani and colleagues (2005), found that sequential use of a prostaglandin followed by oxytocin was associated with a threefold greater risk of rupture compared with spontaneous labor.

Mechanical Methods

Studies concerning the use of a transcervical Foley catheter for cervical ripening and induction of labor in women with a prior cesarean delivery are limited (Ben-Aroya, 2002; Jozwiak, 2014). In a retrospective study of 2479 women with prior cesarean delivery, the uterine rupture risk using a transcervical Foley catheter for labor induction (1.6 percent) was not significantly greater than that with spontaneous labor (1.1 percent) or with using amniotomy with or without oxytocin (1.2 percent) (Bujold, 2004). In contrast, Hoffman (2004) described 138 women who underwent preinduction cervical ripening with a Foley catheter compared with 536 women who entered labor spontaneously. They observed a significant and inordinately high uterine rupture risk during labor following Foley catheter cervical ripening compared with spontaneous onset of labor—6.5 versus 1.9 percent.

Epidural Analgesia

Concerns that epidural analgesia for labor might mask the pain of uterine rupture have not been verified. Fewer than 10 percent of women with scar separation experience pain and bleeding, and fetal heart rate decelerations are the most likely sign (Kieser, 2002). That said, Cahill and coworkers (2010a) documented that more frequent episodes of epidural dosing were associated with increasing uterine rupture rates. VBAC rates are similar, and in some cases higher, among women with labor epidural analgesia compared with those using other forms of analgesia (Aviram, 2017; Shmudi, 2017). Perhaps related, almost a fourth of VBAC deliveries were completed with either forceps or vacuum (Inbar, 2017). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) have concluded that epidural analgesia may safely be used during TOLAC.

Uterine Scar Exploration

Following VBAC, some clinicians routinely document the integrity of a prior scar by placing a hand through the dilated cervix and along the inner surface of the lower uterine segment. But routine uterine exploration is considered by others to be unnecessary. In a longitudinal study of 3469 women who had a VBAC, seven uterine dehiscences and one uterine rupture yielded an overall event rate of 0.23 percent (Silberstein, 1998). They concluded that transcervical evaluation need only be performed in symptomatic patients.

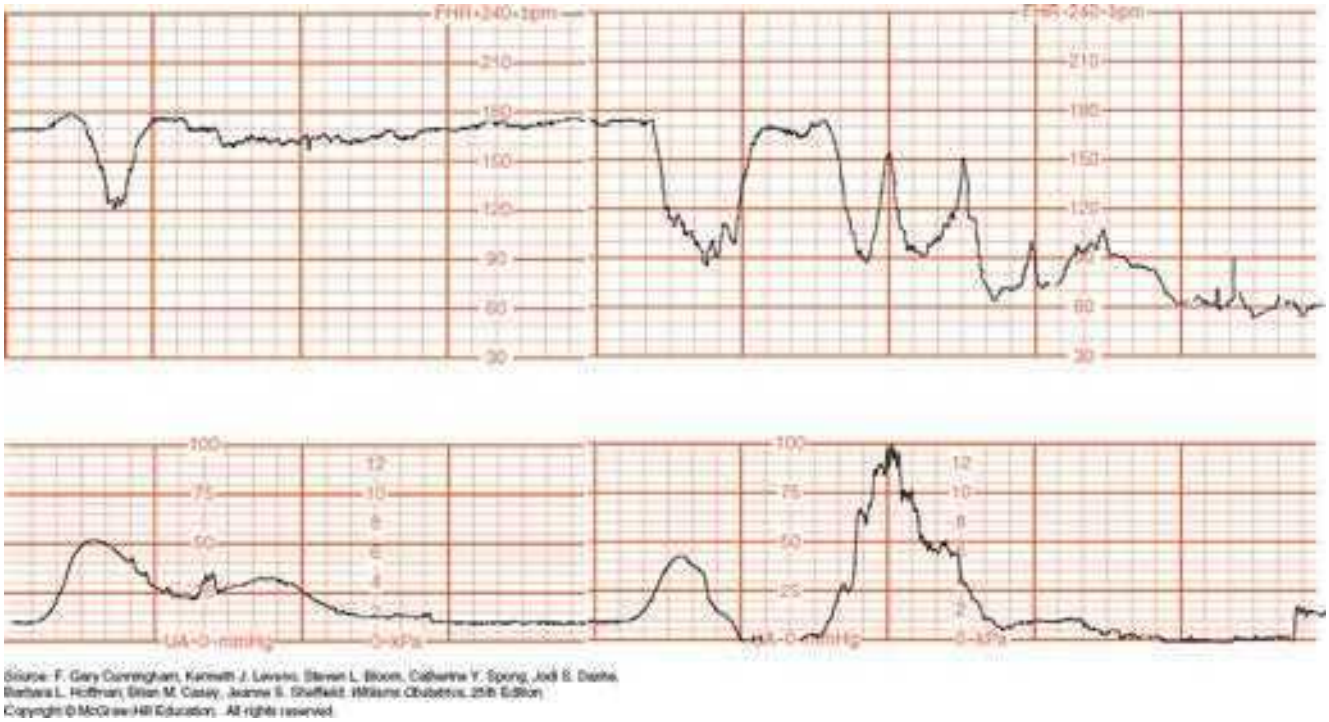
Currently, the benefits of routine scar evaluation in the asymptomatic woman are unclear, however, surgical correction of a dehiscence is necessary if significant bleeding is encountered. Our practice is to routinely examine these prior hysterotomy sites. Any decision for laparotomy and repair takes into consideration the extent of the tear, whether the peritoneal cavity has been entered, and the presence of active bleeding.

UTERINE SCAR RUPTURE

Diagnosis

Progress of labor in women attempting TOLAC is similar to normal labor, and no specific pattern presages uterine rupture (Graseck, 2012; Harper, 2012b; Sondgeroth, 2017). Before hypovolemic shock develops, symptoms and physical findings in women with uterine rupture may appear bizarre unless the possibility is kept in mind. For example, hemoperitoneum from a ruptured uterus may result in diaphragmatic irritation with pain referred to the chest. This may direct one to a diagnosis of pulmonary or amnionic fluid embolism instead of uterine rupture. As shown in Figure 31-5, the most common sign of uterine rupture is a nonreassuring fetal heart rate pattern with variable decelerations that may evolve into late decelerations and bradycardia. In 36 cases of such rupture during TOLAC, there were fetal signs of uterine rupture in 24, maternal signs in eight, and a combination of maternal and fetal in three (Holmgren, 2012). Few women experience cessation of contractions following uterine rupture, and the use of intrauterine pressure catheters does not assist reliably in the diagnosis (Rodriguez, 1989).

FIGURE 31-5
Fetal heart rate tracing in a woman whose uterus ruptured during labor while pushing. The rupture apparently stimulated a reflex push, after which uterine tone diminished and fetal bradycardia worsened.



In some women, the clinical appearance of uterine rupture mirrors that of placental abruption. In most, however, there is remarkably little appreciable pain or tenderness. Also, because most women in labor are treated for discomfort with either narcotics or epidural analgesia, pain and tenderness may not be readily apparent. The condition usually becomes evident because of fetal distress and occasionally because of maternal hypovolemia from concealed hemorrhage.

If the fetal presenting part has already entered the pelvis with labor, loss of station may be detected by pelvic examination. If the fetus is partly or totally extruded from the uterine rupture site, abdominal palpation or vaginal examination may be helpful to identify the presenting part, which will have moved away from the pelvic inlet. A firm contracted uterus may at times be felt alongside the fetus. Sonography may be helpful.

Decision-to-Delivery Time

With rupture and expulsion of the fetus into the peritoneal cavity, the chances for intact fetal survival are dismal, and reported mortality rates range from 50 to 75 percent. *Fetal condition depends on the degree to which placental implantation remains intact, although this can change within minutes.* With rupture, the only chance of fetal survival is afforded by immediate delivery—most often by laparotomy—otherwise, hypoxia is inevitable. If rupture is followed by total placental separation, then very few neurologically intact fetuses will be salvaged. *Thus, even in the best of circumstances, some fetal outcomes will be impaired.* The Utah experiences are instructive here (Holmgren, 2012). Of the 35 laboring patients with uterine rupture, the decision-to-delivery time was <18 minutes in 17, and none of these infants had an adverse neurological outcome. Of the 18 born >18 minutes from decision time, the three infants with long-term neurological impairments were delivered at 31, 40, and 42 minutes. There were no deaths, thus severe neonatal neurological morbidity developed in 8 percent of this group of 35 women with uterine rupture.

In a study using the Swedish Birth Registry, Kaczmarczyk and coworkers (2007) found that the risk of neonatal death following uterine rupture was 5 percent. In the Network study cited earlier, seven of the 114 uterine ruptures associated with TOLAC—6 percent—were complicated by development of neonatal HIE (Spong, 2007).

Maternal deaths from uterine rupture are uncommon. Of 2.5 million women who gave birth in Canada between 1991 and 2001, there were 1898 cases of uterine rupture, and four of these—0.2 percent—resulted in maternal death (Wen, 2005). In other regions of the world, however, maternal mortality rates are much higher. From rural India, the maternal mortality rate associated with uterine rupture was 30 percent (Chatterjee, 2007).

Management

With complete rupture during TOLAC, hysterectomy may be required. In selected cases, however, suture repair with uterine preservation may be performed. Sheth (1968) described outcomes from a series of 66 women in whom repair of a uterine rupture was elected rather than hysterectomy. Thirteen of the 41 mothers who did not have tubal sterilization had a total of 21 subsequent pregnancies. Uterine rupture recurred in four of these—approximately 20 percent. Usta and associates (2007) reported similar results. In another study, however, women with a uterine dehiscence were not more likely to have a subsequent uterine rupture (Baron, 2014).

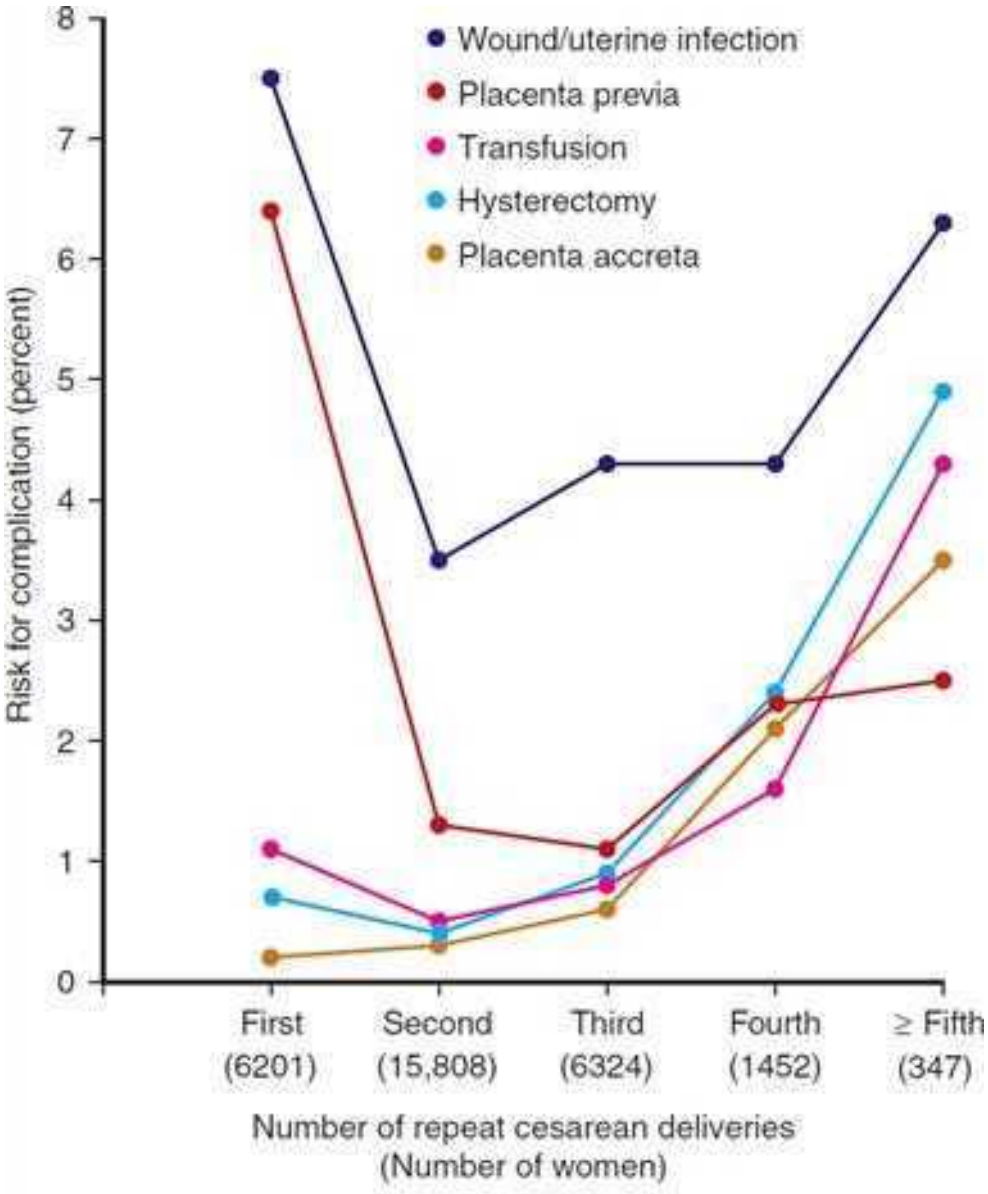
MULTIPLE REPEAT CESAREAN DELIVERIES

Because of the aforementioned concerns with TOLAC, most women in the United States undergo ERCD. This choice has several significant maternal complications, and rates of these rise in women who have multiple repeat operations. The incidences of some common complications for women with one prior transverse cesarean delivery who undergo an ERCD were shown in Table 31-2. Of note, half of cesarean hysterectomies done at Parkland Hospital are in women with one or more prior cesarean deliveries (Hernandez, 2013).

The Network addressed issues of increased morbidity in a cohort of 30,132 women who had from one to six repeat cesarean deliveries (Silver, 2006). The rates of some of the more frequent or serious complications are depicted in Figure 31-6. In addition, rates of bowel or bladder injury, admission to an intensive care unit or need for ventilator therapy, and maternal mortality, as well as operative and hospitalization length, showed significantly rising trends. Similar results have been reported by others (Nisenblat, 2006; Usta, 2005). More difficult to quantify are risks for bowel obstruction and pelvic pain from peritoneal adhesive disease, both of which increase with each successive cesarean delivery (Andolf, 2010; Mankuta, 2013).

FIGURE 31-6

Maternal-Fetal Medicine Units Network: rates of some complications with increasing number of repeat cesarean deliveries. (Data from Silver RM, Landon MB, Rouse DJ, et al: Maternal morbidity associated with multiple repeat cesarean deliveries. Obstet Gynecol 207:1226, 2006.)



Cook and colleagues (2013) from the United Kingdom Obstetric Surveillance System (UKOSS) described adverse sequelae of women with five or more cesarean deliveries. These women had significantly higher rates of morbidity. Namely, the major hemorrhage rate increased 18-fold; visceral damage, 17-fold; critical care admissions, 15-fold; and delivery <37 weeks, sixfold. Much of this morbidity was in the 18 percent who had a placenta previa or an accrete syndrome (Chap. 41, Placenta Previa).

VAGINAL BIRTH AFTER CESAREAN—2017

For providers and their patients, unfortunately, no large randomized trials have compared outcomes of women with an intent to pursue either TOLAC or ERCD. Most studies to date have compared *actual* routes of delivery rather than the *intended* route of delivery. Thus, we agree with Scott (2011) regarding a "common-sense" approach. The woman—and her partner if she wishes—are encouraged to actively participate with her provider in informed consent. Counseling should include documentation of the prior uterine incision and discussion of risks, benefits, and success rates of TOLAC or ERCD. This includes consideration of risks involving future pregnancies. Ideally, counseling begins preconceptionally and continues throughout pregnancy, with flexible options extending up to delivery. For women who desire TOLAC despite a factor that increases their specific risk, additions to the consent form are recommended by the American College of Obstetricians and

Gynecologists (2017a). Bonanno and colleagues (2011) have provided such an example. Brief synopses of professional society guidelines are shown in Table 31-4. Guidelines that tend to be more conservative are shown in Table 31-5.

TABLE 31-4

Some Recommendations of Professional Societies Concerning a Trial of Labor to Attempt VBAC

	Counseling	Facilities	Other
American College of Obstetricians and Gynecologists (2017a)	Offer to most women with one prior low-transverse incision; consider for two prior low-transverse incisions	Safest with ability for immediate cesarean delivery; patients should be allowed to accept increased risk when not available	Not precluded: twins, macrosomia, prior low-vertical or unknown type of incision
Society of Obstetricians and Gynaecologists of Canada (2005)	Offer to women with one prior transverse low-segment cesarean delivery; with >1 prior CD then VBAC likely successful but increased risks	Should deliver in hospital in which timely cesarean delivery is available; approximate timeframe of 30 minutes	Oxytocin or Foley catheter induction safe, but prostaglandins should not be used; macrosomia, diabetes, postterm pregnancy, twins are not contraindications
Royal College of Obstetricians and Gynaecologists (2007)	Discuss VBAC option with women with prior low-segment cesarean delivery; decision between obstetrician and patient	Suitable delivery suite with continuous care and monitoring; immediate cesarean delivery capability	Caution with twins and macrosomia

CD = cesarean delivery; VBAC = vaginal birth after cesarean.

TABLE 31-5

Conservative Guidelines to Approach a Trial of Labor Following Cesarean Delivery

Follow ACOG practice guidelines
Education and counseling Preconceptionally Provide ACOG patient pamphlet Early during prenatal care Develop preliminary plan Revisit at least each trimester Be willing to alter decision Have facilities availability
Risk assessment Review previous operative note(s) Review relative and absolute contraindications Reconsider risks as pregnancy progresses Tread carefully: >1 prior transverse CD, unknown incision, twins, macrosomia
Labor and delivery Cautions for induction—unfavorable cervix, high station Consider AROM Avoid prostaglandins Respect oxytocin—know when to quit Beware of abnormal labor progress Respect EFM pattern abnormalities Know when to abandon a trial of labor

ACOG = American College of Obstetricians and Gynecologists; AROM = artificial rupture of membranes; CD = cesarean delivery; EFM = electronic fetal monitoring.

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CHAPTER 32: The Newborn

Normally the newly born child begins to cry almost immediately after its exit from the vulva. This act indicates the establishment of respiration, which is accompanied by important modifications in the circulatory system.

—J. Whitridge Williams (1903)

INTRODUCTION

In most instances at delivery, the newborn is healthy and vigorous, but at times, special care may be needed. For this reason, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017b) recommend that every birth should be attended by at least one qualified individual. This person should be skilled in the initial steps of newborn care and positive-pressure ventilation, and their only responsibility is management of the newborn. This usually is a pediatrician, nurse practitioner, anesthesiologist, nurse anesthetist, or specially trained nurse. However, in their absence, the responsibility for neonatal resuscitation falls to the obstetrical attendant. Thus, obstetricians should be well versed in measures for immediate care of the newborn.

The number and qualifications of personnel who attend the delivery will vary depending on the anticipated risk, the number of babies, and the hospital setting. A qualified team with full resuscitation skills should be present for high-risk deliveries and immediately available for every resuscitation (Wyckoff, 2015). This team should not be on call at home or in a remote area of the hospital. Moreover, team training through frequent simulation practice is recommended for all who may be called to attend deliveries (Perlman, 2015).

TRANSITION TO AIR BREATHING

Immediately following birth, the newborn must promptly convert from placental to pulmonary gas exchange. Pulmonary vascular resistance must fall, pulmonary perfusion must rapidly rise, and unique fetal vascular shunts must begin to close to separate the systemic and pulmonary circulations (Rudolph, 1979). These shunts include the patent ductus arteriosus and patent foramen ovale, described in Chapter 7 (Cardiovascular System). Lung aeration is not only critical for pulmonary gas exchange. Recent studies suggest that it is significantly responsible for initiating cardiovascular changes at birth (Hooper, 2016).

In utero, the fetal lungs are filled with amnionic fluid, which must be cleared quickly for air breathing. This clearance occurs through various means, and the contributions of these mechanisms may depend on gestational age and mode of delivery. First, a large release of fetal adrenaline late in labor stimulates pulmonary epithelial cells to stop secreting and instead to start reabsorbing lung liquid as a result of sodium-channel activation (te Pas, 2008). The contribution of this mechanism is unlikely to be major, as blockade of the receptors for sodium channel activation reduces or delays but does not prevent lung liquid clearance at birth (O'Brodovich, 1990).

As a second method, mechanical forces aid lung fluid clearance during labor. Early reports described compression of the fetal thorax and abdomen as they passed through the birth canal leading to lung liquid expulsion (Karlberg, 1962; Saunders, 1978). By this mechanism, up to a third of lung liquid is expelled in a jet of fluid from the nose and mouth once the respiratory tract is exposed to the lower outside pressure. However, it may be that uterine contractions force a change in fetal posture leading to compression of the thorax and increased intrathoracic pressures. This prompts expulsion of lung liquid early in labor more so than the "vaginal squeeze" theory (Lines, 1997; te Pas, 2008; Vyas, 1981).

In a third mechanism, a significant amount of lung liquid is cleared after birth (Hooper, 2016). In animal studies, most lung aeration occurs during inspiration—within three to five breaths after birth. But, no liquid clears between breaths (Hooper, 2007). Specifically, the transpulmonary pressure gradient during inspiration promotes movement of fluid into the interstitial tissue. From here, it is gradually cleared, probably by the pulmonary circulation and lymphatic vessls. It is possible for lung interstitial tissue pressure to rise to a point that fluid can actually move back into the airspaces during expiration unless positive end-expiratory pressure opposes liquid reentry (Siew, 2009a,b). This may be a contributing factor in the development of *transient tachypnea of the newborn*.

As fluid is replaced by air, compression of the pulmonary vasculature is reduced considerably, and in turn, resistance to blood flow is lowered. With the fall in pulmonary arterial blood pressure, the ductus arteriosus normally closes.

High, negative intrathoracic pressures are required to permit the initial entry of air into the fluid-filled alveoli. Normally, from the first breath after birth, progressively more residual air accumulates in the lung. And, with each successive breath, lower pulmonary opening pressure is required. In the normal mature newborn, by approximately the fifth breath, pressure-volume changes achieved with each respiration are very similar to those of the adult. Thus, the breathing pattern shifts from shallow episodic inspirations characteristic of the fetus to regular, deeper inhalations (Chap. 17, Fetal Breathing).

As a last mechanism, surfactant, which is synthesized by the type II pneumocytes, lowers alveolar surface tension and helps maintain lung inflation by preventing alveolar collapse. Insufficient surfactant, which is common in preterm neonates, leads promptly to respiratory distress syndrome (Chap. 34, Respiratory Distress Syndrome).

In utero, umbilical venous return is the main source of preload for the left ventricle, particularly as fetal pulmonary blood flow is very low due to high pulmonary vascular resistance and is unable to provide sufficient venous return to maintain left ventricular output (Hooper, 2015).

Clamping the umbilical cord reduces preload for the left ventricle and thus reduces cardiac output. Until the lungs aerate and pulmonary blood flow increases, the reduced cardiac output will manifest as bradycardia. If cord clamping is delayed until after the lungs have aerated, the transition is smoother and cardiac ouput does not fall (Bhatt, 2013). This understanding has led to interest in delayed (physiological) cord clamping, especially if it can be done after successful inflation of the lung. Randomized trials are currently underway.

CARE IN THE DELIVERY ROOM

The International Liaison Committee on Resuscitation (ILCOR) updated its scientific review for neonatal delivery room care and resuscitation (Perlman, 2015). The ILCOR scientific review is used by the American Academy of Pediatrics and the American Heart Association to develop the neonatal resuscitation guidelines for North America (Wyckoff, 2015).

Immediate Care

Before and during delivery, careful consideration must be given to several determinants of neonatal well-being. These include: (1) maternal health status; (2) prenatal complications, including any suspected fetal malformations; (3) gestational age; (4) labor complications; (5) duration of labor and ruptured membranes; (6) type and duration of anesthesia; (7) difficulty of delivery; and (8) medications given during labor and their dosages, administration routes, and timing.

When risk factors are present, neonatal resuscitation providers should be present for the delivery. This team readies equipment, ensures that adequate personnel are present, delegates roles and responsibilities, and considers contingency plans to stabilize the newborn. Four questions a neonatal provider will ask pertain to expected gestional age, amnionic fluid color, fetal number, and additional fetal risks. Several conditions are associated with a nonvigorous presentation. These may include immaturity, hypoxemia or acidosis from any cause, sepsis syndrome, recent drugs administered to the mother, and central nervous system developmental abnormalities. Those related to the respiratory tract are lung abnormalities, upper airway obstruction, pneumothorax, and meconium aspiration.

Umbilical Cord Clamping

Ideally, obstetrical and pediatric teams discuss plans regarding umbilical cord management. Delayed cord clamping provides transfusion of placental blood to the newborn. In term infants, delay of cord clamping by 30 to 60 seconds raises hemoglobin levels at birth, improves iron stores during infancy, and enhances neurodevelopment at 4 years of age (Katheria, 2017). As discussed in Chapter 33 (Neonatal Abstinence Syndrome), the only reported negative outcome of delayed cord clamping is hyperbilirubinemia, leading to a higher rate of phototherapy (American College of Obstetricians and Gynecologists, 2017a). In preterm neonates, delayed cord clamping reduces rates of blood transfusion, intraventricular hemorrhage, and necrotizing enterocolitis.

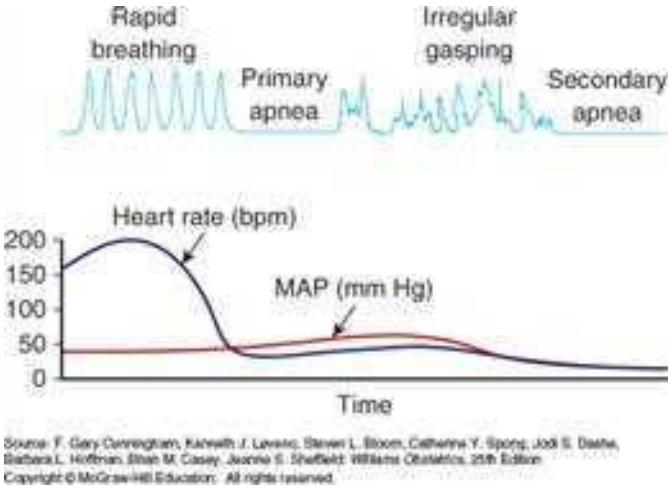
Delayed cord clamping should be performed in preterm and term newborns who do not require resuscitation at birth (American Academy of Pediatrics, 2017a; American College of Obstetricians and Gynecologists, 2017a; Perlman, 2015). There should be no delay if a newborn requires resuscitation or if the placental circulation is disrupted by abruption, cord avulsion, or bleeding placenta previa or vasa previa.

Newborn Resuscitation

Approximately 10 percent of newborns require some degree of active resuscitation to stimulate breathing, and 1 percent need extensive care. Perhaps not coincidentally, the risk of death for newborns delivered at home compared with those delivered in hospitals is increased two- to threefold (American College of Obstetricians and Gynecologists, 2017d).

When deprived of adequate gas exchange, either before or after birth, neonates demonstrate a well-defined sequence of events leading to apnea (Fig. 32-1). With oxygen deprivation and carbon dioxide (CO_2) elevation, there is a transient period of rapid breathing, and if it persists, breathing stops, which is termed *primary apnea.* This stage is accompanied by a fall in heart rate and loss of neuromuscular tone. Simple stimulation will usually reverse primary apnea. If oxygen deprivation and asphyxia persist, however, the newborn will develop deep gasping respirations, followed by *secondary apnea.* This latter stage is associated with a further decline in heart rate, fall in blood pressure, and loss of neuromuscular tone. Neonates in secondary apnea will not respond to stimulation and will not spontaneously resume respiratory efforts. Unless ventilation is assisted, death follows.

FIGURE 32-1
Physiological changes associated with primary and secondary apnea in the newborn. bpm = beats per minute; HR = heart rate; MAP = mean arterial pressure. (Adapted with permission from Kattwinkel J: Textbook of Neonatal Resuscitation, 6th ed. Elk Grove Village, American Academy of Pediatrics and American Heart Association, 2010.)



Clinically, primary and secondary apneas are indistinguishable, and thus, secondary apnea must be assumed. And, when a response to stimulation is not immediate, resuscitation with effective ventilation of the apneic newborn must be started quickly.

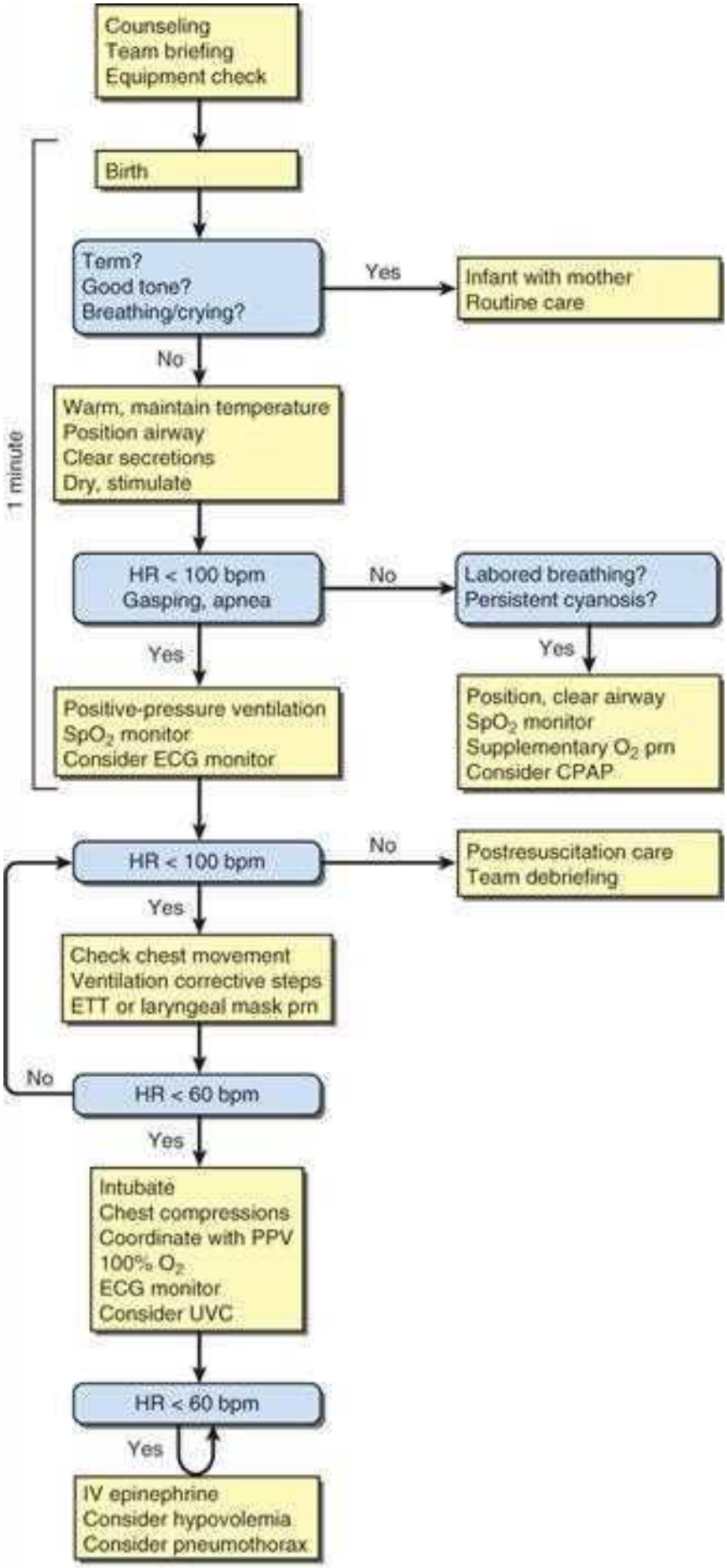
Resuscitation Protocol

Initial Assessment

Immediately after birth and usually during the delay for umbilical cord clamping, newborn tone, respiratory effort, and heart rate are evaluated (Fig. 32-2). Most term neonates are vigorous by 10 to 30 seconds after birth (Ersdal, 2012). For these, initial steps of warming the newborn can be done on the mother's chest or abdomen. Direct skin-to-skin contact with the mother and drying and covering the newborn with a warm blanket will help maintain euthermia (36.5 to 37.5°C). A vigorously crying newborn does not require routine oral suctioning (Carrasco, 1997; Gungor, 2006). Instead, bulb suctioning to remove secretions is best reserved for those who cannot clear secretions on their own due to apnea or copious secretions. Additional routine care steps include drying, gentle stimulation by rubbing the newborn's back, and continued observation during the transition period.

FIGURE 32-2

Algorithm for resuscitation of the newborn based on the International Liaison Committee on Resuscitation scientific review and recommended by the American Academy of Pediatrics and American Heart Association (Perlman, 2015; Wyckoff, 2015). bpm = beats per minute; CPAP = continuous positive airway pressure; ECG = electrocardiogram; ETT = endotracheal tube; HR = heart rate; IV = intravenous; PPV = positive-pressure ventilation; SpO_2= peripheral oxygen saturation; UVC = umbilical venous catheter.

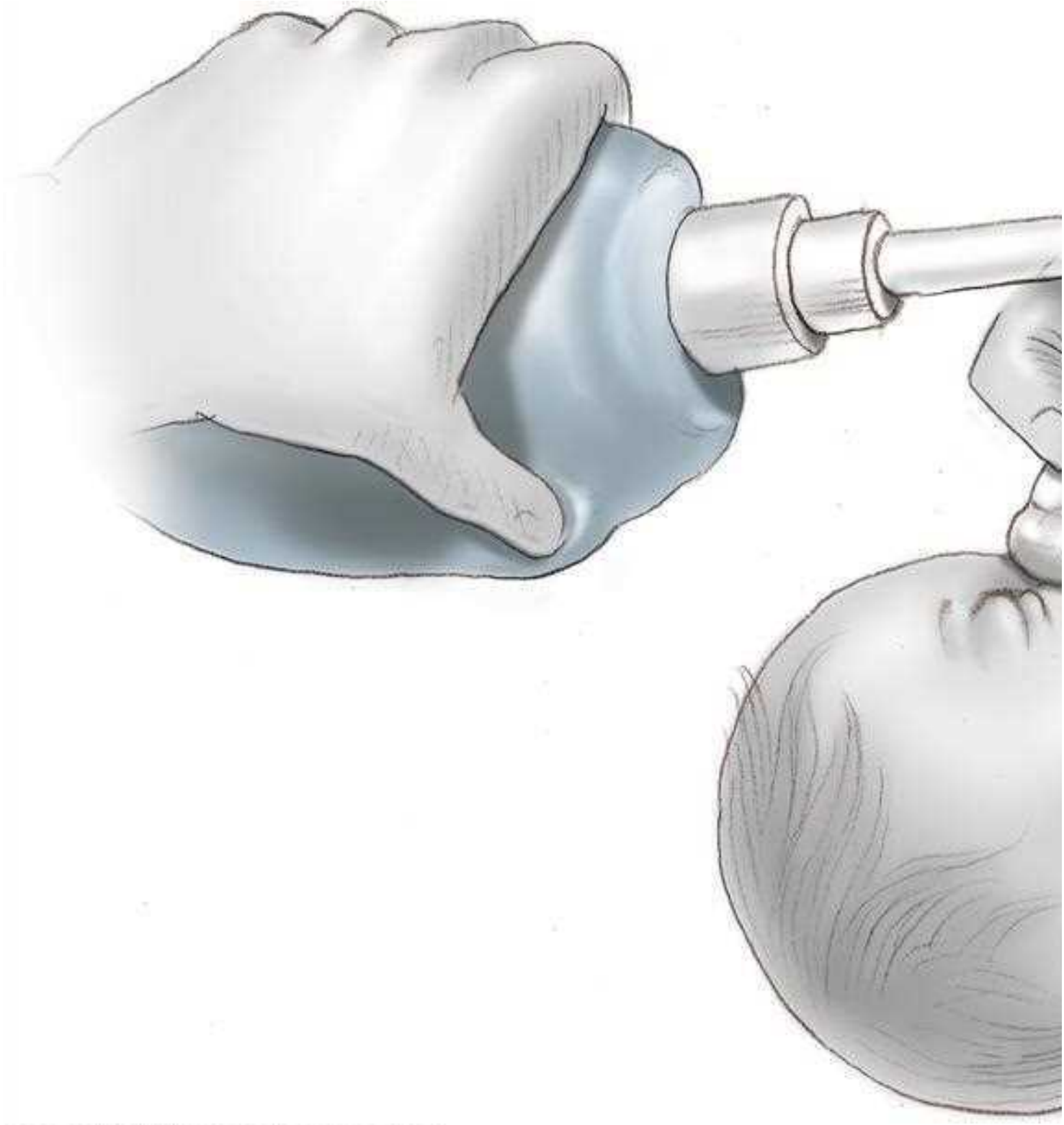


If not vigorous or if preterm, the neonate is carried to a prewarmed radiant warmer for the initial newborn care steps. The initial wet birth blanket is removed to allow newborn drying. Cold stress is associated with multiple neonatal morbidities and mortality. Preterm infants are particularly vulnerable, and special steps to maintain euthermia include providing a warmer delivery room (>25°C), covering the neonatal head with either a plastic or wool hat, application of polyethylene plastic "ponchos" or wraps to slow evaporative heat losses, use of chemically activated thermal mattresses to reduce conductive heat loss, and administration of warm, humidified respiratory gases during respiratory stabilization (Perlman, 2015).

At the radiant warmer, newborns must be positioned to maximally open the airway, with mild extension of the neck. If the newborn is apneic or has copious secretions that it cannot clear, a bulb syringe or suction catheter may be used to clear the mouth and then the nose. Routine intubation and suctioning of meconium-stained amnionic fluid is no longer recommended for the nonvigorous newborn (American College of Obstetricians and Gynecologists, 2017b; Perlman, 2015). Intubation and suction are reserved for suspected airway obstruction.

After completion of the initial stabilization steps, apnea, gasping respirations, or heart rate ≤100 beats per minute (bpm) should prompt immediate administration of positive-pressure ventilation with room air (Fig. 32-3). This should be started by 60 seconds of life, if not sooner, once the initial steps are completed.

FIGURE 32-3
Correct use of bag-and-mask ventilation. The head should be in a sniffing position with the tip of the nose pointing to the ceiling. The neck should not be hyperextended.



Mask Ventilation

Assisted ventilation by facemask at a rate of 40 to 60 breaths per minute is recommended. Oxygen saturation is monitored by pulse oximetry. Supplemental oxygen can be given in graduated, rising percentages to maintain oxygen saturation values within a normal range per minute of life. Adequate ventilation is best indicated by an improved heart rate. Colorimetric end-tidal carbon dioxide ($ETCO_2$) monitoring placed between the positive-pressure device and facemask serves as a helpful adjunct for detection of successful gas exchange during mask ventilation (Weiner, 2016).

If the heart rate remains ≤100 bpm after 5 to 10 positive pressure breaths, the attempted ventilation is inadequate and corrective steps must be taken. These can be remembered by the pneumonic MR. SOPA (Table 32-1). The two most common problems are mask leak due to an ineffective seal and malposition of the airway (Schmolzer, 2011). If corrective steps do not improve the heart rate, either intubation with an endotracheal tube or placement of a laryngeal mask airway is required.

TABLE 32-1

Ventilation Corrective Steps (MR. SOPA)

M—Mask adjustment	Check the seal of the mask and reapply if needed.
R—Reposition airway	Make sure the newborn is truly in the open airway (mild extension) position.
S—Suction mouth and nose	Remove obstructing secretions.
O—Open the mouth	In an effort to achieve a good seal, providers sometimes accidentally close the mouth. The higher resistance of the narrow-diameter nasal passages will limit effective ventilation.
P—Pressure increase	Try increasing the inflation pressure.
A—Advanced airway	If all prior steps fail to achieve chest rise, intubate or place a laryngeal mask.

Data from Weiner, 2016.

Alternative Airway

If mask ventilation is ineffective or prolonged, an alternative airway is placed. For tracheal intubation, a laryngoscope with a straight blade—size 0 for a preterm newborn and size 1 for a term neonate—is used. Gentle cricoid pressure may be useful. An increasing heart rate and $ETCO_2$ detection after several breaths are the primary methods of confirming intubation of the trachea and not the esophagus. One can also look for symmetrical chest wall motion; auscultate for equal breath sounds, especially in the axillae; and auscultate for the absence of breath sounds or gurgling over the stomach.

Once in place, the tube is used for tracheal suctioning only for a suspected obstructed airway. Otherwise, an appropriate positive-pressure device is attached to the endotracheal tube. Air puffs are delivered at a rate of 40 to 60 per minute with a force adequate to stabilize the heart rate. In term infants, opening pressures of 30 to 40 cm H_2O typically will expand the alveoli without causing barotrauma. Once the lung is inflated, less pressure is typically needed (20 to 25 cm H_2O). For preterm infants, pressures of 20 to 25 cm H_2O are typically used. An increase in heart rate and peripheral oxygen saturation (SpO_2) levels within acceptable ranges reflect a positive response.

Chest Compressions

Most commonly, effective ventilation is all that is required to stabilize the newborn in the delivery room. If the heart rate remains <60 bpm despite ventilation corrective steps, including placement of tracheal tube, chest compressions are initiated. Once the tracheal tube has been secured, compressions are done from the head of the bed rather than the side so that space is opened up for a provider to have umbilical venous access. When compressions are initiated, the oxygen concentration is increased to 100 percent. With the two-thumb compression method, hands encircle the chest, while the thumbs depress the sternum. Compressions are delivered on the lower third of the sternum at a depth sufficient to generate a palpable pulse. This is typically one third of the anterior-posterior diameter of the chest. Compared with other techniques, this method offers less provider fatigue over time, yields higher generated perfusion pressures, and lessens hand malpositioning that could cause traumatic injury (Kapadia, 2012).

A 3:1 compressions-to-ventilation ratio is recommended, and 90 compressions and 30 breaths achieve approximately 120 events each minute. Coordinated chest compressions and ventilations should continue until the spontaneous heart rate is ≥60 bpm.

Epinephrine

Intravenously administered epinephrine is indicated if the heart rate remains ≤60 bpm after adequate ventilation and chest compressions. The recommended intravenous dose is 0.01 to 0.03 mg/kg. Epinephrine may be given through the endotracheal tube if venous access has not been established, but its action is less reliable (Kapadia, 2017). If given through the endotracheal tube, higher doses are employed—0.05 to 0.1 mg/kg.

Discontinuation of Resuscitation

ILCOR concludes that it is reasonable to discontinue resuscitative efforts for a neonate who remains without a heartbeat despite at least 10 minutes of continuous and adequate resuscitative efforts. Notably, the decision to continue or discontinue resuscitative efforts must be individualized (Perlman, 2015).

EVALUATION OF NEWBORN CONDITION

Apgar Score

The scoring system described by Dr. Virginia Apgar in 1953 remains a useful clinical tool to classify newborn health immediately after birth and to assess the effectiveness of resuscitative measures (American Academy of Pediatrics, 2017). As shown in Table 32-2, each of five easily identifiable characteristics—heart rate, respiratory effort, muscle tone, reflex irritability, and color—is assessed and assigned a value of 0, 1, or 2. In the currently recommended expanded form, concurrent resuscitation interventions are also recorded over time. The total score, based on the sum of the five components, is determined in all neonates at 1 and 5 minutes after delivery. In those with a score <7, the score may be calculated at further 5-minute intervals until a 20-minute Apgar score is assigned or resuscitation efforts are halted.

TABLE 32-2

20-Minute Expanded Apgar Score

Sign	0 point	1 point	2 point	1 min	5 min	10 min	15 min	20 min
Color	Blue or pale	Acrocyanotic	Completely pink					
Heart rate	Absent	<100/min	>100/min					
Reflex irritability	No response	Grimace	Cry or active withdrawal					
Muscle tone	Limp	Some flexion	Active motion					
Respiration	Absent	Weak cry; hypo- ventilation	Good, crying					
			Total					
Comments:			**Resuscitation**					
			Minutes	1	5	10	15	20
			Oxygen					
			PPV/CPAP					
			ETT					
			Chest compressions					
			Epinephrine					

CPAP = continuous positive airway pressure; ETT = endotracheal tube; PPV = positive-pressure ventilation.

Data from Weiner, 2016.

In an analysis of more than 150,000 newborns delivered at Parkland Hospital, Casey and associates (2001b) assessed the significance of the 5-minute score for predicting survival during the first 28 days of life. They found that in term neonates, the risk of neonatal death was approximately 1 in 5000 for those with Apgar scores of 7 to 10. This risk compares with a mortality rate of 25 percent for term newborns with 5-minute scores ≤3. Low 5-minute scores were comparably predictive of neonatal death in preterm neonates. These investigators concluded that the Apgar scoring system remains relevant for the prediction of neonatal survival.

There have been attempts to use Apgar scores to define asphyxial injury and to predict subsequent neurological outcome—uses for which the Apgar score was never intended (Chap. 33, Neuroimaging Studies in Encephalopathy and Cerebral Palsy). Such associations are difficult to measure with reliability given that both asphyxial injury and low Apgar scores are infrequent outcomes. For example, according to United States birth certificate records for 2010, only 1.8 percent of newborns had a 5-minute score below 7 (Martin, 2012). Similarly, in a population-based study of more than 1 million term newborns in Sweden between 1988 and 1997, the incidence of 5-minute Apgar scores of ≤3 approximated 2 per 1000 (Thorngren-Jerneck, 2001).

Previously, many groups established erroneous definitions of asphyxia based solely on low Apgar scores. These prompted the American College of Obstetricians and Gynecologists and American Academy of Pediatrics (2017f) to issue a series of joint opinions with important caveats regarding Apgar score limitations. Certain elements of the Apgar score are partially dependent on the physiological maturity of the newborn, and a healthy, preterm neonate may receive a low score only because of immaturity. Other influencing factors include fetal malformations, maternal medications, and infection. Therefore, it is inappropriate to use an Apgar score alone to diagnose asphyxia. Moreover, the Apgar score alone cannot establish hypoxia as the cause of cerebral palsy, as discussed in Chapter 33 (Neuroimaging Studies in Encephalopathy and Cerebral Palsy).

Umbilical Cord Blood Acid–Base Studies

Blood taken from umbilical vessels may be used for acid–base studies to assess the metabolic status of the neonate. Blood collection is performed following delivery by immediately isolating a 10- to 20-cm segment of cord with two clamps placed near the neonate and another two clamps positioned nearer the placenta. The cord is then cut between the two proximal clamps and then the two distal clamps (Blickstein, 2007).

Arterial blood is drawn from the isolated cord segment into a 1- to 2-mL commercially prepared plastic syringe containing lyophilized heparin or a similar syringe that has been flushed with a heparin solution containing 1000 U/mL. Once sampling is completed, the needle is capped and the syringe transported, on ice, to the laboratory. Although efforts should be made for prompt transport, neither the pH nor partial pressure of CO_2 (pCO_2) values change significantly in blood kept at room temperature for up to 60 minutes (Lynn, 2007). Mathematical models have been developed that allow reasonable prediction of birth acid–base status in

properly collected cord blood samples analyzed as late as 60 hours after delivery (Chauhan, 1994). Acid–base measurements can show significant variances between different analyzing devices (Mokarami, 2012).

Fetal Acid–Base Physiology

The fetus produces both carbonic and organic acids. Carbonic acid (H_2CO_3) is formed by oxidative metabolism of CO_2. The fetus usually rapidly clears CO_2 through the placental circulation. If CO_2 clearance is lowered, then carbonic acid levels rise. This often follows impaired placental exchange. When H_2CO_3 accumulates in fetal blood and organic acids do not concurrently rise, the result is *respiratory acidemia*.

In contrast, organic acids primarily include lactic and β-hydroxybutyric acids. Levels of these increase with persistent placental exchange impairment, and they result from anaerobic glycolysis. These organic acids are cleared slowly from fetal blood. When they accumulate, without a concurrent increase in H_2CO_3, the result is *metabolic acidemia*. With the development of metabolic acidemia, bicarbonate (HCO_3^-) levels drop because it is used to buffer the organic acid. A rise in H_2CO_3 concentrations accompanied by greater organic acid levels, reflected by decreased HCO_3^- levels, causes *mixed respiratory-metabolic acidemia*.

In the fetus, respiratory and metabolic acidemia and ultimately tissue acidosis are most likely part of a progressively worsening continuum. This is different from adult pathophysiology, in which distinct conditions result either in respiratory acidosis—for example, pulmonary disease, or in metabolic acidosis—for example, diabetes. In the fetus, the placenta serves as both the lungs and, to a certain degree, the kidneys. One principal cause of fetal acidemia is a drop in uteroplacental perfusion. This creates retention of CO_2, that is, respiratory acidemia, and if protracted and severe enough, yields a mixed or metabolic acidemia.

Assuming that maternal pH and blood gases are normal, the actual pH of fetal blood is dependent on the proportion of carbonic and organic acids and the amount of bicarbonate, which is the major buffer in blood. This can best be illustrated by the Henderson–Hasselbalch equation:

$$pH = pK + \log \frac{[base]}{[acid]} \text{ or, } pH = pK + \log \frac{HCO_3^-}{H_2CO_3}$$

For clinical purposes, HCO_3^- represents the metabolic component and is reported in mEq/L. The H_2CO_3 concentration reflects the respiratory component and is reported as the pCO_2 in mm Hg. Thus:

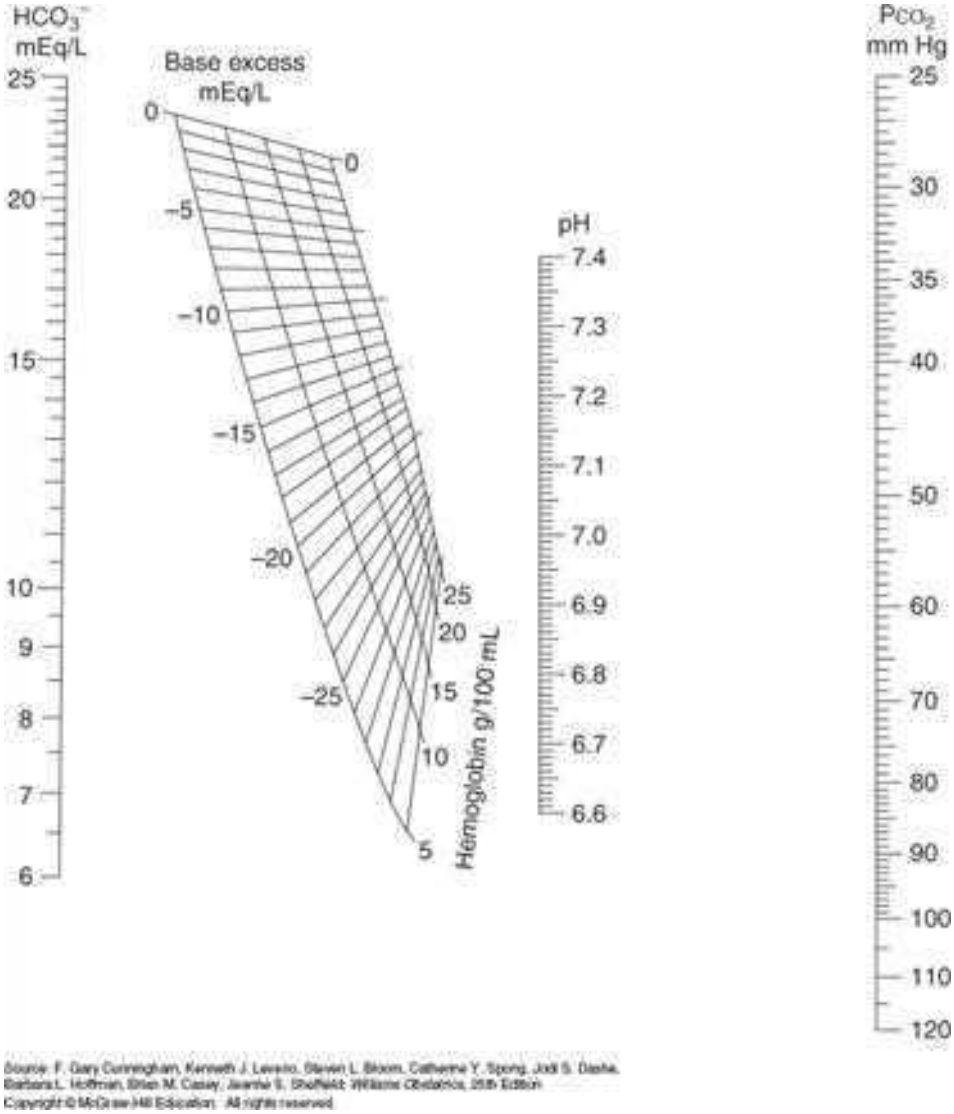
$$pH = pK + \log \frac{\text{metabolic } (HCO_3^- \text{ mEq/L})}{\text{respiratory } (Pco_2 \text{ mm Hg})}$$

The result of this equation is a pH value. Because pH is a logarithmic term, it does not give a linear measure of acid accumulation. For example, a change in hydrogen ion concentration associated with a fall in pH from 7.0 to 6.9 is almost twice that which is associated with a fall in pH from 7.3 to 7.2. For this reason, the change in base—termed delta base— offers a more linear measure of the degree of accumulation of metabolic acid (Armstrong, 2007). The delta base is a calculated number used as a measure of the change in buffering capacity of bicarbonate (HCO_3^-). The formula for calculating the base excess (BE) is as follows:

$$BE = 0.02786 \times pCO_2 \times 10^{(pH-6.1)} \times 13.77 \times pH - 124.58$$

Shown in Figure 32-4 is a nomogram developed from which these can be calculated if only two parameters are known. For example, the HCO_3^- concentration declines with a metabolic acidemia as it is consumed to maintain a normal pH. A base deficit develops when the HCO_3^- concentration drops below normal levels, and a base excess occurs when HCO_3^- values are above normal. Importantly, a mixed respiratory–metabolic acidemia with a large base deficit and a low HCO_3^-, for example 12 mmol/L, is more often associated with a depressed neonate than is a mixed acidemia with a minimal base deficit and a more nearly normal HCO_3^- level.

FIGURE 32-4
Nomogram for determining the delta base. (Adapted with permission from Siggaard- Anderson O: Blood acid–base alignment nomogram, Scand J Clin Lab Invest. 1963;15:211–7.)



Clinical Significance of Acidemia

Fetal oxygenation and pH generally decline during the course of normal labor. Normal umbilical cord blood pH and blood gas values at delivery in term newborns are summarized in Table 32-3. Similar values have been reported for preterm neonates (Dickinson, 1992; Ramin, 1989; Riley, 1993). The lower limits of normal pH in the newborn have been found to range from 7.04 to 7.10 (Thorp, 1996). Thus, these values should be considered to define neonatal acidemia. Even so, most fetuses will tolerate intrapartum acidemia with a pH as low as 7.00 without incurring neurological impairment (Freeman, 1988; Gilstrap, 1989). That said, in a study of newborns with a pH <7.0 from Parkland Hospital, there were inordinate proportions of neonatal deaths—8 percent, intensive care admissions—39 percent, intubations—14 percent, and seizures—13 percent (Goldaber, 1991). And, in a study from Oxford of more than 51,000 term newborns, the incidence of neonatal encephalopathy in those with a birth pH <7.0 was 3 percent (Yeh, 2012). Even those with who had normal 5-minute Apgar scores but an arterial cord pH values <7.0 had a significantly higher risk of morbidity that included respiratory distress, neonatal intensive care unit admission, and sepsis (Sabol, 2016). The speed of acidemia resolution after birth is associated with outcome (Casey, 2001a).

TABLE 32-3

Umbilical Cord Blood pH and Blood Gas Values in Normal Term Newborns

Values	Ramin, 1989[a] Spontaneous Delivery n = 1292[c]	Riley, 1993[b] Spontaneous Delivery n = 3522[c]	Kotaska, 2010[b] Spontaneous Delivery n = 303[d]	Kotaska, 2010[e] Cesarean Delivery n = 189[d]
Arterial Blood				
pH	7.28 (0.07)	7.27 (0.069)	7.26 (7.01–7.39)	7.3 (7.05–7.39)
P_{CO_2} (mm Hg)	49.9 (14.2)	50.3 (11.1)	51 (30.9–85.8)	54 (37.5–79.5)
HCO_3^- (mEq/L)	23.1 (2.8)	22.0 (3.6)	—	—
Base excess (mEq/L)	−3.6 (2.8)	−2.7 (2.8)	—	—
Venous Blood				
pH	—	7.34 (0.063)	7.31 (7.06–7.44)	7.34 (7.10–7.42)
P_{CO_2} (mm Hg)	—	40.7 (7.9)	41 (24.9–70.9)	44 (29.1–70.2)
HCO_3^- (mEq/L)	—	21.4 (2.5)	—	—
Base excess (mEq/L)	—	−2.4 (2)	—	—

[a]Newborns of selected women with uncomplicated vaginal deliveries.

[b]Newborns of unselected women with vaginal deliveries.

[c]Data shown as mean (SD).

[d]Data shown as range with 2.5 or 97.5 percentile.

[e]Cesarean delivery—labor not stated.

From Centers for Disease Control and Prevention, 2012; Watson, 2006.

Respiratory Acidemia

Acute interruption in placental gas exchange is accompanied by subsequent CO_2 retention and respiratory acidemia. The most common antecedent factor is transient umbilical cord compression. Generally, respiratory acidemia is not harmful to the fetus (Low, 1994).

The degree to which pH is affected by pCO_2—the respiratory component of the acidosis—can be calculated. First, the upper normal neonatal pCO_2 of about 50 mm Hg is subtracted from the cord blood gas pCO_2 value. Each additional 10 mm Hg pCO_2 increment will lower the pH by 0.08 units (Eisenberg, 1987). Thus, in a mixed respiratory–metabolic acidemia, the benign respiratory component can be calculated. As an example, acute cord prolapse during labor prompts cesarean delivery of a neonate 20 minutes later. The umbilical artery blood gas pH was 6.95 and the pCO_2 was 90 mm Hg. The degree to which the cord compression and subsequent impairment of CO_2 exchange affected the pH is calculated using the relationship given earlier and shown below.

$$90 \text{ mm Hg} - 50 \text{ mm Hg} = 40 \text{ mm Hg excess } CO_2$$

$$\text{To correct pH: } (40 \div 10) \times 0.08 = 0.32;\ 6.95 + 0.32 = 7.27$$

Therefore, the pH before cord prolapse was approximately 7.27, well within normal limits. Thus, the low pH resulted from respiratory acidosis.

Metabolic Acidemia

The fetus begins to develop metabolic acidemia when oxygen deprivation is sufficiently long and severe to require anaerobic metabolism for cellular energy needs. Low and associates (1997) defined fetal acidosis as a base deficit ≥12 mmol/L, and severe fetal acidosis as a base deficit ≥16 mmol/L. In the Parkland study of more than 150,000 newborns cited earlier, metabolic acidemia was defined using umbilical cord blood gas thresholds that were two standard deviations below the mean (Casey, 2001b). Thus, metabolic acidemia was an umbilical artery blood pH <7.00 accompanied by a pCO_2 ≤76.3 mm Hg, with higher values indicating a respiratory

component; HCO_3^- concentration ≤17.7 mmol/L; and base deficit ≥10.3 mEq/L. From the standpoint of *possible* neurological injury, the American College of Obstetricians and Gynecologists (2014) defines metabolic acidosis as umbilical arterial pH <7.0 and a base deficit ≥12 mmol/L.

Metabolic acidemia is associated with a high rate of multiorgan dysfunction. In rare cases, such hypoxia-induced metabolic acidemia may be so severe that it causes subsequent neurological impairment—*hypoxic-ischemic encephalopathy* (Chap. 33, Neonatal Encephalopathy). In fact, a fetus without such acidemia cannot by definition have suffered recent hypoxic-induced injury. That said, severe metabolic acidosis is poorly predictive of subsequent neurological impairment in the term neonate (King, 1998; Socol, 1994). In very-low-birthweight neonates, that is, those <1000 g, newborn acid–base status may be more closely linked to intraventricular hemorrhage and possibly long-term neurological outcome (Lavrijsen, 2005; Salhab, 2005; Victory, 2003).

Casey and coworkers (2001b) described the association between metabolic acidemia, low Apgar scores, and neonatal death in term and preterm newborns. Regarding term neonates, the risk of neonatal death was more than 3200-fold greater in term neonates with metabolic acidemia and 5-minute scores ≤3 compared with those with a 5-minute Apgar score ≥7.

Recommendations for Cord Blood Gas Determinations

In some centers, cord gas analysis is performed in all neonates at birth (Casey, 2001b; Sabol, 2016). Cost-effectiveness analysis for universal cord blood gas measurements suggest benefit and potential cost savings (White, 2010, 2016). It seems reasonable to obtain cord blood gas determinations for intrapartum cases of cesarean delivery for fetal compromise, abnormal fetal heart rate tracing, fever, and low 5-minute Apgar score. Multifetal gestation and severely growth-restricted fetuses are others.

Although umbilical cord acid–base blood determinations are poorly predictive of either immediate or long-term adverse neurological outcome, they provide the most objective evidence of the fetal metabolic status at birth.

PREVENTIVE CARE

Eye Infection Prophylaxis

Ophthalmia neonatorum is mucopurulent conjunctivitis of newborns. Some form of conjunctivitis affects 1 to 12 percent of all neonates, and gonococcal and chlamydial infections are among the most common (Zuppa, 2011).

Neisseria gonorrhoeae infection acquired at birth was a common cause of childhood blindness in the past. However, the practice of instilling a 1-percent ophthalmic solution of silver nitrate largely eliminated this. Various other antimicrobial agents have also proven effective, and gonococcal prophylaxis is now mandatory for all neonates in most states (American Academy of Pediatrics, 2017b). For *prophylaxis* soon after delivery, recommendations include a single application of either 1-percent silver nitrate solution or 0.5-percent erythromycin ointment. In North America, a previously used 1-percent tetracycline ophthalmic ointment is no longer available (Mabry-Hernandez, 2010; Moore, 2015).

For a neonate born to a mother with untreated gonorrhea, *treatment* of presumptive neonatal gonococcal conjunctivitis is a single ceftriaxone dose, 100 mg/kg, given either intramuscularly or intravenously. Before treatment, testing for both gonococcal and chlamydia infections should be obtained.

With *chlamydial conjunctivitis,* adequate neonatal prophylaxis is complex. Ideally, prenatal screening and treatment for *Chlamydia trachomatis* obviates conjunctival infection (Hammerschlag, 2011). In neonates delivered vaginally of mothers with an active chlamydial infection, 12 to 25 percent will develop conjunctivitis up to 20 weeks after birth (Teoh, 2003). *Prophylactic topical eye treatments do not reliably reduce the incidence of chlamydial conjunctivitis.* In a study from Kenya, 2.5-percent povidone-iodine solution was reported to be superior to either 1-percent silver nitrate solution or 0.5-percent erythromycin ointment in preventing chlamydial conjunctivitis (Isenberg, 1995). In another study from Iran, povidone-iodine eye drops were twice as effective in preventing clinical conjunctivitis as erythromycin drops—9 versus 18 percent failure rate, respectively (Ali, 2007).

Conjunctivitis in a newborn up to age 3 months should prompt consideration for chlamydial infection (Moore, 2015). Treatment for pediatric chlamydial infection is with oral azithromycin for 5 days or oral erythromycin for 14 days.

Hepatitis B Immunization

Routine immunization with thimerosal-free vaccine against hepatitis B before hospital discharge is standard practice for all medically stable newborns with birthweights greater than 2000 g (American Academy of Pediatrics, 2017b). If the mother is seropositive for hepatitis B surface antigen, then the neonate is also passively immunized with hepatitis B immune globulin. As discussed in Chapter 55 (Pregnancy and Hepatitis B), some advocate treatment of high-risk or even all seropositive women with antiviral nucleoside or nucleotide analogues during pregnancy to minimize fetal transmission (Dusheiko, 2012; Tran, 2012).

Zika Virus

This virus is primarily spread by mosquito bites. Infection is asymptomatic in most people but can cause severe birth defects (Chap. 64, Coronavirus Infections). Screening begins with an interrogation for recent travel to endemic areas. For women at risk, serological screening is then completed. All newborns of mothers who have laboratory evidence of Zika virus infection during pregnancy should receive a comprehensive examination, a neurological assessment, postnatal head ultrasound, standard newborn hearing screen before hospital discharge, and Zika virus laboratory testing (Reynolds, 2017).

Vitamin K

Supplemental vitamin K injection will prevent vitamin K-dependent hemorrhagic disease of the newborn (Chap. 33, Polycythemia and Hyperviscosity). A single intramuscular dose of vitamin K, 0.5 to 1 mg, is given within 1 hour of birth (American Academy of Pediatrics, 2017b).

Newborn Screening

Numerous mass-screening tests are now available for 29 newborn conditions. Shown in Table 32-4, many are mandated by various state laws (American College of Obstetricians and Gynecologists, 2017c). Most states require that all tests in the core panel be performed. Supplemental conditions—*secondary targets*—are also listed on the Maternal and Child Health Bureau website. Some states require some of these in addition to their mandated core panel. Each practitioner should be familiar with their individual state requirements, which are available at http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm.

TABLE 32-4

Newborn Screening Core Panel

Acylcarnitine Disorders[a]				
Organic Acid Metabolism	**Fatty Acid Metabolism**	**Amino Acid Metabolism**[a]	**Hemoglobin Disorders**	**Others**
Isovaleric Glutaric type I 3-Hydroxy-3-methylglutaric Multiple carboxylase Methylmalonic mutase 3-Methylcrotonyl-CoA carboxylase Methylmalonic acid (cobalamin A, B) Propionic β-Ketothiolase	Medium-chain acyl-CoA dehydrogenase Very long-chain acyl-CoA dehydrogenase Long-chain 3-OH acyl-CoA dehydrogenase Trifunctional protein Carnitine uptake	Phenylketonuria Maple syrup (urine) Homocystinuria Citrullinemia Arginosuccinic Tyrosinemia I	SS disease S-β-thalassemia SC disease	Congenital hypothyroidism Biotinidase Congenital adrenal hyperplasia Galactosemia Hearing loss Cystic fibrosis Critical congenital heart disease[b] Severe combined immunodeficiency[b]

[a]Determined by tandem mass spectrometry.

[b]Added after 2006.

From Centers for Disease Control and Prevention, 2012; Watson, 2006.

ROUTINE NEWBORN CARE

Gestational-Age Estimation

Newborn gestational age can be estimated very soon after delivery. The relationship between gestational age and birthweight can identify neonates at risk for complications. For example, neonates who are either small or large for gestational age are at greater risk for hypoglycemia and polycythemia, and measurements of blood glucose and hematocrit are indicated.

Care of Skin and Umbilical Cord

All excess vernix, blood, and meconium is gently wiped off after delivery while keeping the newborn warm. Any remaining vernix is readily absorbed and disappears within 24 hours. The first bath is postponed until the neonate's temperature is stable.

Aseptic precautions are observed in the immediate care of the cord. The American Academy of Pediatrics has concluded that keeping the cord dry is sufficient care (Stewart, 2016). The umbilical cord begins to lose water from Wharton jelly shortly after birth. Within 24 hours, the cord stump loses its characteristic bluish-white, moist appearance and soon becomes dry and black. Within several days to weeks, the stump sloughs and leaves a small, granulating wound, which after healing forms the umbilicus. Separation usually takes place within the first 2 weeks. The range is 3 to 45 days (Novack, 1988). The umbilical cord dries more quickly and separates more readily when exposed to air. Thus, a dressing is not recommended.

In resource-poor countries, local antimicrobial prophylaxis is reasonable (Salam, 2014). Triple-dye applied to the cord was reported to be superior to soap and water care in preventing colonization and exudate formation (Janssen, 2003). In a Nepalese study, cleaning the cord stump with 4-percent chlorhexidine reduced severe infection by 75 percent compared with soap and water (Mullany, 2006). Likewise, 0.1-percent chlorhexidine powder was superior to dry cord care (Kapellen, 2009). The World Health Organization (2014) recommends cleansing with chlorhexidine.

Despite precautions, a serious umbilical infection—*omphalitis*—sometimes develops. In a German study of more than 750 newborns with aseptic cord care, 1.3 percent suffered such infections (Kapellen, 2009). The most likely offending organisms are *Staphylococcus aureus, Escherichia coli,* and group B streptococcus.

Typical signs of cellulitis and stump discharge usually aid diagnosis. Mild erythema and some bleeding at the stump site with cord detachment is also common, but some cases present with no outward signs.

Feeding and Weight Loss

In 2016, 81 percent of U.S. newborns were initially breastfed, 52 percent were still breastfed at 6 months, and 31 percent at 1 year (Centers for Disease Control and Prevention, 2016). According to the American College of Obstetricians and Gynecologists (2017e), exclusive breastfeeding is preferred until 6 months. In many hospitals, breastfeeding begins in the delivery room. Most term newborns thrive best when fed 8 to 12 times daily for approximately 15 minutes each episode. Preterm or growth-restricted newborns require feedings at shorter intervals. Breastfeeding is discussed further in Chapter 36 (Lactation And Breastfeeding).

Because most neonates actually receive little nutriment for the first 3 or 4 days of life, they progressively lose weight until the flow of maternal milk is established or other feeding is instituted. Preterm neonates lose relatively more weight and regain their birthweight more slowly. Conversely, growth-restricted but otherwise healthy newborns regain their initial weight more quickly than those born preterm. With proper nourishment, birthweight of term newborns usually is regained by 10 days.

Stools and Urine

For the first 2 or 3 days after birth, the colon contains soft, brown-green meconium. This consists of desquamated epithelial cells from the intestinal tract, mucus, epidermal cells, and lanugo (fetal hair) that have been swallowed along with amnionic fluid. The characteristic color results from bile pigments. During fetal life and for a few hours after birth, the intestinal contents are sterile, but bacteria quickly colonize the bowel contents.

Meconium stooling is seen in 90 percent of newborns within the first 24 hours, and most of the rest within 36 hours. Usually, newborns first void shortly after birth but may not until the second day. Meconium and urine passage indicates patency of the gastrointestinal and urinary tracts, respectively. Failure of the newborn to stool or urinate after these times suggests a congenital defect, such as Hirschsprung disease, imperforate anus, or posterior urethral valve. After the third or fourth day, as a result of milk ingestion, meconium is replaced by light-yellow, softer, homogenous feces.

Neonatal Hyperbilirubinemia

Between the second and fifth day of life approximately one third of all neonates develop physiological jaundice of the newborn. It has special significance considering most hospitals have policies for early discharge. Guidelines regarding standard phototherapy equipment and monitoring, as well as treatment recommendations per gestational age, hour of life, and risk factors are used (Bhutani, 2011; Maisels, 2009). Hyperbilirubinemia is discussed further in Chapter 33 (Polycythemia and Hyperviscosity).

Male Circumcision

Indications

Neonatal circumcision of male infants has been a controversial topic in the United States for at least 30 years. Even so, scientific evidence supports several medical benefits that include prevention of phimosis, paraphimosis, and balanoposthitis. Circumcision also lowers the incidence of penile cancer and of cervical cancer among their sexual partners. Previously, the American Academy of Pediatrics Task Force on Circumcision (1999) concluded that existing evidence was insufficient to recommend *routine* neonatal circumcision. It seems that this policy has had only a negligible effect on practices in this country. Specifically, the Centers for Disease Control and Prevention (2011) estimated that the newborn male circumcision rate declined during a 12-year period from approximately 60 percent in 1999 to only 55 percent in 2010.

Other studies have endorsed health benefits of circumcision. In large randomized trials from regions of Africa with a high prevalence of human immunodeficiency virus (HIV), male circumcision was found to lower the risk of HIV acquisition in the adult by half (Bailey, 2007; Gray, 2007). And, male circumcision was also reported to decrease adult incidences of HIV, HPV, and herpes infections (Tobian, 2009). In its subsequent policy statement, the American Academy of Pediatrics Task Force on Circumcision (2012) concluded that health benefits of newborn male circumcision outweigh the risks. Thus, access to the procedure is justified for families who choose it. The Task Force stopped short of recommending circumcision for *all* newborns.

Surgical Technique

Circumcision is performed only in a healthy neonate. Other contraindications include any genital abnormalities such as hypospadias and a family history of a bleeding disorder, unless excluded in the newborn.

The Task Force (2012) recommends procedural analgesia. Various pain relief techniques include lidocaine-prilocaine topical cream, local analgesia infiltration, dorsal penile nerve block, or ring block (Arnett, 1990; Stang, 1988). The dorsal penile nerve block or the ring block is superior to topical analgesia (Hardwick-Smith, 1998; Lander, 1997; Taddio, 1997). The use of a pacifier dipped in sucrose is a useful adjunct to these methods (Kaufman, 2002).

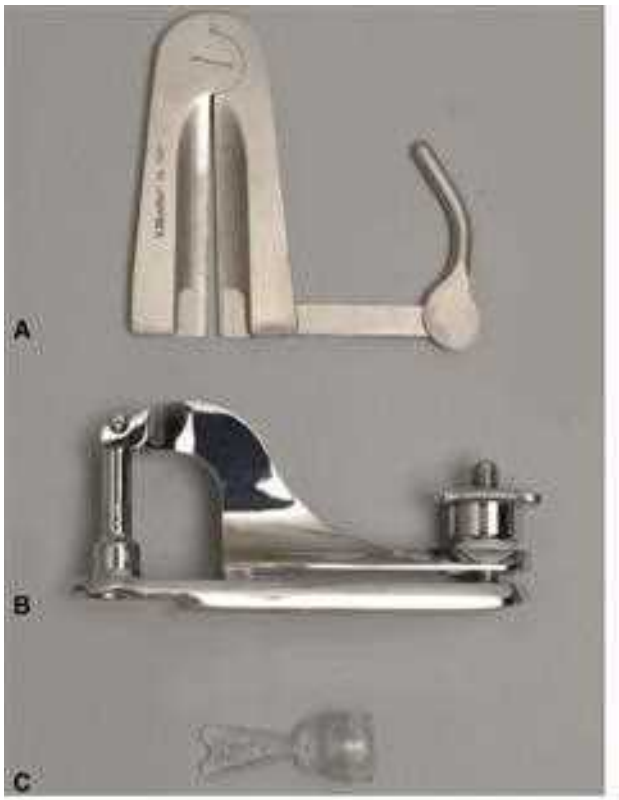
After appropriate penile cleansing, the ring block places a wheal of 1-percent lidocaine at the base of the penis and then advances the needle in a 180-degree arc around the base of the penis. The needle is advanced first to one side and then to the other to achieve a circumferential ring of analgesia. The maximum dose of lidocaine is 1.0 mL. *No vasoactive compounds such as epinephrine should ever be added to a local analgesic agent for circumcision.*

The most commonly used instruments are shown in Figure 32-5 and are Gomco and Mogen clamps and the Plastibell device. Compared with the Gomco procedure, Kaufman and colleagues (2002) reported that the Mogen technique required less time to perform and was associated with less apparent discomfort for the newborn. Regardless of the method used, the goal is to remove enough shaft skin and inner preputial epithelium so that the glans is exposed sufficiently to prevent phimosis. In all techniques: (1) the amount of external skin to be removed must be accurately estimated, (2) the preputial orifice must be dilated to visualize the glans and

ensure that it is normal, (3) the inner preputial epithelium must be freed from the glans epithelium, and (4) the circumcision device must be left in place long enough to produce hemostasis before amputating the prepuce (Lerman, 2001).

FIGURE 32-5

Three different tools used for circumcision. **A.** Mogen clamp. The arms of the clamp open to a 3-mm maximum width. **B.** Gomco clamp, assembled. **C.** Plastibell device.



The risks for bleeding, infection, and hematoma formation are low (Christakis, 2000). Unusual complications include distal glans amputation, acquisition of HIV infection or other sexually transmitted disease, meatal stenosis, penile denudation, penile destruction with electrosurgical coagulation, subsequent epidermal inclusion cyst and urethrocutaneous fistula, and ischemia following the inappropriate use of lidocaine with epinephrine (Amukele, 2003; Neulander, 1996; Nicoll, 1997; Pippi-Salle, 2013; Upadhyay, 1998).

Rooming In and Hospital Discharge

Hospital *rooming in* places newborns in their mothers' rooms instead of central nurseries. This practice attempts to make all phases of childbearing as natural as possible and to foster early mother-child relationships. By 24 hours, the mother is generally fully ambulatory. Thereafter, with rooming-in, she can usually provide routine care for herself and her newborn. An obvious advantage of this is her ability to assume full care when she arrives home.

Traditionally, the newborn is discharged with its mother, and in most cases, maternal stay has determined that of the neonate. From 1970 to the mid-1990s, average maternal postpartum length of stay declined steadily, and many mothers were discharged before 48 hours. The World Health Organization (2014) cites a minimal stay of only 24 hours. Although it is clear that most newborns can be safely discharged within 48 hours, this is not uniformly true. For example, in more than 2.1 million neonates in Canada, Liu and associates (2000) examined readmission rates following initial neonatal discharge. As the length of hospital stay dropped from 4.2 days in 1990 to 2.7 days in 1997, the readmission rate rose from 27 to 38 per 1000. Dehydration and jaundice accounted for most of these readmissions. Using Washington state data, Malkin and coworkers (2000) found that the 28-day mortality rate was increased fourfold in newborns discharged within 30 hours of birth, and the 1-year mortality rate grew twofold. Safe discharge for late-preterm newborns has special concerns (Whyte, 2012).

Because of the increased scrutiny regarding short hospital stays, federal legislation—*The Newborns' and Mothers' Health Protection Act of 1996*—was enacted to prohibit insurers from restricting hospital stays for mothers and newborns to less than 2 days for vaginal delivery or 4 days for cesarean delivery. In an analysis of more than 662,000 births in California, Datar and Sood (2006) found that readmission rates declined by 9, 12, and 20 percent, respectively, at 1, 2, and 3 years after the legislation was implemented.

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CHAPTER 33: Diseases and Injuries of the Term Newborn

In a small number of cases fractures of the skull are met with. This accident usually follows violent attempts at delivery, though occasionally it may occur spontaneously.

—J. Whitridge Williams (1903)

INTRODUCTION

In the first edition of this book, Williams wrote very little of the disorders of the term newborn. That said, it is well known that these neonates are susceptible to a wide variety of illnesses and injuries. In many instances, clinical manifestations of these disorders are extensions of pathological effects already incurred by the fetus. A common example is the newborn who is depressed and acidotic because of intrapartum septicemia. Because many of these disorders manifest differently, those more common in term newborns are considered here. Those more frequent in preterm neonates are discussed in Chapter 34. Specific disorders that are the direct consequence of maternal diseases are discussed in pertinent chapters.

RESPIRATORY DISTRESS

At the time of delivery, the newborn must convert rapidly to air breathing as described in Chapter 32 (Transition to Air Breathing). With inspiration, there is alveolar expansion, fluid clearance, and surfactant secretion by type II pneumocytes to prevent alveolar collapse. Interference with these functions can create respiratory insufficiency with hypoxemia and compensatory tachypnea, nasal flaring, retractions, and grunting (Reuter, 2014). In preterm infants, this is caused by lung immaturity and insufficient surfactant—*respiratory distress syndrome (RDS)*—and variants may be seen in severely ill older children and adults (Chap. 47, Acute Respiratory Distress Syndrome). All of these have some element of surfactant deficiency because the inciting agent damages alveolar epithelium. As fetuses approach term, surfactant deficiency as a cause of respiratory distress diminishes. The leading causes in term newborns are transient tachypnea of the newborn, RDS, meconium aspiration syndrome, pneumonia, persistent pulmonary hypertension, and hypoxic-ischemic encephalopathy (Lin, 2015).

Respiratory Distress Syndrome

In a report from Beijing that described 125 term infants with RDS, the most frequent causes were perinatal infection with sepsis syndrome in 50 percent, elective cesarean delivery in 27 percent, severe asphyxia in 10 percent, and meconium aspiration in 7 percent (Liu, 2010). Notably, even with a low incidence in term infants, RDS from surfactant deficiency is not rare (Berthelot-Ricou, 2012). Chorioamnionitis, male gender, and white race are independent risks (Anadkat, 2012; Higgins, 2016). Also, mutations of genes that encode for surfactant protein synthesis may augment the deficiency (Wambach, 2012). Regardless of etiology, when surfactant secretion is diminished, the pulmonary pathophysiology, clinical course, and management are similar to that for preterm infants. Treatment includes mechanical ventilation and replacement of surfactant (Chap. 34, Clinical Course). Evidence now supports that antenatal maternal corticosteroid treatment will enhance surfactant synthesis in late-preterm fetuses, that is, those 34 to 37 weeks' gestation (Gyamfi-Bannerman, 2016). At Parkland Hospital, corticosteroids are not given for this indication in the late-preterm period. Neonatal hypoglycemia is a concern with such treatment, and long-term effects are unknown. However, data indicate that hypoglycemia, if promptly treated, creates no adverse sequelae (McKinlay, 2015). The prognosis in term newborns with RDS largely depends on the cause, severity, and response to treatment.

Meconium Aspiration Syndrome

The physiology of meconium passage and amnionic fluid contamination is considered in Chapter 24 (Meconium in the Amnionic Fluid). In some instances, inhalation of meconium-stained fluid at or near delivery causes acute airway obstruction, chemical pneumonitis, surfactant dysfunction or inactivation, and pulmonary hypertension (Lee, 2016; Lindenskov, 2015). If severe, hypoxemia may lead to neonatal death or long-term neurological sequelae in survivors.

Given the high incidence—10 to 20 percent—of meconium-stained amnionic fluid in laboring women at term, one may reasonably assume that meconium aspiration must be relatively common. Fortunately, severe aspiration leading to overt respiratory failure is much less frequent. And although the exact incidence of meconium aspiration syndrome is unknown, Singh and associates (2009) reported it to complicate 1.8 percent of all deliveries. In a French study of nearly 133,000 term newborns, the prevalence of severe aspiration syndrome was 0.07 percent, and this rose progressively from 37 to 43 weeks' gestation (Fischer, 2012). Mortality rates depend on severity.

Fetal morbidity is more often associated with thicker meconium content. Presumably, in most cases, amnionic fluid is ample to dilute the meconium to permit prompt clearance by normal fetal physiological mechanisms. Meconium aspiration syndrome still occasionally develops with light staining. Many newborns are affected after a normal labor and uncomplicated delivery. However, some associated obstetrical factors include postterm pregnancy and fetal-growth restriction. These fetuses are at highest risk because diminished amnionic fluid and labor with cord compression or uteroplacental insufficiency are often comorbid. These can enhance the likelihood of meconium passage that is thick and undiluted (Leveno, 1984).

Prevention

Previously, aspiration was thought to be stimulated by fetal hypoxic episodes, and fetal heart rate tracing abnormalities were used to identify fetuses at greatest risk during labor. Unfortunately, this was found to be an unreliable predictor (Dooley, 1985). As another potential prevention, oropharyngeal suctioning was standard care for a time. However, this was abandoned when evidence failed to support a reduction in syndrome incidence or severity (Davis, 1985; Wiswell, 1990). At the same time, reports described that pulmonary hypertension caused by aspirated meconium was characterized by abnormal arterial muscularization beginning well before birth. These findings led some to conclude that only chronically asphyxiated fetuses developed meconium aspiration syndrome (Katz, 1992). But, correlation was not found between meconium aspiration and markers of *acute* asphyxia—for example, umbilical artery acidosis (Bloom, 1996; Richey, 1995). Others, however, have reported that thick meconium is an independent risk factor for neonatal acidosis (Maisonneuve, 2011).

In response to conflicting results regarding suctioning, an 11-center randomized trial was designed to compare suctioning with no suctioning (Vain, 2004). There was an identical 4-percent incidence of meconium aspiration syndrome in both groups. Subsequently, a committee that represented the American Heart Association updated its guidelines (Wyckoff, 2015). Adopted by the American College of Obstetricians and Gynecologists (2017c) and the World Health Organization (2012), these recommend *against* routine intrapartum oro- and nasopharyngeal suctioning at delivery. For vigorous newborns, no treatment is required. For depressed newborns, management includes intervention to support ventilation and oxygenation, and intubation is used as indicated (Chap. 32, Chest Compressions).

Intrapartum amnioinfusion has been used successfully in laboring women with diminished amnionic fluid volume and frequent variable fetal heart rate decelerations (Chap. 24, Management Options). Earlier, it was studied as a preventive measure in labors complicated by meconium staining. This practice failed to lower meconium aspiration syndrome rates because fetuses usually inhaled meconium before labor (Bryne, 1987; Wenstrom, 1995). To further settle this issue, a trial was conducted with almost 2000 women at 36 weeks' gestation or later and in whom labor was complicated by thick meconium (Fraser, 2005). The perinatal death rate with and without amnioinfusion was 0.05 percent in both groups. Rates of moderate or severe meconium aspiration were also not significantly different—4.4 percent with and 3.1 percent without amnioinfusion. Finally, cesarean delivery rates were similar—32 versus 29 percent, respectively. Currently, the American College of Obstetrics and Gynecologists (2016a) does not recommend amnioinfusion to reduce meconium aspiration syndrome.

Treatment

Ventilatory support and intubation are carried out as needed (Wyckoff, 2015). Because some aspects of meconium aspiration syndrome are caused by surfactant deficiency, replacement therapy is beneficial (Natarajan, 2016a). Also, inhaled corticosteroids may ameliorate the severity (Garg, 2016). *Extracorporeal membrane oxygenation—ECMO*—therapy is reserved for neonates who remain poorly oxygenated despite maximal ventilatory assistance (Hirakawa, 2017). In their review of randomized trials, El Shahed and colleagues (2014) found that surfactant replacement may reduce the need for ECMO but did not lower the mortality rate. The proportion that requires ECMO treatment varies. In a report by Singh and coworkers (2009), 1.4 percent of 7518 term newborns with the syndrome required such treatment, and these had a 5-percent mortality rate. Ramachandrappa and associates (2011) reported a higher mortality rate in late-preterm neonates with meconium aspiration compared with affected term newborns. Finally, pulmonary lavage with surfactant is being evaluated (Choi, 2012).

NEONATAL ENCEPHALOPATHY AND CEREBRAL PALSY

Few events evoke more apprehension in parents and obstetricians than the specter of "brain injury," which immediately prompts concerns for disabling cerebral palsy and intellectual disability. Although most brain disorders or injuries are less profound, history has helped to perpetuate the more dismal outlook. In his first edition of this textbook, Williams (1903) limited discussions of brain injury to those sustained from birth trauma. When later editions introduced the concept that *asphyxia neonatorum* was another cause of cerebral palsy, this too was linked to traumatic birth. Even as brain damage caused by traumatic delivery became uncommon during the ensuing decades, the belief—albeit erroneous—was that intrapartum events caused most neurological disability. This was a major reason for the escalating cesarean delivery rate beginning in the 1970s. Unfortunately, because in most cases the genesis of cerebral palsy occurs long before labor, this did little to mitigate risks for cerebral palsy (O'Callaghan, 2013).

These realizations stimulated scientific investigations to determine the etiopathogenesis of fetal brain disorders, including those leading to cerebral palsy. Seminal observations include those of Nelson and Ellenberg (1984, 1985, 1986a), discussed subsequently. These investigators are appropriately credited with proving that these neurological disorders are due to complex multifactorial processes caused by a combination of genetic, physiological, environmental, and obstetrical factors. Importantly, these studies showed that few neurological disorders were associated with peripartum events. Continuing international interest was garnered to codify the potential role of intrapartum events. In 2000, a task force of the American College of Obstetricians and Gynecologists was appointed to study the vicissitudes of neonatal encephalopathy and cerebral palsy. The multispecialty coalition reviewed contemporaneous data and provided criteria to define various neonatal brain disorders. Their findings were promulgated by the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2003).

Ten years later, a second task force of these organizations updated the findings (American College of Obstetricians and Gynecologists, 2014c). The 2014 Task Force findings are more circumspect in contrast to the earlier ones. Specifically, more limitations are cited in identifying cause(s) of peripartum *hypoxic-ischemic encephalopathy (HIE)* compared with other etiologies of neonatal encephalopathy. The 2014 Task Force recommends multidimensional assessment of each affected infant. They add the caveat that no one strategy is infallible, and thus, no single strategy will achieve 100-percent certainty in attributing a cause to neonatal encephalopathy.

Neonatal Encephalopathy

The 2014 Task Force defined neonatal encephalopathy as a syndrome of neurological dysfunction identified in the earliest days of life in neonates born at ≥35 weeks' gestation. It is manifested by subnormal levels of consciousness or seizures and often accompanied by difficulty with initiating and maintaining respiration and by depressed tone and reflexes. The incidence of encephalopathy has been cited to be 0.27 to 1.1 per 1000 term liveborn neonates, and it is much more frequent in

preterm newborns (Ensing, 2013; Plevani, 2013; Takenouchi, 2012; Wu, 2011). Although the 2014 Task Force concluded that there are many causes of encephalopathy and cerebral palsy, it focused on HIE and those that were thought to be incurred intrapartum. To identify affected infants, a thorough evaluation is necessary and includes maternal history, obstetrical antecedents, intrapartum factors, placental pathology, and newborn course. These are complemented by laboratory and neuroimaging findings.

There are three clinically defined levels. *Mild encephalopathy* is characterized by hyperalertness, irritability, jitteriness, and hypertonia and hypotonia. *Moderate encephalopathy* is manifest by lethargy, severe hypertonia, and occasional seizures. S*evere encephalopathy* is manifest by coma, multiple seizures, and recurrent apnea.

The 2014 Task Force also concluded that of the several forms of cerebral palsy, only the *spastic quadriplegic* type can result from acute peripartum ischemia. Other forms—*hemiparetic* or *hemiplegic cerebral palsy, spastic diplegia,* and *ataxia*—are unlikely to result from an intrapartum event. Purely dyskinetic or ataxic cerebral palsy, especially when accompanied by a learning disorder, usually has a genetic origin (Nelson, 1998).

Criteria for Hypoxic-Ischemic Encephalopathy

The 2014 Task Force radically revised its 2003 criteria used to define an acute peripartum event that is consistent with an HIE and neonatal encephalopathy. These are outlined in Table 33-1 and are considered with the following caveats.

TABLE 33-1

Findings Consistent with an Acute Peripartum or Intrapartum Event Leading to Hypoxic-Ischemic Encephalopathy

Neonatal Findings
Apgar score: <5 at 5 and 10 minutes
Umbilical arterial acidemia: pH <7.0 and/or base deficit ≥12 mmol/L
Neuroimaging evidence of acute brain injury: MR imaging or MRS consistent with HIE
Multisystem involvement consistent with HIE
Type and Timing of Contributing Factors
Sentinel hypoxic or ischemic event occurring immediately before or during delivery
Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event

HIE = hypoxic ischemic encephalopathy; MR = magnetic resonance; MRS = magnetic resonance spectroscopy.

Summarized from the American College of Obstetricians and Gynecologists, 2014b.

First, *Apgar Scores* that are low at 5 and 10 minutes are associated with greater risk for neurological impairment. Low scores stem from many causes, and most of these infants will not develop cerebral palsy. With a 5-minute Apgar ≥7, it is unlikely that peripartum HIE caused cerebral palsy.

Acid-base study results define a second HIE criterion. Low pH and base deficit levels raise the likelihood that neonatal encephalopathy was caused by HIE. Decreasing levels form a continuum of increasing risk, but most acidemic neonates will be neurologically normal (Wayock, 2013). A cord artery pH ≥7.2 is very unlikely to be associated with HIE.

Magnetic resonance (MR) imaging or *MR spectroscopy (MRS)* is the best modality with which to visualize findings consistent with HIE. The 2014 Task Force concludes that cranial sonography and computed tomography (CT) lack sensitivity in the term newborn. Normal imaging findings after the first 24 hours of life, however, effectively exclude a hypoxic-ischemic cause of encephalopathy. MR imaging between 24 and 96 hours may be more sensitive for the timing of peripartum cerebral injury, and MR imaging at 7 to 21 days following birth is the best technique to delineate the full extent of cerebral injury.

Last, *multisystem involvement* of injury is consistent with HIE. These include renal, gastrointestinal, hepatic, or cardiac injury; hematological abnormalities; or combinations of these. The severity of neurological injury does not necessarily correlate with injuries to these other systems.

The 2014 Task Force also found that certain contributing factors may be consistent with an acute peripartum event. Of these, *sentinel events* are considered adverse obstetrical events that may lead to catastrophic clinical outcomes. Examples include ruptured uterus, severe placental abruption, cord prolapse, and amnionic fluid embolism. Martinez-Biarge and associates (2012) studied almost 58,000 deliveries and identified 192 cases with one of these sentinel events. Of these 192 fetus/newborns, 6 percent died intrapartum or in the early neonatal period, and 10 percent developed neonatal encephalopathy. Other risk factors for neonatal acidosis include prior or emergent cesarean delivery, maternal age ≥35 years, thick meconium, chorioamnionitis, and general anesthesia (Ahlin, 2016; Johnson, 2014; Nelson, 2014).

Differentiating an *abnormal fetal heart rate (FHR) tracing* on presentation versus one that develops subsequently was also emphasized by the 2014 Task Force. A category 1 or 2 FHR tracing associated with Apgar scores ≥7 at 5 minutes, normal cord gases (±1 SD), or both are not consistent with an acute HIE event (Graham, 2014). An FHR pattern at the time of presentation with persistently minimal or absent variability and lacking accelerations, with duration ≥60 minutes, and even without decelerations is suggestive of an already compromised fetus (Chap. 24, Cardiac Arrhythmia). The 2014 Task Force further recommended that if fetal well-being cannot be established with these findings present, the woman should be evaluated for the method and timing of delivery.

Prevention

Most prophylactic measures for neonatal encephalopathy have been evaluated in preterm infants (Chap. 42, Magnesium Sulfate for Neuroprotection). One of these—postnatally induced hypothermia—may prevent death and mitigate moderate to severe neurological disability in term newborns (Garfinkle, 2015; Nelson, 2014; Shankaran, 2012). MR imaging studies have demonstrated a slowing of diffusional abnormalities and fewer infarctions with hypothermia (Bednarek, 2012; Natarajan, 2016b). Most randomized trials have shown improved outcomes with induced hypothermia in those born at 36 weeks' gestation or older (Azzopardi, 2014; Guillet, 2012; Jacobs, 2011). In a metaanalysis of more than 1200 newborns, Tagin and colleagues (2012) concluded that hypothermia improves survival rates and neurodevelopment. Clinical trials to evaluate concomitant neonatal erythropoietin therapy for neuroprophylaxis have reported conflicting results (Fauchère, 2015; Malla, 2017). Preliminary data from one multicenter trial of maternal *allopurinol* therapy indicate some mitigation of cerebral damage caused by hypoxia and ischemia (Kaandorp, 2013).

Cerebral Palsy

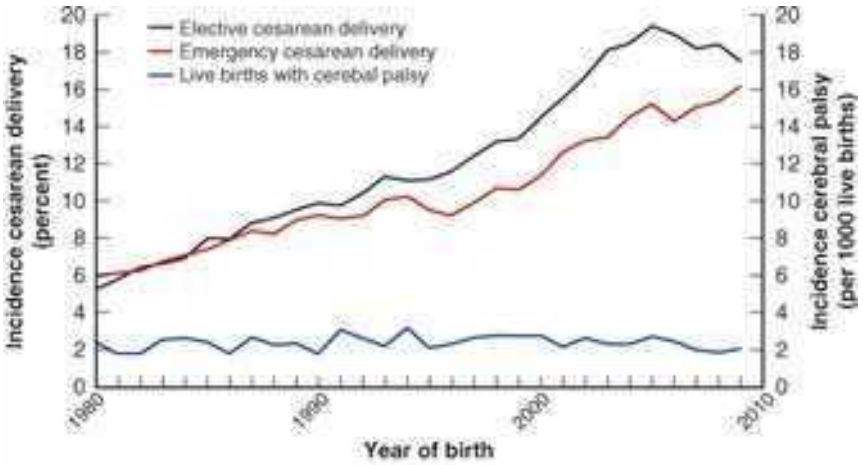
This term refers to a group of nonprogressive disorders of movement or posture caused by abnormal development or damage to brain centers for motor control. Cerebral palsy is further classified by the type of neurological dysfunction—spastic, dyskinetic, or ataxic—and by the number and distribution of limbs involved—quadriplegia, diplegia, hemiplegia, or monoplegia. Together, the major types are s*pastic quadriplegia*—the most common—which has a strong association with mental retardation and seizure disorders; *diplegia,* which is common in preterm or low-birthweight infants; *hemiplegia; choreoathetoid types;* and *mixed varieties*. Although epilepsy and mental retardation frequently accompany cerebral palsy, these two disorders seldom are associated with perinatal asphyxia in the absence of cerebral palsy.

Incidence and Epidemiological Correlates

According to Nelson and coworkers (2015), the prevalence of cerebral palsy in the United States averages 2 of every 1000 children. *It is crucial to emphasize that this rate is derived from all children—including those born preterm.* Because of the remarkably greater survival rates of the latter currently, and despite the elevated cesarean delivery rate, the overall rate of cerebral palsy has remained essentially unchanged (Fig. 33-1). For example, follow-up studies of more than 900,000 Norwegian nonanomalous term infants cite an incidence of 1 per 1000, but the incidence was 91 per 1000 for those born at 23 to 27 weeks (Moster, 2008). Similar findings have been reported for Australian births (Smithers-Sheedy, 2016). In absolute numbers, term newborns comprise half of cerebral palsy cases because there are proportionately far fewer preterm births. It is again emphasized that most studies of cerebral palsy rates have not made distinctions between term and preterm infants.

FIGURE 33-1

Elective and emergency cesarean deliveries and live births with cerebral palsy. (Reproduced with permission from Nelson KB, Blair E: Prenatal factors in singletons with cerebral palsy born at or near term, N Engl J Med. 2015 Sep 3;373(10):946–953.)



As noted earlier, Nelson and Ellenberg (1984, 1985, 1986a) made many fundamental observations concerning cerebral palsy. Their initial studies emanated from data from the Collaborative Perinatal Project. This included children from almost 54,000 pregnancies who were followed until age 7. They found that the most frequently associated risk factors for cerebral palsy were: (1) evidence of genetic abnormalities such as maternal mental retardation or fetal congenital malformations; (2) birthweight <2000 g; (3) birth before 32 weeks; and (4) perinatal infection. They also found that obstetrical complications were not strongly predictive, and only a fifth of affected children had markers of perinatal asphyxia. *For the first time, there was solid evidence that the cause of most cases of cerebral palsy was unknown, and importantly, only a small proportion was caused by neonatal HIE.* Equally importantly, there was no foreseeable single intervention that would likely prevent a large proportion of cases.

Numerous studies have since confirmed many of these findings and identified an imposing list of other risk factors that are shown in Table 33-2. As expected, preterm birth continues to be the single most important risk factor (Nelson, 2015; Thorngren-Jerneck, 2006). Small-for-gestational-age neonates are also at higher risk. Stoknes and associates (2012) showed that in more than 90 percent of growth-restricted newborns, cerebral palsy was due to antepartum factors. Many other placental and neonatal risk factors have been correlated with neurodevelopmental abnormalities (Ahlin, 2013; Avagliano, 2010; Blair, 2011; Redline, 2008). Some placental factors are discussed further in Chapter 6 (Normal Placenta). One example is the substantively greater risk from chorioamnionitis (Gilbert, 2010; Shatrov, 2010). An example of a neonatal cause is arterial ischemic stroke, which may be associated with inherited fetal thrombophilias (Harteman, 2013; Kirton, 2011). Also, newborns with isolated congenital heart lesions have an elevated risk for microcephaly, possibly due to chronic fetal hypoxemia (Barbu, 2009). Other miscellaneous etiologies of cerebral palsy include fetal anemia, twin-twin transfusion syndrome, intrauterine transfusions, and fetal alcohol syndrome (DeJong, 2012; Lindenburg, 2013; O'Leary, 2012; Rossi, 2011; Spruijt, 2012).

TABLE 33-2

Perinatal Risk Factors Reported to Be Increased in Children with Cerebral Palsy

Risk Factors	Risk Ratio	95% CI
Hydramnios	6.9	1.0–49.3
Placental abruption	7.6	2.7–21.1
Interval between pregnancies <3 mo or >3 yr	3.7	1.0–4.4
Spontaneous preterm labor	3.4	1.7–6.7
Preterm delivery at 23–27 weeks	78.9	56.5–110
Breech or face presentation, transverse lie	3.8	1.6–9.1
Severe birth defect	5.6	8.1–30.0
Nonsevere birth defect	6.1	3.1–11.8
Time to cry >5 minutes	9.0	4.3–18.8
Obesity	1.2–2	1.1–2.8
Low placental weight	3.6	1.5–8.4
Placental infarction Chorioamnionitis	2.5	1.2–5.3
Clinical Histological	2.4 1.8	1.5–3.8 1.2–2.9
Others[a]	—	—

[a]Includes respiratory distress syndrome, meconium aspiration, emergent cesarean or operative vaginal delivery, hypoglycemia, gestational hypertension, hypotension, advanced maternal age, genetic factors, twins, thrombotic states, nighttime delivery, seizures, fetal-growth restriction, male gender, and nulliparity.

CI = confidence interval.

From Ahlin, 2013; Blair, 2011; McIntyre, 2013; Moster, 2008; Nelson, 2015; O'Callaghan, 2011; Shatrov, 2010; Takenouchi, 2012; Torfs, 1990; Villamor, 2017; Wu, 2012.

Apart from these causes, intrapartum hypoxemia was linked to only a minority of cerebral palsy cases by the National Collaborative Perinatal Project. However, because the study was carried out in the 1960s, there were inconsistent criteria to accurately assign cause. The contribution of HIE to subsequent neurological disorders is discussed in detail in Neonatal Encephalopathy. The 2003 Task Force applied these criteria to more contemporaneous outcomes and determined that only 1.6 cases of cerebral palsy per 10,000 deliveries are attributable solely to intrapartum hypoxia. This finding is supported by a study from Western Australia that spanned from 1975 to 1980 (Stanley, 1991). Other studies concluded that very few cases were due to intrapartum events and therefore preventable (Phelan, 1996; Strijbis, 2006).

Intrapartum Fetal Heart Rate Monitoring

Despite persistent attempts to validate continuous intrapartum electronic fetal monitoring as effective to prevent adverse perinatal outcomes, evidence does not support its ability to predict or reduce cerebral palsy risk (Clark, 2003; Thacker, 1995). Importantly, no specific fetal heart rate patterns predict cerebral palsy. Further, no relationship has been found between the clinician's response to abnormal patterns and neurological outcome. And, efforts using assisted computer analysis of

fetal heart tracings have not enhanced predictability (Alfirevic, 2017; INFANT Collaborative Group, 2017). Indeed, an abnormal heart rate pattern in fetuses that ultimately develop cerebral palsy may reflect a preexisting neurological abnormality (Phelan, 1994). Because of these studies, the American College of Obstetricians and Gynecologists (2017a,d) has concluded that electronic fetal monitoring does not reduce the incidence of long-term neurological impairment. This is discussed further in Chapter 24 (Benefits of Electronic Fetal Heart Rate Monitoring).

Apgar Scores

In general, 1- and 5-minute Apgar scores are poor predictors of long-term neurological impairment (American College of Obstetricians and Gynecologists, 2017e). When the 5-minute Apgar score is ≤3, however, neonatal death or the risk of neurological sequelae rises substantially (Dijxhoorn, 1986; Nelson, 1984). In a Swedish study, 5 percent of such children subsequently required special schooling (Stuart, 2011). In a Norwegian study, the incidence of these low Apgar scores was 0.1 percent in more than 235,000 newborns. Almost a fourth of those with such scores died, and 10 percent of survivors developed cerebral palsy (Moster, 2001).

Persistence past 5 minutes of these extremely low scores correlates strongly with a higher risk for neurological morbidity and death (Grünebaum, 2013). This of course is not absolute, and the 2003 Task Force cited a 10-percent risk for cerebral palsy for infants with 10-minute scores of 0 to 3. For 15-minute scores ≤2, there is a 53-percent mortality rate and a 36-percent cerebral palsy rate. For 20-minute scores ≤2, mortality rate is 60 percent, and a cerebral palsy rate is 57 percent. Some outcomes in the Norwegian Study of infants with these low 5-minute Apgar scores are shown in Table 33-3. Survivors who had Apgar scores of 0 at 10 minutes have even worse outcomes. In a review of 94 such newborns, 78 died, and *all* survivors assessed had long-term disabilities (Harrington, 2007).

TABLE 33-3

Comparison of Mortality and Morbidity in Norwegian Infants Weighing >2500 g According to 5-Minute Apgar Scores

Outcome	Apgar 0–3 (%)	Apgar 7–10 (%)	Relative Risk (95% CI)
Number	292	233, 500	
Mortality rates			
Neonatal	16.5	0.05	386 (270–552)
Infant	19.2	0.3	76 (56–103)
1–8 yr	3	0.2	18 (8–39)
Morbidity rates			
Cerebral palsy	6.8	0.09	81 (48–128)
Mental retardation	1.3	0.1	9 (3–29)
Other neurological	4.2	0.5	9 (5–17)
Non-neurological	3.4	2.0	2 (0.8–5.5)

CI = confidence interval.

Data from Moster, 2001.

Umbilical Cord Blood Gas Studies

As outlined in Neonatal Encephalopathy, objective evidence for metabolic acidosis—cord arterial blood pH <7.0 and base deficit ≥12 mmol/L—is a risk factor for encephalopathy and for cerebral palsy. The risk accrues as acidosis worsens. From their review of 51 studies, Malin and coworkers (2010) found that low cord arterial pH correlates with greater risk for neonatal encephalopathy and cerebral palsy. When used alone, however, these determinations are not accurate in predicting long-term neurological sequelae (Dijxhoorn, 1986; Yeh, 2012).

Data from several studies corroborate that a pH <7.0 is the threshold for clinically significant acidemia (Gilstrap, 1989; Goldaber, 1991). The likelihood of neonatal death grows as the cord artery pH falls to 7.0 or less. Casey and colleagues (2001) reported that when the pH was ≤6.8, the neonatal mortality rate rose 1400-fold. When the cord pH was ≤7.0 *and* the 5-minute Apgar score was 0 to 3, the risk of neonatal death was increased 3200-fold.

In the study from Oxford, adverse neurological outcomes were 0.36 percent with pH <7.1 and 3 percent with pH <7.0 (Yeh, 2012). As mentioned, newborn complication rates rise coincident with increasing severity of acidemia at birth. In a Swedish study, researchers observed that cord blood lactate levels may prove to be superior to base deficit for prognostication of neurological disorders (Wiberg, 2010).

Nucleated Red Blood Cells and Lymphocytes

Both immature red cells and lymphocytes enter the circulation of term newborns in response to hypoxia or hemorrhage. During the past two decades, quantification of these cells has been proposed as a measure of hypoxia, but most studies do not support this premise (Boskabadi, 2017; Silva, 2006; Walsh, 2011, 2013).

Neuroimaging Studies in Encephalopathy and Cerebral Palsy

Various neuroimaging techniques have provided important insight into the etiology and evolution of perinatal HIE and later cerebral palsy (Neonatal Encephalopathy). Importantly, findings are highly dependent on fetal age. The preterm neonatal brain responds quite differently to an ischemic episode compared with that of a term newborn. Other factors include insult severity and duration as well as restoration of cerebrovascular hypoperfusion. *Thus, precise timing of an injury with neuroimaging studies is not a realistic goal.* Moreover, the grade of neonatal encephalopathy, that is, mild, moderate, or severe, does not correlate with MR imaging findings (Walsh, 2017).

Neuroimaging in Neonatal Period

Regarding early use, the 2014 Task Force concluded that these imaging techniques provide the following information:

1. Sonographic studies are generally normal on the day of birth. With injury, increasing echogenicity in the thalami and basal ganglia is seen beginning at approximately 24 hours. This progresses over 2 to 3 days and persists for 5 to 7 days.
2. Computed tomography scans are usually normal the first day in term infants. With injury, decreased density in the thalami or basal ganglia is seen beginning at about 24 hours and persists for 5 to 7 days.
3. Magnetic resonance imaging will detect some abnormalities on the first day. Within 24 hours, MR imaging may show restricted water diffusion that peaks at approximately 5 days and disappears within 2 weeks. Acquisitions with T1- and T2-weighted images show variable abnormalities, which have an onset from less than 24 hours to several days. In a study of 175 term neonates with acute encephalopathy, it was reported that MR imaging showing basal ganglia lesions accurately predicted motor impairment at 2 years of age (Martinez-Biarge, 2012).

The 2014 Task Force concluded that for term newborns, imaging studies are helpful in timing an injury, but they provide only a window in time that is imprecise. In one study, the optimal range was 3 to 10 days (Lee, 2017).

Neuroimaging in Older Children with Cerebral Palsy

Imaging studies performed in children diagnosed with cerebral palsy frequently show abnormal findings. Wu and associates (2006) used CT or MR imaging to study 273 children who were born after 36 weeks' gestation and who were diagnosed later in childhood with cerebral palsy. Although a third of these studies were normal, focal arterial infarction was seen in 22 percent; brain malformations in 14 percent; and periventricular white-matter injuries in 12 percent. In another study of 351 children with cerebral palsy—approximately half were born near term—MR imaging findings were abnormal in 88 percent (Bax, 2006). Similar findings were reported in an Australian study (Robinson, 2008).

CT and MR imaging techniques have also been used in older children to help define the timing of fetal or perinatal cerebral injury. Wiklund and coworkers (1991a,b) studied 83 children between ages 5 and 16 years who were born at term and who developed hemiplegic cerebral palsy. Nearly 75 percent had abnormal CT findings, and these investigators concluded that more than half had CT changes that suggested a *prenatal injury.* Approximately 20 percent were attributed to a *perinatal injury*. In a similar study, Robinson and associates (2008) used MR imaging. They reported pathological findings in 84 percent of children with spastic quadriplegia. Remember, this is the neurological lesion that the 2014 Task Force concluded correlated with neonatal encephalopathy.

Intellectual Disability and Seizure Disorders

The term *intellectual disability* describes a spectrum of disabilities and seizure disorders that frequently accompany cerebral palsy. But, when either of these manifests alone, they are seldom caused by perinatal hypoxia (Nelson, 1984, 1986a,b). Severe mental disability has a prevalence of 3 per 1000 children, and its most frequent causes are chromosomal, gene mutation, and other congenital malformations. Finally, preterm birth is a common association for these (Moster, 2008).

The major predictors of seizure disorders are fetal malformations—cerebral and noncerebral; family history of seizures; and neonatal seizures (Nelson, 1986b). Neonatal encephalopathy causes a small proportion of seizure disorders. Reports from the Neonatal Research Network and other studies concluded that increasing severity of encephalopathy correlates best with seizures (Glass, 2011; Kwon, 2011).

Autism Spectrum Disorders

According to the Centers for Disease Control and Prevention, the frequency of autism spectrum disorders is 14.6 per 1000 in 8-year-old children (Christensen, 2016). Although these may be associated with maternal metabolic conditions, none has been linked convincingly to peripartum events (Krakowiak, 2012).

NEONATAL ABSTINENCE SYNDROME

This is a drug-withdrawal syndrome that most commonly follows in utero exposure to maternal opioids. It also may complicate exposure to ethanol or benzodiazepines. The syndrome is characterized by hypertonia, autonomic instability, irritability, poor sucking reflex, and seizures (Finnegan, 1975). The incidence of abstinence syndrome has risen six- to sevenfold during the past decade, coincidental with the growing opioid use described in Chapter 1 (Family Planning Services). For example, Tolia and colleagues (2015) reported that 4 percent of all neonatal intensive care unit (NICU) days in 2013 were attributed to care of these affected newborns.

Affected neonates undergo close observation, and pharmacotherapy is usually given. In addition to morphine and methadone, other treatment may include phenobarbital, benzodiazepines, and clonidine (Tolia, 2015). More recently, buprenorphine compared with morphine was reported to result in shorter lengths of stay (Kraft, 2017). Consensus is lacking regarding the most effective regimen. The American College of Obstetricians and Gynecologists and the American Society of Addiction Medicine (2017f) have taken the lead in screening, intervention, and treatment of opioid use disorders in pregnant women (Chap. 12, Cocaine).

HEMATOLOGICAL DISORDERS

There are a few neonatal disorders of erythrocytes, platelets, and coagulation with which the obstetrician should be familiar. As is the case for most other conditions manifest by the newborn shortly after birth, many of these hematological problems were manifest by the fetus and persist in the newborn.

Anemia

After 35 weeks' gestation, the mean cord hemoglobin concentration approximates 17 g/dL, and values below 14 g/dL are considered abnormal. The American College of Obstetricians and Gynecologists (2017b) now recommends a 30- to 60-second delay in cord clamping in all healthy newborns. A review of nearly 4000 deliveries found that this delayed cord clamping was associated with a mean neonatal hemoglobin rise of 1.5 g/dL (McDonald, 2013). At the same time, this practice almost doubled the incidence of hyperbilirubinemia requiring phototherapy.

Fetal anemia results from many causes (Colombatti, 2016; Yaish, 2017). Many of these are discussed in more detail in Chapter 15 (Fetal Anemia). Acute anemia with hypovolemia is seen with deliveries in which the placenta is cut or torn, if a fetal vessel is perforated or lacerated, if there is recent fetal-maternal hemorrhage, or if the newborn is held well above the level of the placenta for some time before cord clamping. Intracranial or extracranial injury or trauma to fetal intraabdominal organs can also cause hemorrhage with acute anemia (Akin, 2011; McAdams, 2017).

Polycythemia and Hyperviscosity

Neonatal polycythemia with hyperviscosity can be associated with chronic hypoxia in utero, twin-twin transfusion syndrome, placental- and fetal-growth restriction, fetal macrosomia from maternal diabetes, and transfusion at delivery. When the hematocrit rises above 65, blood viscosity markedly increases and may cause neonatal plethora, cyanosis, or neurological aberrations. Because of the shorter life span of macrocytic fetal erythrocytes, hyperbilirubinemia commonly accompanies polycythemia. Other findings include thrombocytopenia, fragmented erythrocytes, and hypoglycemia. Cui and associates (2017) reported a case of unilateral macular hemorrhage in a newborn with polycythemia and platelets of 1 million/μL. Partial exchange transfusion may be necessary in some neonates.

Hyperbilirubinemia

Even in term fetuses, hepatic maturation is not complete, and thus some unconjugated bilirubin—either albumin bound or free—is cleared by placental transfer to be conjugated in the maternal liver (Chap. 7, Urinary System). Fetal protection from unconjugated bilirubin is lost after delivery if not cleared rapidly. Because clearance is totally dependent on neonatal hepatic function, varying degrees of neonatal hyperbilirubinemia result. Even in the mature newborn, serum bilirubin levels usually rise for 3 to 4 days to reach up to 10 mg/dL. After this, concentrations usually fall rapidly. In one large study, 1 to 2 percent of neonates delivered at 35 weeks' gestation or later had a maximum serum bilirubin level >20 mg/dL (Eggert, 2006). Concomitant glucose-6-phosphate deficiency worsens hyperbilirubinemia (Chang, 2017). In approximately 15 percent of term newborns, bilirubin levels cause clinically visible skin yellowing termed *physiological jaundice* (Burke, 2009). As expected, in preterm neonates, the bilirubin elevation is greater and more prolonged.

Acute Bilirubin Encephalopathy and Kernicterus

Excessive serum bilirubin levels can be neurotoxic for newborns (Dijk, 2012; Watchko, 2013). The pathogenesis is complex, and toxicity has two forms. *Acute bilirubin encephalopathy* is encountered in the first days of life and is characterized by hypotonia, poor feeding, lethargy, and abnormal auditory-evoked responses (Kaplan, 2011). Immediate recognition and treatment will usually mitigate progressive neurotoxicity. The chronic form is termed *kernicterus*. With this, neurotoxicity follows bilirubin deposition and staining of the basal ganglia and hippocampus and is further characterized by profound neuronal degeneration. Survivors have spasticity, muscular incoordination, and varying degrees of mental deficiencies (Frank, 2017). Although there is a positive correlation between kernicterus and unconjugated bilirubin levels above 18 to 20 mg/dL, it can develop at much lower concentrations, especially in very preterm neonates (Sgro, 2011). Continuing hemolysis is a risk factor for kernicterus (El Houchi, 2017; Vandborg, 2012).

Prevention and Treatment

Various forms of phototherapy are used to prevent and treat neonatal hyperbilirubinemia (Ree, 2017). These "bili-lights" emit a spectrum of 460 to 490 nm, which augments bilirubin oxidation to enhance its renal clearance and lower serum levels. Sunlight filtered to remove ultraviolet light has been used in resource-poor countries (Slusher, 2015). Light that penetrates the skin also increases peripheral blood flow, which further enhances photo-oxidation. It is problematic that available devices are not standardized (Bhutani, 2011). Another advantage is that exchange transfusions are seldom required with phototherapy. Studies in both preterm and term newborns attest to phototherapy efficacy (Watchko, 2013). A Neonatal Research Network study reported that aggressive phototherapy in low-birthweight neonates reduced rates of neurodevelopmental impairment (Newman, 2006). Similar reductions were reported from Canada after implementation of 2007 guidelines (Sgro, 2016).

For term newborns, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) stress early detection and prompt phototherapy to prevent bilirubin encephalopathy. Despite these measures, bilirubin encephalopathy persists, and this is somewhat related to early hospital discharges (Gazzin, 2011; Kaplan, 2011; Sgro, 2011). According to Burke and coworkers (2009), hospitalizations for kernicterus in term newborns were 5.1 per 100,000

in 1988. Since then, however, this rate has dropped to 0.4 to 2.7 cases per 100,000 births (Watchko, 2013). This may be due in part to legislation, discussed in Chapter 36 (Immunizations), to minimize brief postpartum hospital stays.

Hemorrhagic Disease of the Newborn

This disorder is characterized by spontaneous internal or external bleeding beginning any time after birth. Most hemorrhagic disease results from abnormally low levels of the vitamin K-dependent clotting factors—V, VII, IX, X, prothrombin, and proteins C and S (Zipursky, 1999). Newborns whose mothers took anticonvulsant drugs are at higher risk because these suppress maternal hepatic synthesis of some of these factors. Classic hemorrhagic disease is usually apparent 2 to 5 days after birth in neonates not given vitamin K prophylaxis at delivery (Busfield, 2013). Delayed hemorrhage may occur at 2 to 12 weeks in exclusively breastfed infants because breast milk contains little vitamin K. Other causes of neonatal hemorrhage not related to vitamin K include hemophilia, congenital syphilis, sepsis, thrombocytopenia purpura, erythroblastosis, and intracranial hemorrhage.

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend routine prophylaxis for hemorrhagic disease with a 0.5- to 1-mg dose of vitamin K_1 (phytonadione) given intramuscularly. Oral administration is not effective, and maternal vitamin K administration results in very little transport to the fetus (Sankar, 2016).

Thrombocytopenia

Abnormally low platelet concentrations in term newborns may be due to various etiologies such as immune disorders, infections, drugs, or inherited platelet defects, or they may be part of a congenital syndrome (American College of Obstetricians and Gynecologists, 2016b). In many, thrombocytopenia is an extension of a fetal disorder such as infection with B19 parvovirus, cytomegalovirus, toxoplasmosis, and others discussed in Chapters 64 and 65. Neonatal thrombocytopenia has been reported with maternal antiretroviral therapy for human immunodeficiency virus (HIV) infection (Smith, 2016). Term newborns admitted to NICUs, especially those with sepsis, have accelerated platelet consumption (Eissa, 2013).

Immune Thrombocytopenia

In women with an autoimmune disorder such as systemic lupus erythematosus or immunological thrombocytopenia, maternal antiplatelet IgG is transferred to the fetus and can cause accelerated platelet destruction. Most cases are mild, and platelet levels usually reach a nadir at 48 to 72 hours. Maternal corticosteroid therapy generally has no effect on fetal platelets. Fetal blood sampling for platelet determination is seldom necessary, and platelets are usually adequate to prevent fetal hemorrhage during delivery (Chap. 56, Platelet Disorders).

Alloimmune Thrombocytopenia

Alloimmune thrombocytopenia (AIT) or neonatal alloimmune thrombocytopenia (NAIT) is caused by maternal-fetal platelet antigen disparity. If maternal alloimmunization is stimulated, then transplacental antiplatelet IgG antibodies cause severe fetal thrombocytopenia and severe bleeding (Winkelhorst, 2017). This is considered in detail in Chapter 15 (Fetal Thrombocytopenia).

Preeclampsia Syndrome

Maternal platelet function and destruction can be severely affected in women with severe preeclampsia. That said, fetal or neonatal thrombocytopenia is rarely caused by the preeclampsia syndrome even when the mother has severe thrombocytopenia. Findings from the large study of mother-infant pairs delivered at Parkland Hospital dispelled earlier reports of an association of neonatal thrombocytopenia with preeclampsia (Pritchard, 1987). Instead, neonatal thrombocytopenia was found to be associated with preterm delivery and its numerous complications (Chap. 34, Respiratory Distress Syndrome).

INJURIES OF THE NEWBORN

Birth injuries can potentially complicate any delivery. Thus, although some are more likely associated with operative delivery by forceps or vacuum, others are seen with otherwise uncomplicated vaginal or cesarean delivery. In this section, some injuries are discussed in general, but specific injuries are described elsewhere in connection with their associated obstetrical complications.

Incidence

In three population studies that included more than 8 million term newborns, the overall incidence of birth trauma was 20 to 26 per 1000 deliveries (Baskett, 2007; Linder, 2012; Moczygemba, 2010). Data from Nova Scotia show an overall trauma risk of 19.5 per 1000 deliveries (Table 33-4). Only 1.6 cases of major trauma per 1000 were found, and these rates were highest with failed forceps or vacuum delivery and lowest with cesarean delivery without labor. Thus, most traumatic injuries were minor, and these had an incidence of 18 per 1000 deliveries.

TABLE 33-4

Incidence of Major and Minor Birth Trauma—Nova Scotia, 1988–2001

Type of Delivery (Trauma Rate per 1000)		Birth Trauma (Rate per 1000)	
	Number	Major[a]	Minor[b]
Spontaneous (14)	88,324	1.2	13
Assisted			
Vacuum (71)	3175	3.7	67
Forceps (58)	10,478	5.2	53
Failed assisted			
Vacuum (105)	609	8.3	100
Forceps (56)	714	7.0	50
Cesarean (8.6)	16,132	0.3	8.3
Labor (12)	10,731	0.4	11.9
No labor (1.2)	5401	0.2	1.1
All (19.5)	119,432	1.6	18

[a]Major trauma = depressed skull fracture, intracranial hemorrhage, brachial plexopathy, or combination.

[b]Minor trauma = linear skull fracture, other fractures, facial palsy, cephalohematoma, or combination.

Data from Baskett, 2007.

Trauma associated with cesarean delivery from a Maternal-Fetal Medicine Units Network study was described by Alexander and coworkers (2006). There were 400 injuries identified from a total of 37,100 operations—a rate of 11 per 1000 cesarean deliveries. Although skin lacerations predominated—7 per 1000—more serious injuries in these 400 infants included 88 cephalohematomas, 11 clavicular fractures, 11 facial nerve palsies, nine brachial plexopathies, and six skull fractures.

Cranial Injuries

Traumatic head injuries that are associated with labor or delivery can be *external* and obvious, such as a skull or mandibular fracture; they can be *intracranial*; and in some, they are *covert*. The fetal head has considerable plasticity and can undergo appreciable molding. Rarely, severe molding can result in tearing of veins. These may be the bridging cortical veins that empty into the sagittal sinus, the internal cerebral veins, the vein of Galen, or those of the tentorium itself. As a result, intracranial, subdural, and even epidural hemorrhage can be seen after an apparently uneventful vaginal delivery (Scheibl, 2012). Bleeding may also be asymptomatic. Conversely, subgaleal hemorrhages associated with forceps of vacuum delivery can be life threatening (Doumouchtsis, 2008; Swanson, 2012). In rare severe head trauma cases, fetal brain tissue can embolize to the heart or lungs (Cox, 2009).

Intracranial Hemorrhage

Most aspects of neonatal intracranial hemorrhage are related to gestational age. Specifically, most hemorrhage in the preterm neonate results from hypoxia and ischemia. However, in term newborns, trauma is the most frequent cause. Some varieties are shown in Table 33-5. *Importantly, in some newborns, a putative cause is not found.* Intracranial hemorrhage is asymptomatic in many cases. The reported incidence varies, but it is highest with operative deliveries—both vaginal and cesarean deliveries. In the study by Moczygemba and colleagues (2010), for more than 8 million singleton deliveries, the overall intracranial hemorrhage rate approximated 0.2 per 1000 births. In another study, Werner and associates (2011) cited a combined incidence in more than 120,000 nulliparous singleton operative deliveries of 0.12 percent, or about 1 in 750 procedures. The rates of intracranial hemorrhage were 1:385 with vacuum delivery; 1:515 with forceps, and 1:1210 with cesarean delivery. In another study, its incidence was nearly 1 percent following vacuum-assisted deliveries (Simonson, 2007).

TABLE 33-5

Major Types of Neonatal Intracranial Hemorrhage

Type	Etiology and Neuropathogenesis	Clinical Outcomes
Subdural	Trauma—tentorial, falx, or venous (sinus) laceration causing hematoma	Uncommon but potentially serious; symptom onset is variable depending on hematoma expansion, but usually <24 hours: irritability, lethargy, and brainstem compression
Primary subarachnoid	Possibly due to trauma or hypoxia—excludes SAH associated with subdural, intraventricular, intracerebral (AVM, aneurysm), or intracerebellar hemorrhage	Common but almost always benign
Intracerebellar	Trauma and perhaps hypoxia—most cases in preterm infants	Uncommon but serious
Intraventricular	Trauma and hypoxia (no discernible cause in 25 percent)—hemorrhage usually from choroid plexus	Uncommon but serious; symptoms as for subdural hemorrhage
Miscellaneous	Trauma with epidural or intracerebral hemorrhage Hemorrhagic infarction—embolism or thrombosis in artery or vein Coagulopathies—thrombocytopenia or inherited factor deficiencies Vascular defect—aneurysm or AVM	Depends on cause

AVM = arteriovenous malformation; SAH = subarachnoid hemorrhage.

Data from Volpe, 1995.

According to the American College of Obstetricians and Gynecologists (2015), the incidence of intracranial hemorrhage from birth trauma has been substantively lowered by elimination of difficult instrumented vaginal deliveries. This was verified in a report of carefully conducted Kielland forceps deliveries (Burke, 2012).

The prognosis after hemorrhage depends on its location and extent (see Table 33-5). For example, subdural and subarachnoid hemorrhage seldom results in neurological abnormalities, whereas large hematomas are serious. Any bleeding into the parenchyma from intraventricular or intracerebellar hemorrhage often causes serious permanent damage or death. Periventricular hemorrhage rarely causes the type of sequelae that are common in those born preterm (Chap. 34, Retinopathy of Prematurity).

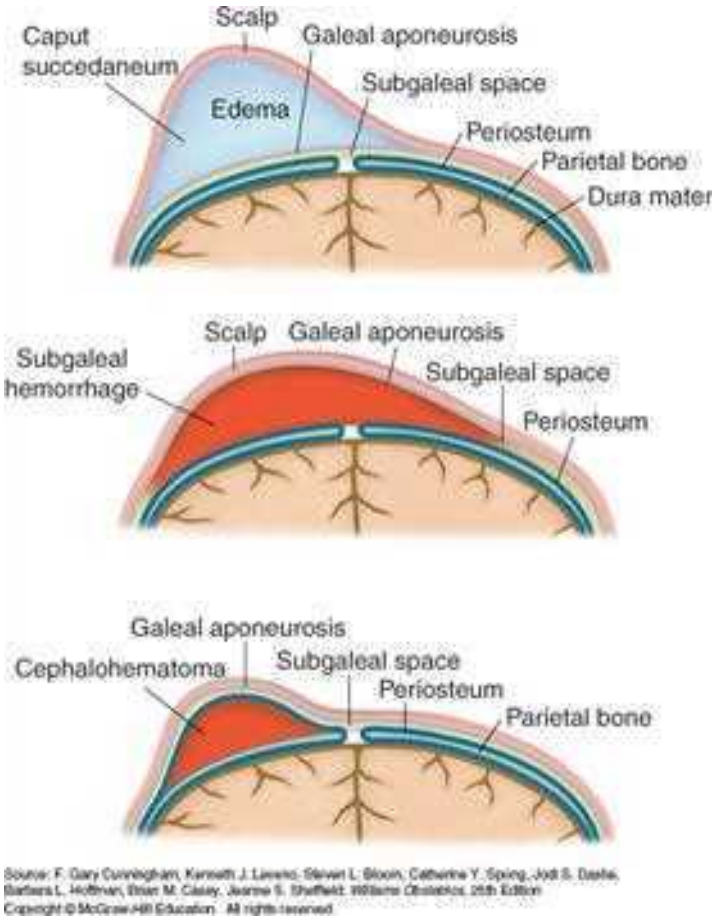
Newborns who have traumatic subdural or infratentorial hemorrhage tears will have neurological abnormalities from the time of birth (Volpe, 1995). Those most severely affected have stupor or coma, nuchal rigidity, and opisthotonos that worsen over minutes to hours. Some newborns who are born depressed appear to improve until about 12 hours of age, when drowsiness, apathy, feeble cry, pallor, failure to nurse, dyspnea, cyanosis, vomiting, and convulsions become evident.

Spontaneous intracranial hemorrhage has also been documented in healthy term neonates (Rutherford, 2012; Shah, 2016). In a prospective MR imaging study, Whitby and coworkers (2004) found that 6 percent of those delivered spontaneously and 28 percent of those delivered by forceps had a subdural hemorrhage. None of these had clinical findings, and hematomas resolved by 4 weeks in all infants.

Extracranial Hematomas

These blood collections accumulate outside the calvarium and are categorized as a *cephalohematoma* or *subgaleal hemorrhage* (Fig. 33-2). From its most superficial surface inward, the scalp is composed of skin, subcutaneous tissue, galea aponeurotica, subgaleal space, and calvarium periosteum. The galea aponeurotica is dense fibrous tissue, whereas the subgaleal space contains loose, fibroareolar tissue. Traversing across the subgaleal space are large, valveless *emissary veins*, which connect the dural sinuses inside the skull with superficial scalp veins. Both the galea aponeurotica and subgaleal space span across the occipital, parietal, and frontal bones. In contrast, periosteum invests each individual skull bone and does not cross suture lines.

FIGURE 33-2
Schematic of extracranial lesions in the neonate that include caput succedaneum, subgaleal hemorrhage, and cephalohematoma.



Cephalohematomas are cranial subperiosteal hematomas. These develop from shearing forces during labor and delivery that lacerate the emissary or diploic veins. Fortunately, the densely adhered periosteum impedes rapid enlargement and limits final hematoma size. Hemorrhage can be over one or both parietal bones, but palpable edges can be appreciated as the blood reaches the limits of the periosteum. These hematomas must be differentiated from *caput succedaneum*, also shown in Figure 33-2. A cephalohematoma may not be apparent until hours after delivery, when bleeding sufficient to raise the periosteum has occurred. After it is identified, it often grows larger and persists for weeks or even months, and bleeding may be sufficient to cause anemia as discussed in Neonatal Abstinence Syndrome. By contrast, with caput succedaneum, swelling of the scalp is from soft-tissue edema that overlies the periosteum. The caput is maximal at birth, rapidly grows smaller, and usually disappears within hours or a few days. Occasionally it becomes infected, and an abscess may form (Kersten, 2008).

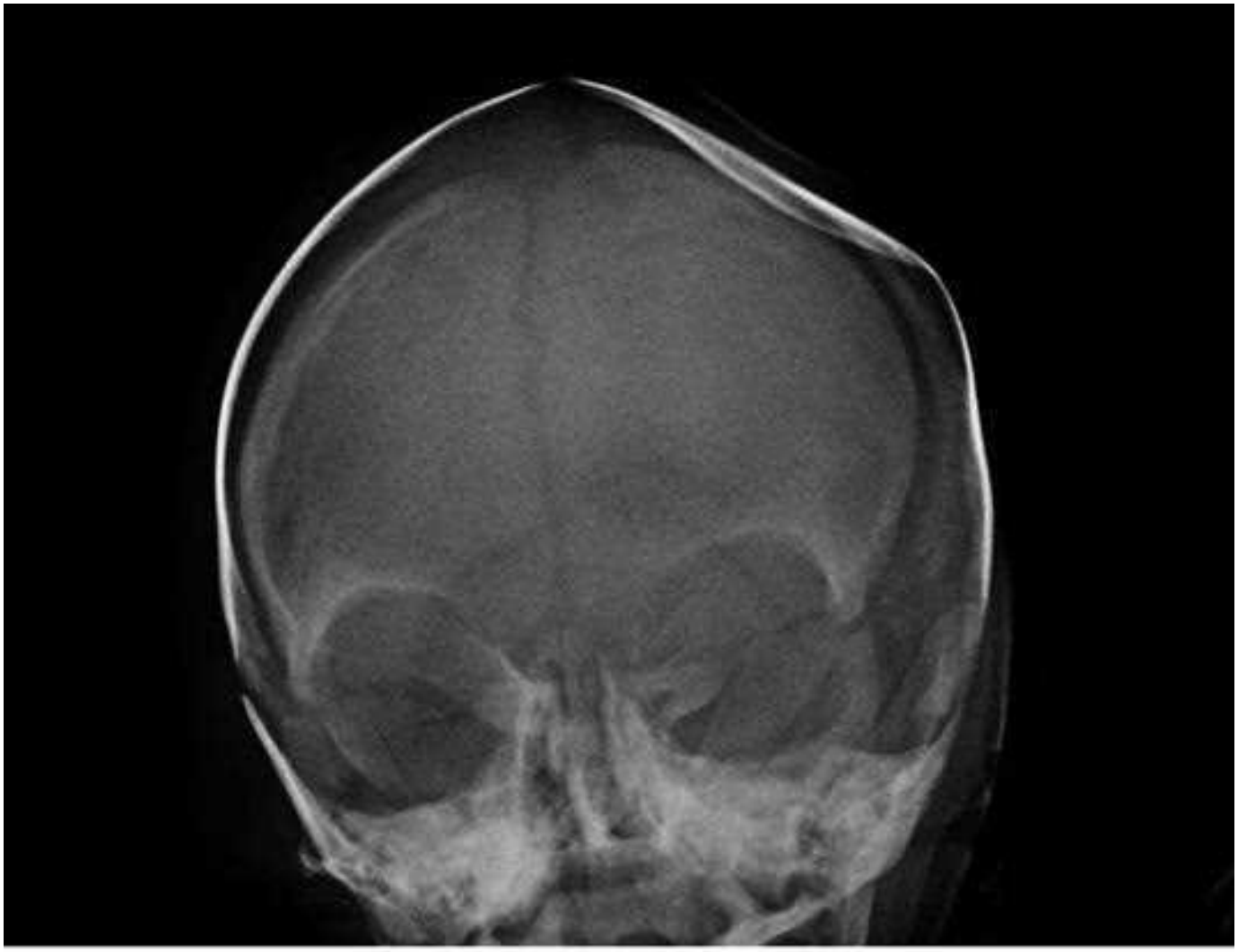
Cephalohematomas are common, and in the study from Nova Scotia shown in Table 33-3, these accounted for 80 percent of traumatic injuries with an incidence of 16 per 1000 (Baskett, 2007). They rarely develop in the absence of birth trauma, and an 11-percent incidence was reported in 913 term newborns delivered by vacuum extraction (Simonson, 2007). In the Network study of cesarean delivery outcomes cited above, the incidence of cephalohematoma was 2.4 per 1000 operations (Alexander, 2006). Others have reported lower incidences, although cephalohematoma is more common with vacuum compared with forceps deliveries—0.8 versus 2.7 per 1000 operative deliveries (Werner, 2011).

Subgaleal hemorrhage results from laceration of one of the emissary veins, with bleeding between the galea aponeurotica and the skull periosteum (Shah, 2016). Although most common with operative deliveries, cases with spontaneous vaginal delivery have been described (Liu, 2017). Because of its loose areolar tissue and large surface area, significant blood volumes can collect in this potential space and can extend from the neck to the orbits and laterally to the temporal fascia above the ears (Modanlou, 2016). Resulting hypotension can lead to significant morbidity, and cited mortality rates range from 12 to 18 percent (Chang, 2007; Kilani, 2006).

Skull Fractures

These are rare but are especially worrisome because of their association with the serious intracranial hemorrhages. Volpe (1995) considers three types of skull injuries to be fractures—linear and depressed fractures and occipital osteodiastasis. In a French study of nearly 2 million deliveries from 1990 to 2000, the incidence of skull fractures was reported to be 3.7 per 100,000 births, and 75 percent were associated with instrumented vaginal deliveries (Dupuis, 2005). These are occasionally seen with spontaneous or cesarean delivery (Fig. 33-3). These latter fractures are more common when the head is tightly wedged in the pelvis. In such cases, there are at least three possible causes. A fracture may result from skull compression against the sacral promontory, by hand pressure used to lift the head at cesarean delivery, or from transvaginally applied upward hand pressure by an assistant. Fractures are managed with surgical decompression, although spontaneous resolution can follow (Basaldella, 2011).

FIGURE 33-3
Depressed skull fracture evident immediately after cesarean delivery. Labor had progressed, and the head was deep in the pelvis. Dislodgment of the head from the birth canal was performed by an assistant using manual pressure upward through the vagina. (Used with permission from Dr. Kimberly M. Spoonts.)



Spinal Cord Injury

Overstretching of the spinal cord and associated hemorrhage and edema are rare. They are usually caused by excessive longitudinal or lateral traction of the spine or by torsion during delivery. In some cases, vertebrae are fractured or dislocated. Menticoglou and associates (1995) described 15 neonates with this type of high cervical spinal cord injury and found that all of the injuries were associated with forceps rotations. Spinal cord injury also can occur during breech delivery. Ross and coworkers (2006) described C_{5-6} vertebral dislocation associated with a Zavanelli maneuver done because of shoulder dystocia (Chap. 27, Shoulder Dystocia Drill).

Peripheral Nerve Injuries

Traumatic injuries to nerves can be serious and distressing, especially if permanent. Injury can involve a single nerve, or it can affect a nerve root, plexus, or trunk (Volpe, 1995).

Brachial Plexopathy

Injuries to the brachial plexus are relatively common. They are identified in 1 to 3 per 1000 term births (Baskett, 2007; Lindqvist, 2012; Wall, 2014). In the study reported by Moczygemba and colleagues (2010), the incidence of brachial nerve injury was 1.5 per 1000 vaginal deliveries and 0.17 per 1000 cesarean deliveries. The incidence among 366,408 neonates born at Parkland Hospital was 3.5 per 1000 births (Wall, 2014). Breech delivery and shoulder dystocia are risks for this trauma. However, severe plexopathy may also occur without risk factors (Torki, 2012).

With plexopathy, the injury damages the nerve roots that supply the brachial plexus—C_{5-8} and T_1. With hemorrhage and edema, axonal function may be temporarily impaired, but the recovery chances are good. However, with avulsion, the prognosis is poor. In 90 percent of cases, damage to the C_{5-6} nerve roots causes *Erb* or *Duchenne paralysis* (Volpe, 1995). Injuries with breech delivery are normally of this type, whereas the more extensive lesions follow difficult cephalic deliveries (Ubachs, 1995). The C_{5-6} roots join to form the upper trunk of the plexus, and injury leads to paralysis of the deltoid, infraspinatus, and flexor muscles of the forearm. The affected arm is held straight and internally rotated, the elbow is extended, and the wrist and fingers flexed. Finger function usually is retained. Because lateral

traction on the fetal head is frequently employed to effect delivery of the shoulders in normal vertex presentations, most cases of Erb paralysis follow deliveries that do not appear difficult.

Damage to the C_8-T_1 roots supplying the lower plexus results in *Klumpke paralysis,* in which the hand is flaccid. Total involvement of all brachial plexus nerve roots results in flaccidity of the arm and hand, and with severe damage, there may also be *Horner syndrome*.

Because of its importance, the American College of Obstetricians and Gynecologists (2014a) convened a task force to review extant studies. This Task Force concluded that shoulder dystocia cannot be accurately predicted, but in most cases, axonal death does not occur and the prognosis is good. Lindqvist and associates (2012) reported complete recovery in 86 percent of children with $C_{5–6}$ trauma, which was the most common injury, and in 38 percent of those with $C_{5–7}$ damage. However, those with global $C_{5–8}$–T_1 injuries always had permanent disability. Associated clavicular fracture is somewhat protective (Wall, 2014). Surgical exploration and possible repair may improve function if there is persistent paralysis (Malessy, 2009).

Facial Paralysis

Trauma to the facial nerve commonly occurs as it emerges from the stylomastoid foramen, and this can cause facial paralysis (Fig. 33-4). The incidence, which ranges from 0.2 to 7.5 per 1000 term births, is likely influenced by the vigor with which the diagnosis is sought (Al Tawil, 2010; Moczygemba, 2010). Facial paralysis may be apparent at delivery or may develop shortly after birth. It most frequently is associated with uncomplicated vaginal delivery. However, in one series, a fourth of cases followed cesarean delivery (Alexander, 2006; Al Tawil, 2010). Facial nerve damage is likely more common with low forceps (Levine, 1984). It is possible that damage is caused by pressure exerted by the posterior blade when forceps have been placed obliquely on the fetal head. In these cases, forceps marks indicate the cause of injury. Spontaneous recovery within a few days is the rule, however, permanent paralysis has been described (Al Tawil, 2010).

FIGURE 33-4
Left facial nerve injury. This was almost completely resolved two days after delivery.

Fractures

Most long-bone fractures follow difficult deliveries, however, this is not always the case. At minimum, palpation of the clavicles and long bones is indicated for all newborns after a difficult delivery. Crepitation or unusual irregularity should prompt radiographic examination.

Clavicular fractures are common, unpredictable, and unavoidable complications of normal birth. Their incidence averages 5 to 10 per 1000 live births (Linder, 2012; Moczygemba, 2010). Other than female gender, no specific risk factors—including birthweight and mode of delivery—have been identified. Clavicular fractures protect against brachial plexopathy when there is shoulder dystocia (Wall, 2014).

Humeral fractures are infrequent, and 70 percent follow an uneventful birth (Turpenny, 1993). Others are associated with difficult delivery of the shoulders in cephalic deliveries and of an extended arm in breech deliveries. Radiographically, they are often of the greenstick type, although complete fractures and distal

humeral epiphyseal fractures can occur (Tharakan, 2016).

Femoral fractures are rare and usually are associated with vaginal breech delivery. They occasionally follow cesarean delivery, and in one report, they were bilateral (Cebesoy, 2009). Because most breech-presenting fetuses now undergo cesarean delivery, most of these fractures are associated with this mode (Alexander, 2006; Cebesoy, 2009).

Mandibular fractures have been reported, are rare, and have been reviewed by Vasconcelos and coworkers (2009). The rare cases of *cervical vertebral dislocation* in fetuses delivered as breech or after the Zavanelli maneuver were discussed earlier (Ross, 2006). Finally, *rib fractures* are occasionally encountered (Khan, 2016).

Muscle Injuries

Sternocleidomastoid muscle injury in the past was usually seen with vaginal breech delivery. Hematomas of the muscle or the fascial sheath may resolve slowly with cicatricial contraction. With normal neck growth, the less-elastic damaged muscle does not elongate appropriately. As a result, the head is gradually turned toward the side of the injury—*torticollis.*

Soft Tissue Injuries

Conceivably, any fetal organ or part could be injured with either vaginal or cesarean delivery. Some of these include subcapsular hepatic hematomas that presented as inguinal and scrotal hematoma. In such cases, ecchymoses of the inguinal region are termed *Stabler sign,* and those of the scrotum are termed *Bryant sign* (Heyman, 2011; Saroha, 2015). Thymic gland traumatic hemorrhage in those with underlying hyperplasia or cyst has been described before, during, and after delivery (Eifinger, 2007; Saksenberg, 2001). Injuries to the sixth cranial nerve with resultant lateral rectus ocular muscle paralysis have also been reported (Galbraith, 1994).

Congenital Deformity Injuries

Several injuries create morphological defects sustained long before delivery. One is the amnionic band syndrome caused when a free strip of amnion forms a focal ring around an extremity or digit. Eventually, deformation or amputation may result. Occasionally, the amputated part may be found within the uterus. The genesis of such bands is debated and discussed in Chapter 6 (Amniochorion). A similar anomaly is a *limb-reduction defect* associated with chorionic villus sampling performed before 9 weeks' gestation (Chap. 14, Fetal Blood Sampling).

Various congenital postural anomalies form when a normally developed fetal structure becomes deformed by intrauterine mechanical factors. Examples of the latter include chronic oligohydramnios, as well as restricted fetal movement imposed by an abnormally shaped or small uterine cavity or by the presence of additional fetuses. Some mechanical deformations include talipes equinovarus (clubfoot), scoliosis, and hip dislocation (Miller, 1981). Talipes and other positional foot abnormalities are associated with membrane rupture from early amniocentesis between 11 and 13 weeks' gestation (Chap. 14, Chorionic Villus Sampling).

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CHAPTER 34: The Preterm Newborn

> *The prognosis for the child depends, of course, upon the degree of development, as well as the pathological condition for which premature delivery is undertaken. Generally speaking, in the case of children born before the thirty-second week, the chances of surviving are very small.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

At the time of this textbook's first edition, preterm delivery of a living newborn was frequently followed by neonatal death. Contrast this with today's technological advances that have advanced the threshold of viability to 22 to 24 weeks' gestation. Even so, the preterm newborn is susceptible to various serious medical complications both early and later in life (Table 34-1). A less commonly cited cause of morbidity and mortality is congenital malformations, which are much more prevalent in preterm births.

TABLE 34-1

Complications of Prematurity

Respiratory distress syndrome (RDS)
Hyaline membrane disease (HMD)
Bronchopulmonary dysplasia (BPD)
Pneumothorax
Pneumonia/sepsis
Patent ductus arteriosus (PDA)
Necrotizing enterocolitis (NEC)
Retinopathy of prematurity (ROP)
Intraventricular hemorrhage (IVH)
Periventricular leukomalacia (PVL)
Cerebral palsy (CP)

These complications of prematurity can be placed in perspective in terms of overall neonatal outcomes. In 2009, two thirds of all infant deaths in the United States were in the 12 percent born before 37 weeks (Mathews, 2013). Fortunately, during the past decade, rates of preterm birth have declined from approximately 12 percent in 2007 to 10 percent in 2014. This is in part due to a decline in births to teen mothers (Ferré, 2016).

RESPIRATORY DISTRESS SYNDROME

The seminal complication of the preterm newborn is *respiratory distress syndrome (RDS)*. This results from immature lungs that are unable to sustain necessary oxygenation. Resulting hypoxia is an underlying associated cause of neurological damage such as cerebral palsy. In addition, hyperoxia, a side effect of RDS treatment, contributes to morbidities such as bronchopulmonary dysplasia, pulmonary hypertension, necrotizing enterocolitis, periventricular leukomalacia, and retinopathy of prematurity.

Etiopathogenesis

To provide blood gas exchange immediately following delivery, the lungs must rapidly fill with air while being cleared of fluid. Concurrently, pulmonary arterial blood flow must rise remarkably. Although some of the fluid is expressed as the chest is compressed during vaginal delivery, most is absorbed through the pulmonary lymphatics via complex mechanisms described in Chapter 32 (Transition to Air Breathing). Sufficient surfactant, synthesized by type II pneumocytes, is essential to stabilize the air-expanded alveoli. It lowers surface tension and thereby prevents lung collapse during expiration (Chap. 7, Respiratory System). If surfactant is inadequate, hyaline membranes form in the distal bronchioles and alveoli, and RDS develops. Although respiratory distress syndrome is generally a disease of preterm neonates, it does develop in term newborns, especially with sepsis or meconium aspiration. In these cases, surfactant can be inactivated by inflammation and/or presence of meconium (Chap. 33, Respiratory Distress).

With inadequate surfactant, alveoli are unstable, and low pressures cause collapse at end expiration. Pneumocyte nutrition is compromised by hypoxia and systemic hypotension. Partial persistence of the fetal circulation may lead to pulmonary hypertension and a relative right-to-left shunt. Eventually, alveolar cells undergo ischemic necrosis. When oxygen therapy is initiated, the pulmonary vascular bed dilates, and the shunt reverses. Protein-filled fluid leaks into the alveolar ducts, and the cells lining the ducts slough. Hyaline membranes composed of fibrin-rich protein and cellular debris line the dilated alveoli and terminal bronchioles. The epithelium underlying the membrane becomes necrotic. At autopsy, with hematoxylin-eosin staining of lung tissue, these membranes appear amorphous and eosinophilic, like hyaline cartilage. Because of this, respiratory distress syndrome is also termed *hyaline membrane disease.*

Clinical Course

In typical RDS, tachypnea develops, the chest wall retracts, and expiration is accompanied by nostril flaring and by grunting—in an attempt to provide a positive end-expiratory pressure to prevent lung collapse. Shunting of blood through nonventilated lung contributes to hypoxemia and to metabolic and respiratory acidosis. Poor peripheral circulation and systemic hypotension may be evident. The chest radiograph shows a diffuse reticulogranular infiltrate and an air-filled tracheobronchial tree—*air bronchogram*.

As discussed further in Chapter 33 Respiratory Distress, respiratory insufficiency can also be caused by sepsis, pneumonia, meconium aspiration, pneumothorax, persistent fetal circulation, heart failure, and malformations involving thoracic structures, such as diaphragmatic hernia. Common mutations in surfactant protein production and the phospholipid transporter (ABCA3) contribute to RDS (Beers, 2017; Tredano, 2003; Wert, 2009).

Treatment

An important factor influencing survival is neonatal intensive care. Although hypoxemia prompts supplemental oxygen, excess oxygen can damage the pulmonary epithelium, retina, and other immature tissues. Despite this, advances in mechanical ventilation technology have improved neonatal survival rates. For example, *continuous positive airway pressure (CPAP)* prevents the collapse of unstable alveoli. This allows high inspired-oxygen concentrations to be reduced, thereby minimizing its toxicity. In an attempt to

minimize the need for tracheal intubation and intermittent positive-pressure ventilation, CPAP has been studied in well-designed multicenter trials (Morley, 2008; SUPPORT Study Group, 2010b). An initial CPAP strategy with subsequent selective surfactant use is a beneficial alternative to immediate intubation and surfactant for many neonates of extremely early gestational age (American Academy of Pediatrics, 2014).

Mechanical ventilation has undoubtedly improved survival rates but is an important factor in the genesis of chronic lung disease of prematurity—*bronchopulmonary dysplasia (BPD)*. Namely, mechanical ventilation places a newborn at risk for barotrauma and volutrauma. Moreover, hyperoxia can create reactive oxygen species that trigger inflammation. Infection can also be contributory. In affected newborns, alveolar and pulmonary vascular development is disrupted and leads to hypoxia, hypercarbia, and chronic oxygen dependence (Davidson, 2017; Kair, 2012).

As prevention, *high-frequency oscillatory ventilation* has been evaluated. However, benefits and risks varied considerably between studies (Cools, 2015).

Treatment of the ventilator-dependent neonate with *glucocorticoids* was also used previously to prevent BPD. The American Academy of Pediatrics now recommends against routine steroid use because of limited benefits and greater rates of impaired motor and cognitive function and school performance in exposed neonates (Doyle, 2014a,b; Watterberg, 2010).

In other efforts for BPD prevention, early animal studies demonstrated significant improvements in lung function with weeks of *inhaled nitric oxide* (McCurnin, 2005). Despite initial enthusiasm, clinical trials failed to demonstrate a consistent benefit. A National Institutes of Health (NIH) consensus statement and the American Academy of Pediatrics (2014) concluded that the available data do not support its use to prevent or treat BPD (Cole, 2011).

Caffeine has been used widely to treat apnea of prematurity, but it also has bronchodilatory effects. One large randomized trial of caffeine versus placebo showed lower BPD rates, improved neurodevelopmental outcomes during early childhood, and good evidence of safety up to 11 years (Schmidt, 2006, 2012, 2017). This therapy is now widely used for newborns weighing ≤1250 g.

The antioxidant *vitamin A* is necessary for normal lung growth and the integrity of respiratory tract epithelial cells. Preterm newborns have low vitamin A levels at birth, and this has been associated with a greater risk of developing BPD. Randomized trials support the use of vitamin A to achieve a modest reduction in BPD rates for very-low-birthweight neonates weighing <1500 g (Darlow, 2016).

Surfactant Prophylaxis and Rescue

Exogenous surfactant products are delivered via endotracheal tube to help prevent RDS. They contain biological or animal surfactants such as bovine—*Survanta*, calf—*Infasurf*, or porcine—*Curosurf*. Synthetic surfactants such as first-generation *Exosurf* and second-generation *Surfaxin R* are equivalent but not superior to animal-derived surfactant (Moya, 2007). In a Cochrane review, Ardell and coworkers (2015) found that

animal-derived surfactants led to better outcomes than synthetic surfactants, which do not contain important surfactant proteins. There are currently no synthetic surfactants available.

Surfactant replacement was established decades ago as an effective and safe therapy for RDS. Treatment reduces rates of mortality and pneumothorax and improves survival without BPD (Polin, 2014). It has been used for *prophylaxis* of preterm, at-risk newborns and for *rescue* of those with established disease. Given together, antenatal corticosteroids and surfactant result in an even greater reduction in the overall death rate. However, randomized trials indicate that in populations with high use of antenatal steroids and routine use of CPAP in the delivery room, prophylactant surfactant is no longer beneficial and is associated with more risk of death or BPD (Rojas-Reyes, 2012; Sardesai, 2017). Exploration of different, less invasive ways to deliver rescue surfactant to spontaneously breathing preterm neonates is currently underway. Potential routes include surfactant application into the pharynx, surfactant nebulization, or application via laryngeal mask or via a thin catheter placed in the trachea (Kribs, 2016).

Prevention

Antenatal Corticosteroids

The NIH (1994, 2000) has concluded that a single course of antenatal corticosteroid therapy reduces RDS and intraventricular hemorrhage rates in preterm neonates born between 24 and 34 weeks' gestation (Cerebral Palsy). The American College of Obstetricians and Gynecologists (2016a) considers all women at risk for preterm birth in this gestational-age range to be potential candidates for therapy. It also may be considered for pregnant women starting at 23 weeks' gestation who are at risk of preterm delivery within 7 days. This is discussed further is Chapter 42 (Corticosteroids for Fetal Lung Maturation). More recently, administration of antenatal corticosteroids to women at risk for late-preterm delivery (34 to 36 weeks' gestation) was found to significantly reduce the rate of neonatal respiratory complications (Gyamfi-Bannerman, 2016).

Amniocentesis to Assess Fetal Lung Maturity

In some instances, when gestational age is uncertain, knowledge of fetal lung maturity may influence plans for delivery. One example is the woman with a prior classical cesarean delivery in whom repeat operation is planned and gestational age cannot be confirmed. Several tests are used to ensure fetal pulmonary maturity by analysis of amnionic fluid obtained by sonographically guided amniocentesis. At Parkland Hospital, we still find an occasional indication for such testing, however, the American College of Obstetricians and Gynecologists (2017a,b) counsels against its use in most of these cases. Instead the College recommends late-term delivery at "41 weeks' gestation" using the best clinical estimate of gestational age (Chap. 10 Gestational Age Assessment).

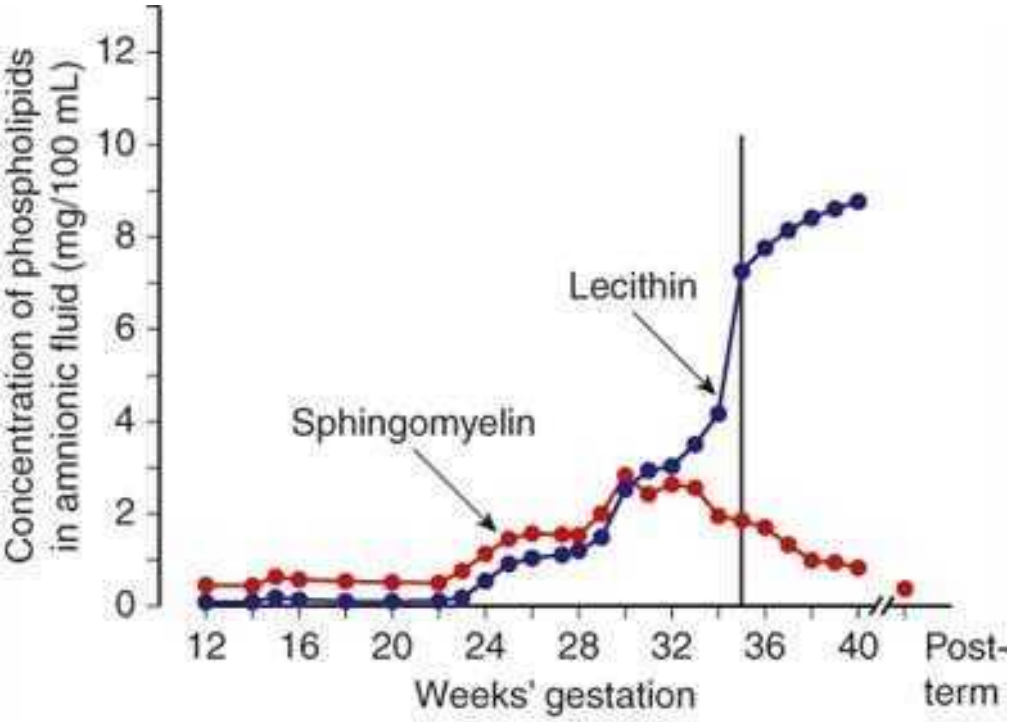
If amniocentesis is elected, fluid acquisition is similar to that described for second-trimester amniocentesis (Chap. 14, Technique). Complications requiring urgent delivery are rare (Zalud, 2008). Following analysis, the probability of RDS developing in a given newborn depends on the test used and fetal gestational age.

Importantly, administration of corticosteroids to induce pulmonary maturation has variable effects on some of these tests. Varner and colleagues (2013) have provided a review of testing options.

Of biochemical tests, the labor-intensive *lecithin-sphingomyelin (L/S) ratio* for many years was the gold-standard test. Dipalmitoylphosphatidylcholine (DPPC), that is, *lecithin*, and *sphingomyelin* are surfactant components. Before 34 weeks, both are present in amnionic fluid in similar concentrations. At 32 to 34 weeks, the concentration of lecithin relative to sphingomyelin begins to rise (Fig. 34-1). The risk of neonatal RDS is slight whenever the concentration of lecithin is at least twice that of sphingomyelin—L/S ratio >2 (Gluck, 1971). Previously, RDS was thought to develop despite an L/S ratio >2 in newborns of women with diabetes. Some recommend that *phosphatidylglycerol*, another surfactant phospholipid, be documented in amnionic fluid of these women. Based on current evidence, it is unclear if either diabetes, per se, or its level of control causes false-positive phospholipid test results for fetal lung maturity (De Luca, 2009).

FIGURE 34-1

Changes in mean concentrations of lecithin and sphingomyelin in amnionic fluid during gestation in normal pregnancy. (Modified with permission from Gluck L, Kulovich MV: Lecithin-sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancy, Am J Obstet Gynecol. 1973 Feb 15;115(4):539–546.)



Of biophysical tests, the *fluorescence polarization test* is an automated assay that measures the surfactant-to-albumin ratio in uncentrifuged amnionic fluid and gives results in less than an hour. Investigators found the TDx-FLM to be equal or superior to the L/S ratio, foam stability index, or phosphatidylglycerol assessment. This included testing in diabetic pregnancies (Karcher, 2005; Varner, 2013). The modified *TDx-FLM II* is used by many hospitals as their primary test of pulmonary maturity. Thresholds vary by gestational age (Bennasar, 2009). The *foam stability* or *shake test* relies on the ability of surfactant in amnionic fluid, when mixed appropriately with ethanol, to generate stable foam at the air–liquid interface (Clements, 1972).

Problems include errors caused by slight contamination and frequent false-negative test results. Of other tests, the *Lumadex-FSI test, fluorescent polarization (microviscometry),* and *amnionic fluid absorbance at 650-nm wavelength* have all been used with variable success.

The *lamellar body count* is a rapid, simple, and accurate method of assessing fetal lung maturity and is comparable to TDx-FLM and L/S ratio accuracy (Karcher, 2005; Varner, 2013).

NECROTIZING ENTEROCOLITIS

This newborn bowel disorder has clinical findings that include abdominal distention, emesis, ileus, bilious gastric aspirates, and bloody stools. There is often radiological evidence of *pneumatosis intestinalis*—bowel wall gas derived from invading bacteria. Other classic imaging findings include hepatobiliary gas and pneumoperitoneum. Bowel perforation may prompt resection. Necrotizing enterocolitis (NEC) is seen primarily in low-birthweight newborns but occasionally is encountered in mature neonates. Various hypothesized causes include perinatal hypotension, hypoxia, sepsis, umbilical catheterization, exchange transfusions, blood transfusions, and the feeding of cow milk and hypertonic solutions (Neu, 2010). The pathophysiology is thought to be multifactorial, and genetic disposition, intestinal immaturity, imbalance in microvascular tone, abnormal microbial colonization in the intestine, exposure to enteral feeds, and highly immunoreactive intestinal mucosa play potential roles (Caplan, 2017; Neu, 2010).

Medical treatment includes abdominal decompression, bowel rest, broad-spectrum antibiotics, and parenteral nutrition. Surgery is reserved for neonates with intestinal perforation or deteriorating clinical or biochemical status. Possible surgical procedures include drain placement, exploratory laparotomy with resection of diseased bowel, or enterostomy with creation of a stoma (Neu, 2010).

RETINOPATHY OF PREMATURITY

By 1950, this condition, formerly known as *retrolental fibroplasia,* became the largest single cause of blindness in this country. After the discovery that the disease resulted from hyperoxemia, its frequency declined but began to rise again with the increasing survival rates of extremely preterm newborns.

Normally, the fetal retina vascularizes centrifugally from the optic nerve starting at approximately the fourth month and continues until shortly after birth. During vascularization, excessive oxygen induces severe retinal vasoconstriction with endothelial damage and vessel obliteration. This is followed by subsequent aberrant neovascularization, in which the new vessels penetrate the retina and extend into the vitreous. Here, they are prone to leak proteins or burst with subsequent hemorrhage. Adhesions can form to detach the retina. Vascular endothelial growth factor (VEGF) plays an important role in normal angiogenesis and is upregulated during retinopathy of prematurity (ROP) development (Sharma, 2017). This understanding has opened new avenues of treatment with anti-VEGF therapies.

Precise levels of hyperoxemia that can be sustained without causing ROP are unknown. After birth, there is a “relative” hyperoxia compared with in utero oxygen content, even in newborns not exposed to higher

inspired oxygen concentrations. To better understand the oxygen saturation threshold necessary to minimize ROP without raising rates of other adverse outcomes, the Neonatal Research Network performed a randomized trial of oxygenation in 1316 neonates born between 24 and 27 weeks' gestation (SUPPORT Study Group, 2010a). The two target ranges of oxygen saturation were 85 to 89 percent in one arm and 91 to 95 percent in the other arm. These targets were both commonly employed in neonatal intensive care units. Death before discharge occurred significantly more frequently in the lower-oxygen saturation group—20 versus 16 percent. However, severe ROP among survivors developed significantly less often in the lower-oxygen saturation group—8.6 versus 17.9 percent.

BRAIN DISORDERS

Central nervous system injury usually creates different neuroanatomical sequelae in preterm newborns compared with those at term (Chap. 33, Neonatal Encephalopathy). In preterm neonates, cerebral lesions detected by neuroimaging include intraventricular hemorrhage, cerebellar hemorrhage, periventricular hemorrhagic infarction, cystic periventricular leukomalacia, and diffuse white matter injury. All of these are strongly associated with adverse neurodevelopmental outcomes (Kwon, 2014).

Cranial sonography remains the preferred approach for detecting frequently occurring brain abnormalities and acute events. It is readily available and reliable for detecting common abnormalities and monitoring brain growth. Because cystic injuries may take 2 to 5 weeks to evolve, serial scans are obtained during this time. In those whose findings are transient and resolve in the neonatal period, prognosis is improved compared with infants whose lesions remain and evolve. At the same time, however, between 4 and 10 percent of prematurely born children may develop cerebral palsy (CP) in the absence of lesions. Put another way, 90 to 96 percent of preterm newborns with CP have cerebral lesions that are detectable using cranial sonography.

Intracranial Hemorrhage

There are five major categories of intracranial hemorrhage in the neonate (Volpe, 2008). *Primary subarachnoid hemorrhage* is more common in those born preterm and is frequently benign. *Cerebellar hemorrhage* is also more frequent in preterm neonates and is increasingly recognized as a cause of serious sequelae. *Intraventricular hemorrhage (IVH)* is almost exclusively seen in preterm newborns, is relatively common, and can have serious effects. *Subdural hemorrhages* are more frequent in term newborns and can be serious. *Miscellaneous intraparenchymal hemorrhage* is also more frequent in those born at term and is of variable concern.

Periventricular–Intraventricular Hemorrhage

In preterm infants, the germinal matrix capillary network is fragile for several reasons. First, the subependymal germinal matrix provides poor support for the vessels coursing through it. Second, venous anatomy in this region causes stasis and congestion, which makes vessels susceptible to bursting if

intravascular pressure rises. Third, vascular autoregulation is impaired in the preterm neonate (Matsuda, 2006; Verhagen, 2014).

If fragile capillaries in the germinal matrix rupture, blood escapes into surrounding tissues and may extend into the ventricular system and brain parenchyma. This type of hemorrhage is common in preterm neonates, especially those born before 32 weeks. However, it can also develop at later gestational ages and even in term neonates. Most hemorrhages develop within 72 hours of birth, but they have been observed as late as 24 days (Whitelaw, 2011). Because IVH usually is recognized within 3 days of delivery, its genesis is often erroneously attributed to birth events. It is important to realize that *prelabor* IVH can also occur (Achiron, 1993; Nores, 1996).

The pathogenesis of IVH is multifactorial and includes hypoxic-ischemic events, carbon dioxide elevations, anatomical factors, blood pressure instability, coagulopathy, genetic factors, and many others (McCrea, 2008; Ment, 2016). Moreover, preterm birth is frequently associated with infection, which further predisposes to endothelial activation, platelet adherence, and thrombi (Redline, 2008). Respiratory distress and mechanical ventilation are commonly associated factors (Sarkar, 2009).

Almost half of hemorrhages are clinically silent. Most small germinal matrix hemorrhages and those confined to the cerebral ventricles resolve without impairment. But, nearly half do show some sign of neurological impairment (Patra, 2006). Survivors of extensive periventricular/intraventricular hemorrhage can have major neurodevelopmental handicaps (Mukerji, 2015). Large lesions can result in hydrocephalus or in degenerated cystic areas termed *periventricular leukomalacia (PVL)*, discussed below. Importantly, the extent of PVL correlates with CP risk (Bassan, 2006).

Incidence and Severity

Ventricular hemorrhage incidences depends on gestational age at birth. From the Neonatal Research Network, approximately 65 percent of all neonates born before 28 weeks' gestation demonstrated some evidence of hemorrhage or PVL (Stoll, 2010). The incidence ranged from 60 percent in those born at 23 weeks to only 23 percent in those at 28 weeks. Importantly, grade IV intraventricular hemorrhage was documented in 21 percent of 23-week-old neonates but in only 3 percent of those at 28 weeks.

The severity of IVH can be assessed by neuroimaging studies. Papile and coworkers (1978) devised the most widely used grading scheme to quantify the extent of a lesion and estimate prognosis:

Grade I—hemorrhage limited to the germinal matrix

Grade II—intraventricular hemorrhage

Grade III—hemorrhage with ventricular dilation

Grade IV—parenchymal extension of hemorrhage.

Antenatal Corticosteroids

If given at least 24 hours before delivery, corticosteroids prevent or reduce the incidence and severity of IVH (Wei, 2016). A Consensus Development Conference of the NIH (1994) concluded that such therapy reduced rates of mortality, RDS, and IVH in preterm neonates born between 24 and 32 weeks' gestation. A second consensus statement by the NIH (2000) recommended that repeated courses of corticosteroids not be given (Chap. 42, Corticosteroids for Fetal Lung Maturation).

Subsequently, the Maternal–Fetal Medicine Units Network reported that repeated corticosteroid courses were associated with some improved preterm neonatal outcomes, but also with reduced birthweight and increased risk for fetal-growth restriction (Wapner, 2006). Surveillance of this cohort through age 2 to 3 years found that children exposed to repeated versus single-dose steroid courses did not differ significantly in physical or neurocognitive measures (Wapner, 2007). It was worrisome, however, that there was a nonsignificant 5.7-fold relative risk of CP in infants exposed to multiple steroid courses.

At the same time, the 2-year follow-up of the Australian Collaborative Trial was reported by Crowther and coworkers (2007). In more than 1100 newborns, the incidence of CP was almost identical—4.2 versus 4.8 percent—in those given repeated versus single-course steroids, respectively. More recently, it was reported that for those born before 28 weeks' gestation, if 10 days or more had passed since betamethasone administration, the incidence of severe IVH was higher (Liebowitz, 2016).

The most recent recommendations from the American College of Obstetricians and Gynecologists (2016a) are for a single course of corticosteroids for pregnant women between $24^{0/7}$ weeks and $33^{6/7}$ weeks' gestation who are at risk for preterm delivery. They further note that those given their initial course more than 14 days prior and who have imminent risk of preterm delivery may receive a second "rescue" course. Antenatal corticosteroids are "considered" for $23^{0/7}$ to $23^{6/7}$ weeks and not recommended for pregnancies <23 weeks (American College of Obstetricians and Gynecologists, 2017c).

Other Preventive Methods

Although antenatal *magnesium sulfate* for those at risk for preterm delivery does not reduce the incidence of IVH, it does offer protection from neurodevelopmental impairment (Crowther, 2007; Doyle, 2009). The American College of Obstetricians and Gynecologists (2016b) recommends its use for this indication, as discussed further in Chapter 42 (Magnesium Sulfate for Neuroprotection). The efficacy of antenatal *vitamin K* and *phenobarbital*, as well as postnatal phenobarbital, have not been shown to consistently reduce the incidence of IVH (Crowther, 2010a,b; Smit, 2013). Although *vitamin E* reduced IVH rates, the associated risk for sepsis was increased (Brion, 2003). One metaanalysis of the many randomized trials of postnatal *indomethacin* showed a reduction in IVH rates, but no improvement in rates of death or neurodevelopmental impairment (Fowlie, 2010).

The benefits of cesarean delivery compared with vaginal birth to lower IVH rates remains controversial. One metaanalysis reported that cesarean delivery for very-low-birthweight neonates had no effect on rates of severe IVH but did reduce overall IVH rates (Barzilay, 2016). Delayed cord clamping compared with immediate cord clamping has been reported to reduce the risk for IVH in preterm newborns (Rabe, 2012).

Periventricular Leukomalacia

This pathological description refers to cystic areas deep in brain white matter that develop after hemorrhagic or ischemic infarction. Tissue ischemia leads to regional necrosis. Because brain tissue does not regenerate and the preterm neonate has minimal gliosis, these irreversibly damaged areas appear as echolucent cysts in neuroimaging studies. Generally, they require at least 2 weeks to form but may develop as long as 4 months after the initial insult. Thus, their presence at birth may help to determine the timing of an inciting event.

CEREBRAL PALSY

This term refers to a group of conditions that are characterized by chronic movement or posture abnormalities that are cerebral in origin, arise early in life, and are nonprogressive (Nelson, 2003). Epilepsy and mental retardation frequently accompany CP. Its cause(s) are different in preterm and term infants (Chap. 33, Cerebral Palsy).

CP is commonly classified by the type of neurological dysfunction—spastic, dyskinetic, or ataxic—as well as the number and distribution of limbs involved—quadriplegia, diplegia, hemiplegia, or monoplegia. The major types and their frequencies were categorized by Freeman (1988) and Rosen (1992) and their associates:

Spastic quadriplegia, which has a strong association with developmental retardation and seizure disorders—20 percent

Diplegia, which is common in preterm or low-birthweight neonates—30 percent

Hemiplegia—30 percent

Choreoathetoid types—15 percent

Mixed varieties.

Incidence

According to the Centers for Disease Control and Prevention (2016), the prevalence of CP in the United States approximates 3 in 1000 children. In some countries, the incidence has risen because advances in care of very preterm newborns have improved their survival but not their neurological prognosis (O'Callaghan, 2011). For example, Moster and coworkers (2008) presented long-term follow-up of more than 900,000 births in Norway. The CP rate was 0.1 percent in nonanomalous term newborns but was 9.1 percent in those born at 23 to 27 weeks.

Risks

Intraventricular Hemorrhage

Various clinical and pathological data link CP with associated severe IVH (grade III or IV) and resulting PVL. In one study of nearly 1500 neonates born before ≤28 weeks, the rate of CP was fivefold greater in those who had grade III or IV hemorrhage compared with those who suffered no IVH (Bolisetty, 2014).

Ischemia

Preterm newborns are most susceptible to brain ischemia and PVL. Before 32 weeks' gestation, the vascular anatomy of the brain is composed of two systems. One penetrates into the cortex—the *ventriculopedal system.* The other reaches down to the ventricles, but then curves to flow outward—the *ventriculofugal system* (Weindling, 1995). There are no vascular anastomoses connecting these two systems. As a result, the area between these systems, through which the pyramidal tracts pass near the lateral cerebral ventricles, is a *watershed area* vulnerable to ischemia. Vascular insufficiency before 32 weeks leading to ischemia would affect this watershed area first. Resulting damage of the pyramidal tracts may cause spastic diplegia. After 32 weeks, vascular flow shifts toward the cortex, and hypoxic injury after this time primarily damages the cortical region.

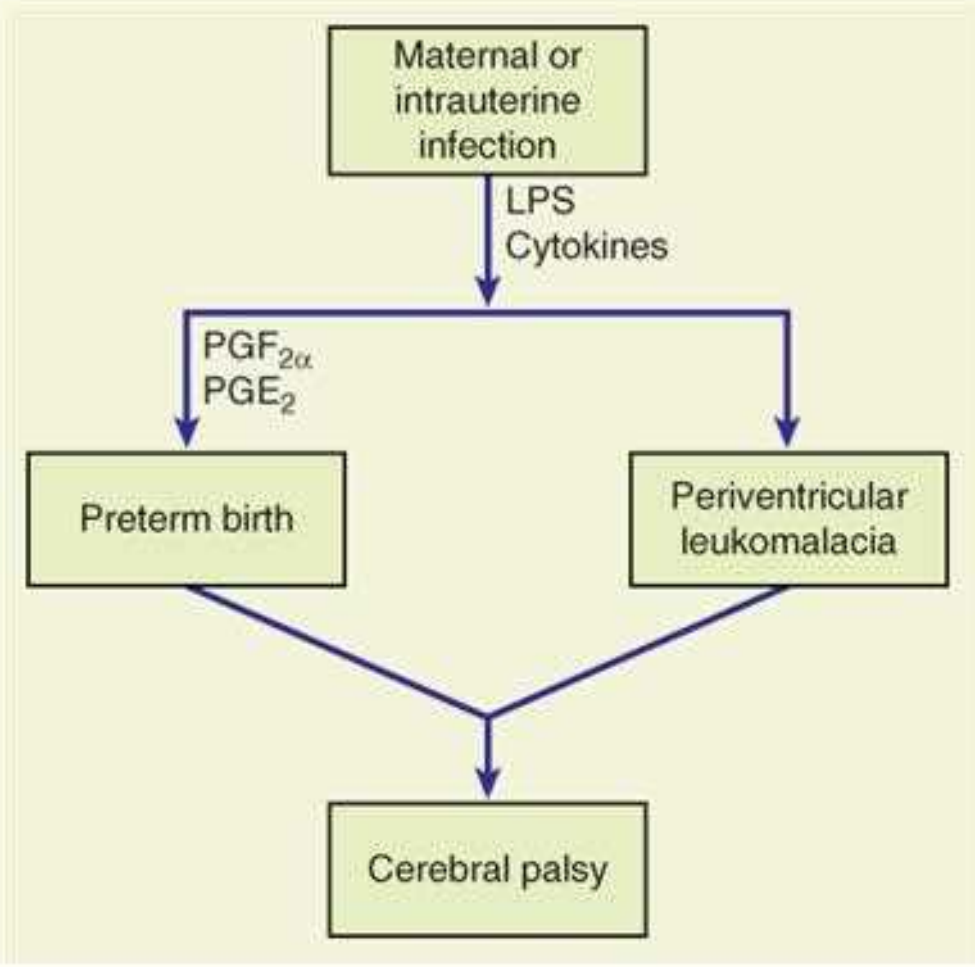
Perinatal Infection/Inflammation

PVL is associated with infection and inflammation. Zupan and colleagues (1996) studied 753 infants born between 24 and 32 weeks, 9 percent of whom developed PVL. Those born before 28 weeks, those who had inflammatory events during the last days to weeks before delivery, and those who had both were at highest risk. In another study, PVL was strongly associated with prolonged membrane rupture, chorioamnionitis, and neonatal hypotension (Perlman, 1996). Bailis and coworkers (2008) reported that chronic—and not acute—placental inflammation was associated with PVL.

Fetal infection may be a key element in the pathway between preterm birth and CP (Burd, 2012; Leviton, 2010). As discussed in Chapter 42 (Cervical Dysfunction), chorioamnionitis is a major cause of spontaneous preterm delivery. In the pathway proposed in Figure 34-2, antenatal reproductive tract infection evokes the production of cytokines such as tumor necrosis factor and interleukins-1, -6, and -8. These in turn stimulate prostaglandin production and preterm labor. Preterm fetal intracranial blood vessels are susceptible to rupture and damage, and the cytokines that stimulate preterm labor also have direct toxic effects on oligodendrocytes and myelin. Vessel rupture, tissue hypoxia, and cytokine-mediated damage result in massive neuronal cell death. Glutamate is released, stimulating membrane receptors to allow excess calcium to enter the neurons. High intracellular calcium levels are toxic to white matter, and glutamate may be directly toxic to oligodendrocytes (Khwaja, 2008).

FIGURE 34-2

Schematic representation of the hypothesized pathway between maternal or intrauterine infection and preterm birth or periventricular leukomalacia. Both potentially lead to cerebral palsy. LPS = lipopolysaccharide; PG = prostaglandin.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition

Many studies have shown that infection and cytokines can directly damage the immature brain (Chau, 2014; Yoon, 1997a). Tumor necrosis factor and interleukin-6 were more frequently found in the brains of infants who died with PVL (Yoon, 1997b). Cytokines are strongly linked to white matter lesions even when organisms cannot be demonstrated (Yoon, 2000).

Andrews and colleagues (2008) provided data that raise questions regarding a higher incidence of adverse neurodevelopmental outcomes related to exposure to chorioamnionitis. In a cohort born between 23 and 32 weeks, they studied several surrogate indicators and direct markers of in utero inflammation. These included clinical findings, cytokine levels, histological findings, and microbial culture results. Infants undergoing comprehensive psychoneurological testing had similar incidences of CP, intelligence quotient (IQ) scores <70, or both, regardless of these markers. The researchers interpreted their findings to support current practices that employ efforts to delay delivery with preterm pregnancies in the absence of overt intrauterine infection. Importantly, this does not apply to preterm pregnancy in which clinical chorioamnionitis is diagnosed. Of 3094 singletons born before 33 weeks' gestation, 15 percent had evidence of clinical chorioamnionitis (Soraisham, 2009). Compared with noninfected infants, cases complicated by infection had significantly higher rates of early-onset sepsis—4.8 versus 0.9 percent—and of IVH—22 versus 12 percent.

Prevention—Neuroprotection

The benefits of antenatal magnesium sulfate and corticosteroids have already been described. Few specific treatments have been identified to reduce or prevent brain injury in the vulnerable preterm newborn. One potential neuroprotective therapy is with erythropoiesis stimulating agents (ESAs) such as erythropoietin and darbepoetin. In addition to stimulating erythropoiesis, ESAs are protective in the developing brain in animal models (Wassink, 2017). Preliminary clinical studies are encouraging, and large trials are now underway (Beirer, 2014).

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CHAPTER 35: Stillbirth

In the latter months of pregnancy, the disappearance of foetal movements usually directs the attention of the patient to the possibility of foetal death. The diagnosis of this condition, however, can be considered absolute only after repeated examinations, when one has failed to hear the foetal heart or perceive the movements of the child.

—J. Whitridge Williams (1903)

INTRODUCTION

In Williams' time, absolute documentation of fetal death was frustrating for both patient and obstetrician. Now, sonography provides prompt confirmation, which allows expedient induction of labor and delivery. However, epidemiologically, defining and reporting fetal deaths was—and continues to be—a challenge. In response, efforts to standardize the definition of stillbirth and analyze varying reports for application into clinical practice and public health policy are now being emphasized. Moreover, stillbirth research and prevention within the United States and abroad has expanded. Global public health efforts were stimulated in part by a six-part series in *The Lancet.* This compilation was considered a call to action after the recognition that an estimated 2.65 million stillbirths occur each year and that 98 percent of stillborn fetuses are from low- and middle-income countries (*The Lancet*'s Stillbirth Series Steering Committee, 2011a–f). Unfortunately, progress in improving these rates has been slow, as outlined in *The Lancet's* subsequent five-part progress report, which emphasized the need for dedicated leadership, measured effects of interventions, and investigation into knowledge gaps (The Lancet's Ending Preventable Stillbirths Series Study Group, 2016a–e).

In the United States, an estimated 1 million fetal losses are reported each year, and most occur before 20 weeks' gestation. Fetal mortality data from the National Vital Statistics system are usually presented for fetal deaths after the 20-week threshold (MacDorman, 2015). Using this definition, numbers of fetal deaths in the United States in 2013 slightly surpassed numbers of infant deaths (Fig. 35-1). As shown in Figure 35-2, fetal death rates are highest at the earliest and latest gestational ages, which suggests etiological differences.

FIGURE 35-1
Percent distribution of fetal deaths at 20 weeks' gestation or more and of infant deaths: United States, 2013. (Data from MacDorman MF, Reddy UM, Silver RM: Trends in stillbirth by gestational age in the United States, 2006–2012, Obstet Gynecol. 2015 Dec;126(6):1146–1150.)

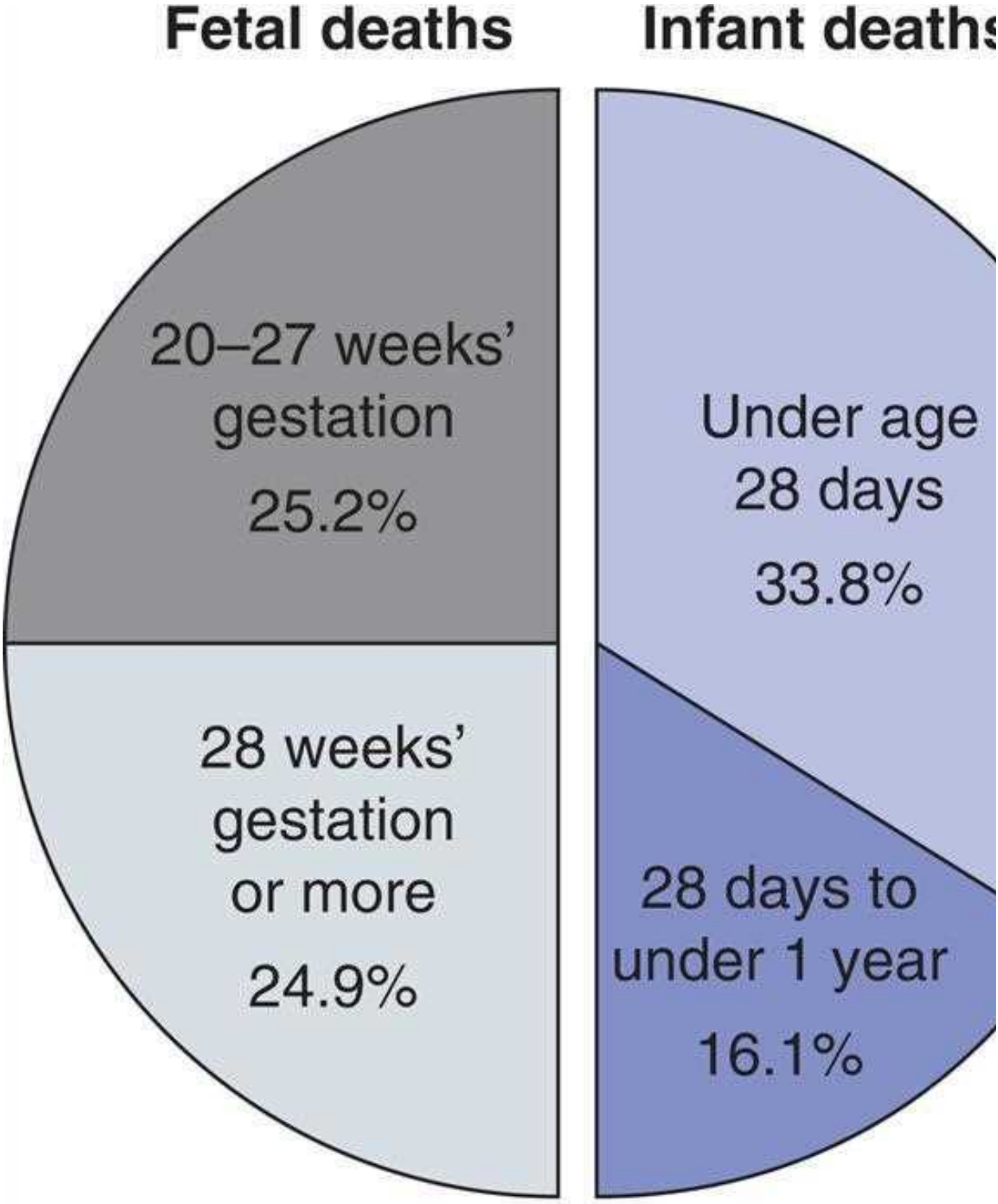
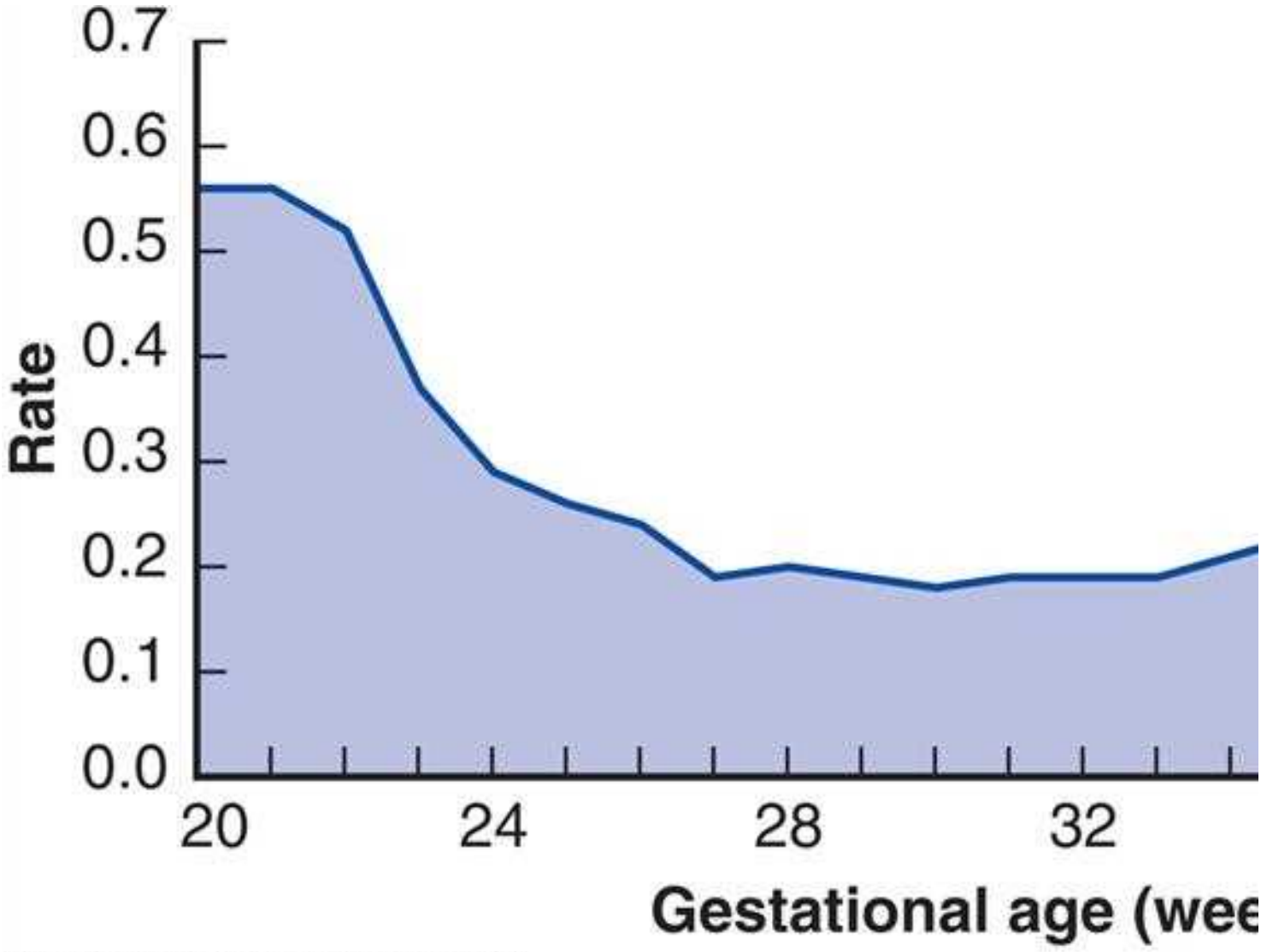


FIGURE 35-2

Prospective fetal mortality rate per 1000 births by weeks of gestation: United States, 2013. (Redrawn from MacDorman MF, Reddy UM, Silver RM: Trends in stillbirth by gestational age in the United States, 2006–2012, Obstet Gynecol. 2015 Dec;126(6): 1146–1150.)



DEFINITION OF FETAL MORTALITY

The current definition of fetal death adopted by the Centers for Disease Control and Prevention National Center for Health Statistics is based on a definition recommended by the World Health Organization (MacDorman, 2015). It states that "*Fetal death means death prior to complete expulsion or extraction from the mother of a product of human conception irrespective of the duration of pregnancy and which is not an induced termination of pregnancy. The death is indicated by the fact that after such expulsion or extraction, the fetus does not breathe or show any other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Heartbeats are to be distinguished from transient cardiac contractions; respirations are to be distinguished from fleeting respiratory efforts or gasps.*"

Reporting requirements for fetal deaths in the United States are determined by each state, and thus, criteria differ significantly (Chap. 1, Definitions). Most states mandate reporting of deaths of fetuses that are 20 weeks' gestation or older or have a minimum birthweight of 350 g (roughly equivalent to 20 weeks) or some combination of these two. However, several states require reporting of fetal deaths at all periods of gestation, and one sets the threshold at 16 weeks. Alternatively, two states require reporting of deaths for fetuses with birthweights of 500 g, which approximates that at 22 weeks. There is substantial evidence that not all fetal deaths for which reporting is required are actually recorded (MacDorman, 2015). This is most likely for those at earlier gestational ages.

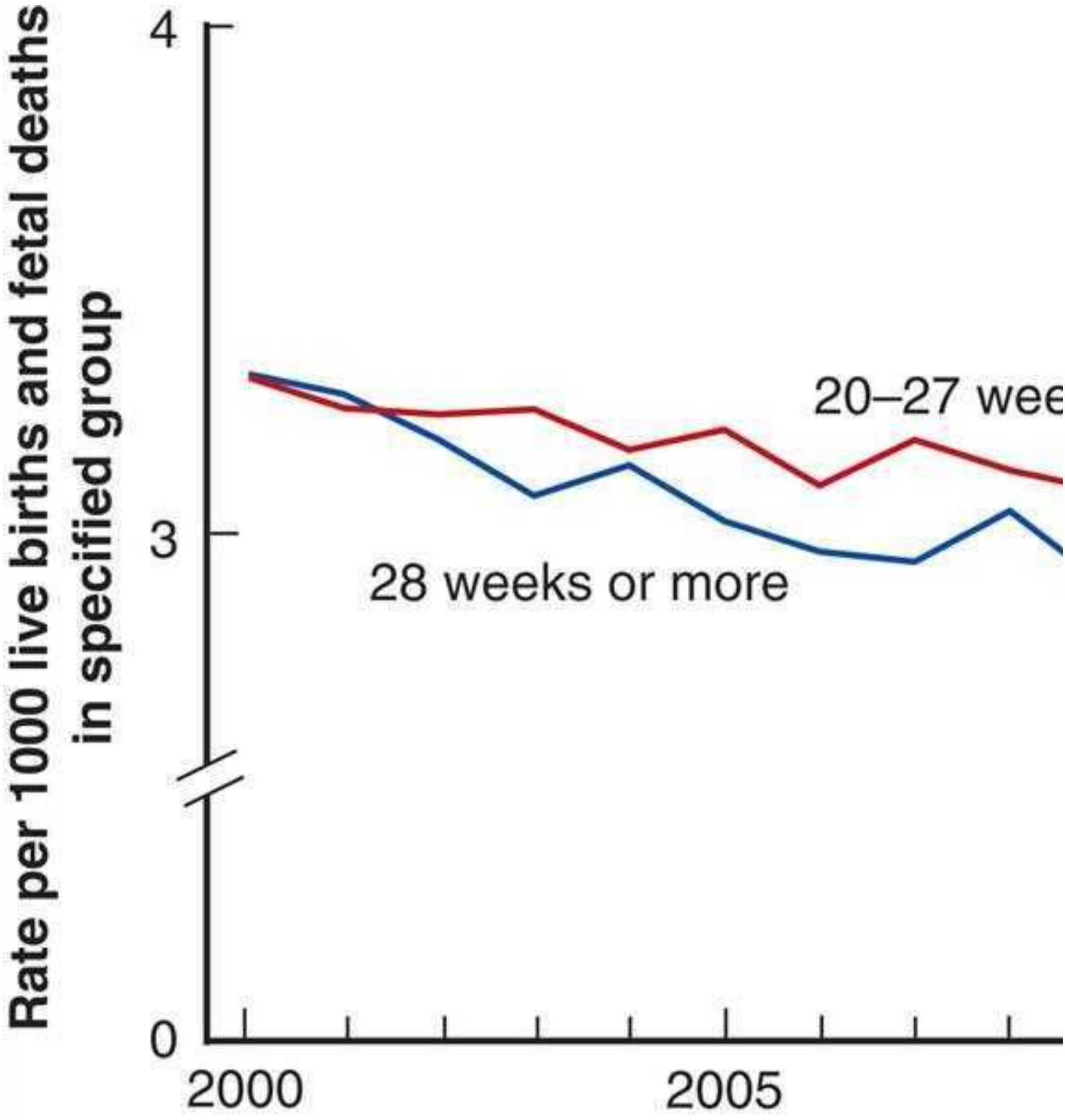
Comparisons of rates among countries are limited by incomplete fetal death data. Namely, internationally, less than 5 percent of neonatal deaths have formalized documentation (The Lancet's Ending Preventable Stillbirths Series Study Group, 2016d). Further, comparative analyses using birthweight versus gestational age among countries do not provide equivalent results. For example, in the United States, if stillbirth would be defined by a birthweight ≥500 g, the stillbirth rate would be reduced by 40 percent compared with a 22-week-age defined cohort (Blencowe, 2016). To address nomenclature differences, some have called for changes to the current definition (Joseph, 2015).

Overall, fetal mortality rates in the United States have remained relatively unchanged since 2006. However, the infant mortality rate has declined 11 percent, and both rates are now essentially equal (MacDorman, 2015). Three fetal mortality epochs are generally described: early (less than 20 completed weeks' gestation);

intermediate (20 to 27 weeks); and late (28 weeks or more). The fetal mortality rate at 20 to 27 weeks in 2013 declined 3 percent from the prior year. Between 2006 and 2012, rates were essentially unchanged in this age group. The late fetal mortality rate has been relatively unchanged since 2006 (Fig. 35-3).

FIGURE 35-3

Fetal mortality rates by period of gestation: United States, 2000–2013. (Data from MacDorman MF, Reddy UM, Silver RM: Trends in stillbirth by gestational age in the United States, 2006–2012, Obstet Gynecol. 2015 Dec;126(6):1146–1150.)



CAUSES OF FETAL DEATH

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) created the Stillbirth Collaborative Research Network to ascertain stillbirth causes in racially and geographically diverse populations in the United States. From this, the Stillbirth Collaborative Research Network Writing Group

(2011b) examined reasons for death at 20 weeks' gestation or later between 2006 and 2008 in 59 tertiary care and community hospitals in five states. Standardized evaluations included autopsy, placental histology, and testing of maternal or fetal blood/tissues, including fetal karyotyping. Evaluations were performed in 500 women with 512 stillbirths. Of these losses, 83 percent were before labor. Causes of stillbirth were divided into eight categories shown in Table 35-1. These categories were then classified as probable, possible, or unknown. As an example, diabetes was considered a *probable cause* if the fetus had diabetic embryopathy with lethal anomalies or the mother had diabetic ketoacidosis. It was a *possible cause* if the mother had poor glycemic control and the fetus had abnormal growth. *Overall, a probable or possible source was identified in 76 percent of cases.*

TABLE 35-1

Causes of 512 Stillbirths in the Stillbirth Collaborative Research Network Study

Cause	Percent	Examples
Obstetrical complications	29	Abruption, multifetal gestation, ruptured membranes at 20–24 weeks
Placental abnormalities	24	Uteroplacental insufficiency, maternal vascular disorders
Fetal malformations	14	Major structural abnormalities and/or genetic abnormalities
Infection	13	Involving the fetus or placenta
Umbilical cord abnormalities	10	Prolapse, stricture, thrombosis
Hypertensive disorders	9	Preeclampsia, chronic hypertension
Medical complications	8	Diabetes, antiphospholipid antibody syndrome
Undetermined	24	Not applicable

Percentages are rounded and total more than 100 percent because some stillbirths had more than one cause.

Overall, a cause was identified in 76 percent of stillbirths.

Data from Stillbirth Collaborative Research Network Writing Group, 2011b.

This Network study is unprecedented in the United States for several reasons. It was a population-based cohort of stillbirths, in which all underwent systematic and thorough evaluation. Each assigned cause of fetal death is reasonably straightforward and comprehensible except for "placental abnormalities." This category contains "uteroplacental insufficiency" and a few other less clearly defined placental entities. This aside, the leading reasons for fetal death were obstetrical and primarily included abruption, multifetal gestation complications, and spontaneous labor or ruptured membranes before viability. Importantly, this study illustrated that systematic evaluation may identify a likely cause in approximately three fourths of stillbirths. This rate is considerably higher than those in most prior analyses and serves to emphasize the importance of careful examination.

RISK FACTORS

Many factors are associated with an increased risk of stillbirth. Among others, these include advanced maternal age; African-American race; smoking; illicit drug use; maternal medical diseases—such as overt diabetes or chronic hypertension; assisted reproductive technology; nulliparity; obesity; and prior adverse pregnancy outcomes—such as prior preterm birth or growth-restricted newborn (Reddy, 2010; Varner, 2014).

Two major studies have assessed whether stillbirth risk factors could be identified either before or shortly after pregnancy confirmation. In the first, Reddy and colleagues (2010) analyzed data from the NICHD Consortium on Safe Labor. Briefly, the pregnancy outcomes of 206,969 women delivered between 2002 and 2008 at 19 hospitals in the United States were analyzed. When the distribution of stillbirths according to gestational age was studied, the tragedy of stillbirth occurred primarily in term pregnancies. These investigators concluded that their results did not support routine antenatal surveillance for any demographic risk factors.

The second analysis of stillbirth risk factors was included in the Stillbirth Collaborative Research Network study described earlier. The validity of stillbirth prediction was assessed based on risks identified in early pregnancy. They found that pregnancy factors known at the start of pregnancy accounted for only a small proportion of stillbirth risk. Except for prior stillbirth or pregnancy loss from causes such as preterm birth or fetal-growth restriction, other risks had limited predictive value (Stillbirth Collaborative Research Network Writing Group, 2011a). The importance of prior stillbirth as a risk for recurrence has been emphasized by Sharma and associates (2006). Specifically, the stillbirth risk was fivefold higher in women with a prior stillbirth. From another report, prior preterm birth, fetal-growth restriction, preeclampsia, and placental abruption were strongly associated with subsequent stillbirth (Rasmussen, 2009). Table 35-2 lists estimates of stillbirth risk according to maternal factors.

TABLE 35-2

Estimated Maternal Risk Factors and Risk of Stillbirth

Condition	Estimated Rate of Stillbirth (per 1000 births)	OR[a]
All pregnancies	6.4	1.0
Low-risk pregnancies	4.0–5.5	0.86
Hypertensive disorders		
Chronic hypertension	6–25	1.5–2.7
PIH		
Mild	9–51	1.2–4.0
Severe	12–29	1.8–4.4
Diabetes		
Diet alone	6–10	1.2–2.2
Insulin + diet	6–35	1.7–7.0
SLE	40–150	6–20
Renal disease	15–200	2.2–30
Thyroid disease	12–20	2.2–3.0
Thrombophilia	18–40	2.8–5.0
Cholestasis of pregnancy	12–30	1.8–4.4
Smoking >10 cigarettes	10–15	1.7–3.0
Obesity		
BMI 25–29.9 kg/m^2	12–15	1.9–2.7
BMI >30	13–18	2.1–2.8
Education (<12 yr vs ≥12 yr)	10–13	1.6–2.0
Prior IUGR (<10%)	12–30	2–4.6
Prior stillbirth	9–20	1.4–3.2
Multifetal gestation		
Twins	12	1.0–2.8
Triplets	34	2.8–3.7
Maternal age		
35–39 yr	11–14	1.8–2.2
≥40 yr	11–21	1.8–3.3
Black women compared with white women	12–14	2.0–2.2

[a]Odds ratio of the factor being present compared with the risk factor being absent.

BMI = body mass index; IUGR = intrauterine growth restriction; PIH = pregnancy-induced hypertension; SLE = systemic lupus erythematosus.

Adapted from Fretts, 2005.

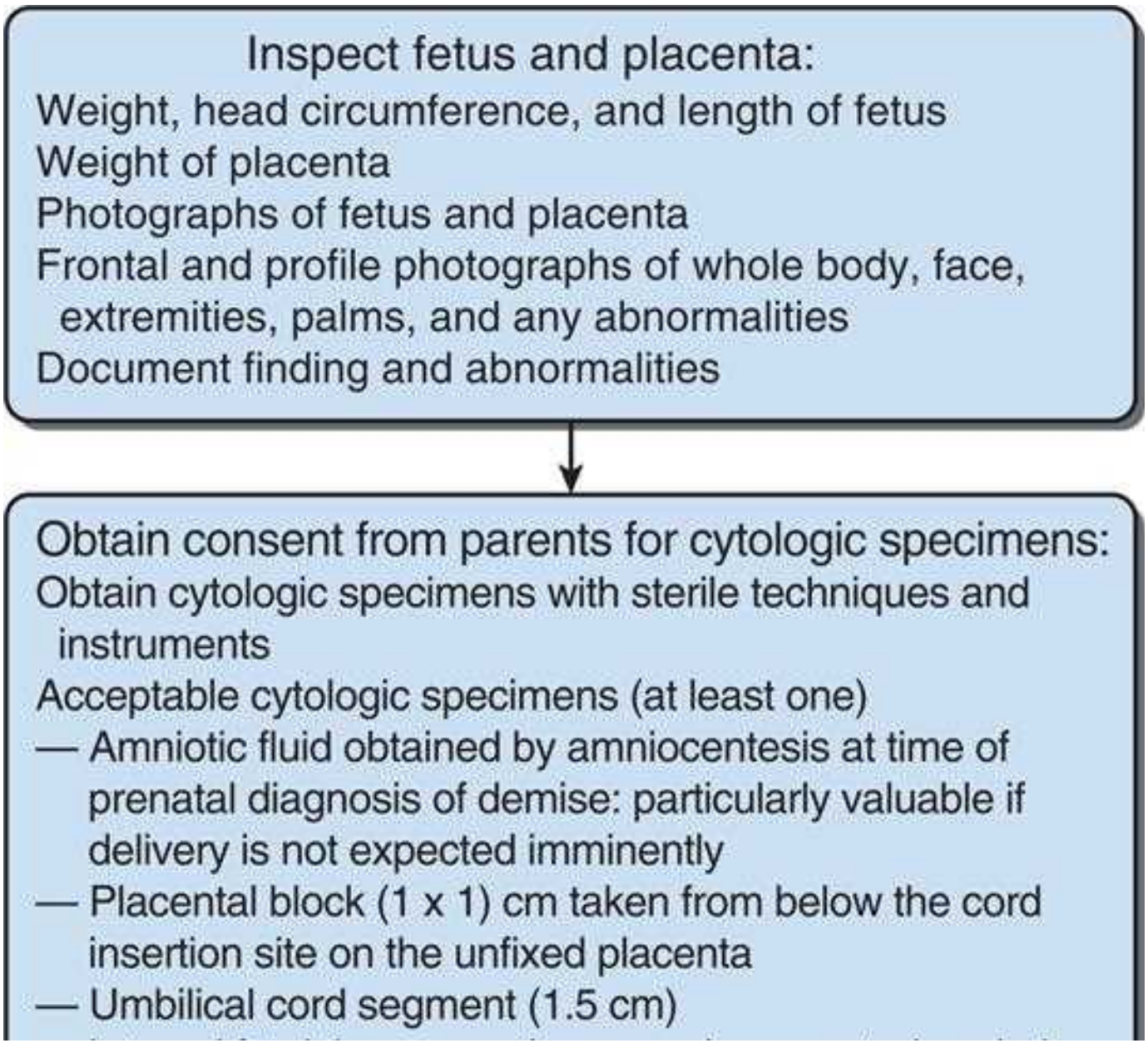
EVALUATION OF THE STILLBORN FETUS

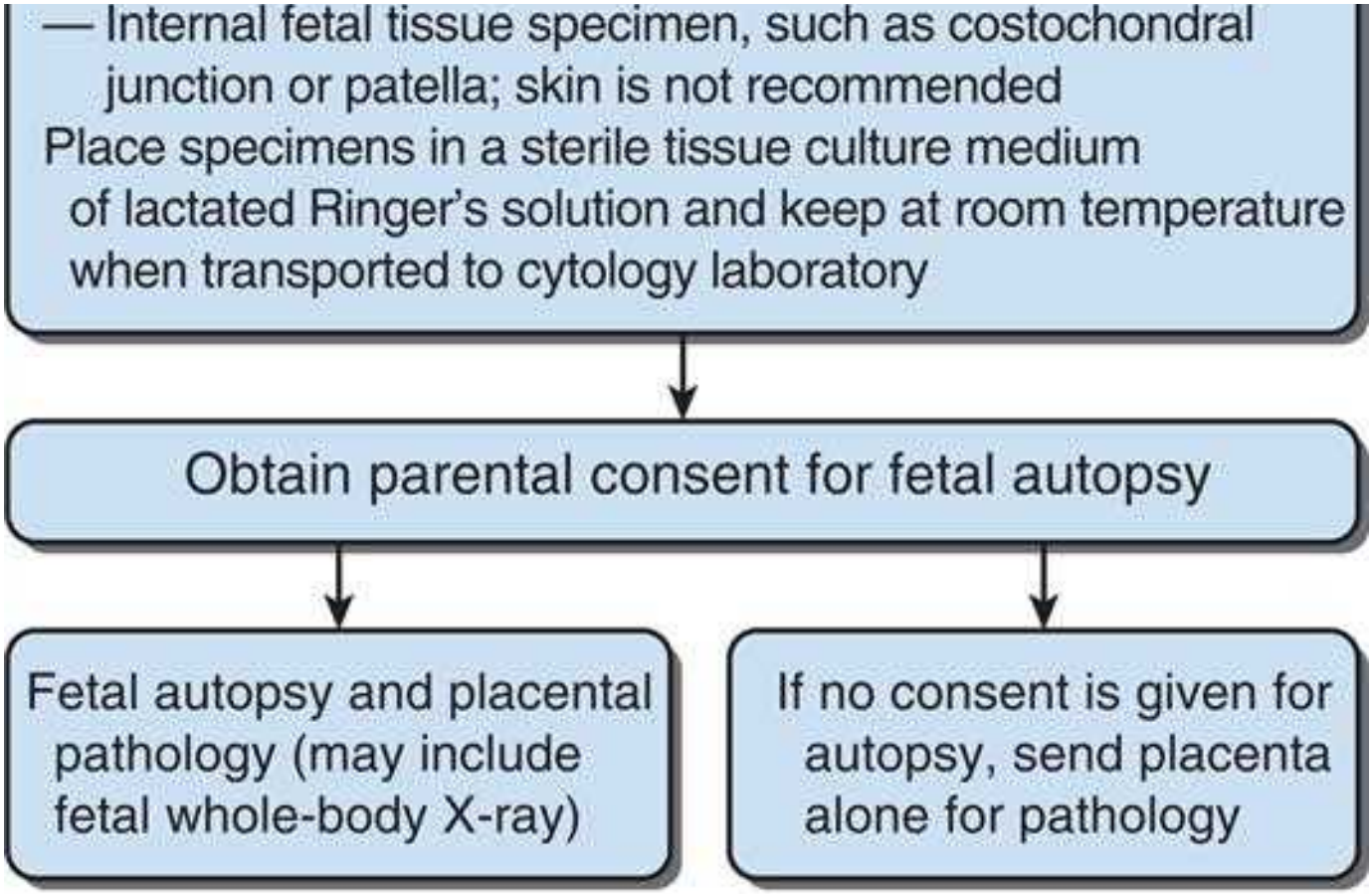
Determining the cause of fetal death aids maternal coping, helps assuage any perceived guilt, permits more accurate counseling regarding recurrence risk, and may prompt therapy or intervention to prevent a similar outcome in subsequent pregnancies (American College of Obstetricians and Gynecologists, 2016a). Identification of inherited syndromes also provides useful information for other family members.

Clinical Examination

Important tests in stillbirth evaluation are neonatal autopsy, chromosomal analysis, and examination of the placenta, cord, and chorioamnionic membranes (Pinar, 2014). Page and coworkers (2017) found placental pathology and fetal autopsy to be the most useful. One algorithm from the American College of Obstetricians and Gynecologists (2016a) is shown in Figure 35-4. Findings are documented in the medical record, and relevant prenatal events are delineated. Photographs are taken whenever possible, and a full radiograph of the fetus—a *fetogram*—may be performed. Postnatal magnetic resonance (MR) imaging or sonography may be especially important in providing anatomical information if parents decline a full autopsy (McPherson, 2017; Shruthi, 2017).

FIGURE 35-4
Flow chart for fetal and placental evaluation. (Modified with permission from ACOG Practice Bulletin No. 102: management of stillbirth, Obstet Gynecol. 2009 Mar;113(3):748–761.)





Laboratory Evaluation

If autopsy and chromosomal studies are performed, up to 35 percent of stillborn fetuses are discovered to have major structural anomalies (Faye-Petersen, 1999). Approximately 20 percent have dysmorphic features or skeletal anomalies, and 8 percent have chromosomal abnormalities (Pauli, 1994; Saller, 1995). In the absence of anatomic dysmorphology, up to 5 percent of stillborn fetuses will have a chromosomal abnormality (Korteweg, 2008). Although the American College of Obstetricians and Gynecologists (2016a) previously recommended karyotyping all stillborn fetuses, technological advancements of high-resolution, whole-genome sequencing—such as with *chromosomal microarray analysis (CMA)*—are now replacing standard karyotyping for chromosomal analysis of stillborn fetuses (Chap. 13, Chromosomal Microarray Analysis). CMA does not require dividing cells and is reported to be more useful in the evaluation of fetal death. This is especially true because the culturing of macerated fetal tissue is frequently unsuccessful (Reddy, 2012). Both the American College of Obstetricians and Gynecologists (2016c) and the Society for Maternal-Fetal Medicine (2016) now endorse the use of CMA for stillborn fetuses.

Appropriate consent must be obtained to take fetal samples, including tissue or fluid obtained postmortem by needle aspiration. As recently outlined by the American College of Obstetricians and Gynecologists (2016c), any type of fetal or placental tissue or amnionic fluid can be submitted for genetic testing by CMA. Contamination with maternal tissue or blood is ideally avoided. If fetal blood cannot be obtained from the umbilical cord or by cardiac puncture, the American College of Obstetricians and Gynecologists (2016a) recommends at least one of the following samples: (1) a placental block measuring about 1 × 1 cm taken below the cord insertion site in the unfixed specimen; (2) umbilical cord segment approximately 1.5 cm long; or (3) internal fetal tissue specimen such as costochondral junction or patella. Tissue is washed with sterile saline before being placed in lactated Ringer solution or sterile cytogenetic medium. Notably, placement in formalin or alcohol kills viable cells. If conventional karyotyping is the only test available and the timing of death is recent, amnionic fluid can be obtained by amniocentesis, as those cells obtained in a sterile fashion provide a greater likelihood of cell growth and eventual result compared with tissue obtained after delivery. Maternal blood is obtained for Kleihauer-Betke staining; for antiphospholipid antibody and lupus anticoagulant testing if indicated; and for serum glucose measurement to exclude overt diabetes (Silver, 2013).

In cases with significant growth restriction, with a family or personal history of thrombosis, or with severe placental pathology, testing for factor V Leiden mutation, prothrombin mutation, antithrombin level, and protein C and S activity may provide some information that could affect future pregnancy management (American College of Obstetricians and Gynecologists, 2016a). Our interpretation of relevant placental pathology includes derangements that stem from maternal vessel obstruction, which are described in Chapter 6. Although some have recommended routine evaluation of heritable thrombophilias, no evidence supports the clinical or financial efficiency of screening in an unselected population. Silver and colleagues (2016), with data from the Stillbirth Collaborative Research Network, found that most maternal and fetal thrombophilias were not associated with stillbirth and recommended against routine testing.

Autopsy

Parents are offered and encouraged to allow a full autopsy. That said, valuable information can still be obtained from limited studies. Pinar and coworkers (2012) described the autopsy protocol used by the Stillbirth Collaborative Research Network. As an alternative, gross external examination combined with photography, radiography, MR imaging, bacterial cultures, and selective use of chromosomal and histopathological studies often aids determination.

A complete autopsy is more likely to yield valuable data. An analysis of 400 consecutive fetal deaths in Wales showed that autopsy altered the presumed cause of death in 13 percent and provided new information in another 26 percent (Cartlidge, 1995). Other investigators have found that autopsy results changed the recurrence risk estimates and parental counseling in 25 to 50 percent of cases (Faye-Petersen, 1999; Silver, 2007). For example, Miller and associates (2016) recently demonstrated that placental examination with autopsy altered future medical management in 45 percent of cases.

According to the survey by Goldenberg and coworkers (2013), most hospitals do not audit stillbirths. In other centers, however, maternal records and autopsy findings are reviewed on a monthly basis by a stillbirth committee composed of obstetricians, maternal-fetal medicine specialists, neonatologists, clinical geneticists, and perinatal pathologists. If possible, the cause of death is assigned based on available evidence. Most importantly, parents are then contacted and offered counseling regarding the reason for the death, the potential recurrence risk, and possible strategies to avoid recurrence.

PSYCHOLOGICAL ASPECTS

Fetal death is psychologically traumatic for a woman and her family. Further stressors are an interval of more than 24 hours between the diagnosis of fetal death and labor induction, not seeing her infant for as long as she desires, having no tokens of remembrance, and poor communication (Radestad, 1996; Siassakos, 2017). The importance of seeing and holding a stillborn fetus for parental psychological well-being was recently summarized by Kingdon and colleagues (2015). As discussed in Chapter 61 (Postpartum Depression), a woman experiencing a stillbirth or early miscarriage is at increased risk for depression and should be closely monitored (Nelson, 2013).

Nuzum and coworkers (2014) reported that few obstetrical providers receive formal training in perinatal bereavement care. At Parkland Hospital, this care includes time with the infant, keepsake items, photographs, chaplaincy consultation, and bereavement support information. Care is coordinated through a dedicated nursing team affiliated with labor and delivery.

PRIOR STILLBIRTH

Table 35-3 lists an outlined approach for women with prior stillbirth. Importantly, these recommendations are based primarily on limited or inconsistent scientific evidence or on expert opinions. Unfortunately, few studies address management of affected women. Those with modifiable risk factors for stillbirth, such as hypertension or diabetes, warrant specific prevention strategies. Given that obesity has been identified as a risk factor for stillbirth and other obstetrical complications, preconceptional weight loss would seem prudent. Logically, women with a prior fetal death due to placental vascular events, that is, placental insufficiency, are also at increased risk for subsequent adverse perinatal outcomes (Monari, 2016). According to Reddy (2007), because almost half of fetal deaths are associated with growth restriction, fetal sonographic anatomical assessment beginning at midpregnancy is recommended. This is followed by serial growth studies beginning at 28 weeks. Supplementation with vitamin C or E in pregnancy has not been demonstrated to reduce the risk of fetal death (Rumbold, 2015a,b).

TABLE 35-3

Management of Subsequent Pregnancy after Stillbirth

Preconceptional or Initial Prenatal Visit
Detailed medical and obstetrical history
Review evaluation of prior stillbirth
Determination of recurrence risk
Discuss recurrence of comorbid obstetric complications
Smoking cessation
Preconceptional weight loss in obese women
Genetic counseling if family genetic condition exists
Diabetes screen
Thrombophilia screen: antiphospholipid antibodies (only if history indicates)
Support and reassurance
First Trimester
Dating sonography
First-trimester screen: pregnancy-associated plasma protein A, human chorionic gonadotropin, and nuchal translucency[a]
Support and reassurance
Second Trimester
Fetal sonographic anatomical survey at 18–20 weeks' gestation
Maternal serum screening (quadruple) *or* single-marker alpha fetoprotein if first-trimester screening elected[a]
Possible uterine artery Doppler studies at 22–24 weeks' gestation[a]
Support and reassurance
Third Trimester
Sonographic screening for fetal-growth restriction, starting at 28 weeks
Kick counts starting at 28 weeks
Antepartum fetal surveillance starting at 32 weeks *or* 1–2 weeks earlier than prior stillbirth
Support and reassurance
Delivery
Elective induction at 39 weeks
Delivery before 39 weeks only with documented fetal lung maturity by amniocentesis

[a]Provides risk modification but does not alter management.

Modified from Reddy, 2007.

Weeks and associates (1995) evaluated fetal biophysical testing in 300 women whose only indication was prior stillbirth. There was one subsequent stillbirth, and only three fetuses had abnormal testing results before 32 weeks. Notably, no relationship was found between the gestational age of the previous stillborn fetus and the incidence or timing of abnormal test results or fetal jeopardy in the subsequent pregnancy. These investigators concluded that antepartum surveillance should begin at 32 weeks or later in the otherwise healthy woman with a history of stillbirth. This recommendation is supported by the American College of Obstetricians and Gynecologists (2016a) with the caveat that it increases the iatrogenic preterm delivery rate. Although fetal movement counting strategies are routinely employed as described in Chapter 17 (Clinical Application), few data guide its use in clinical practice for those with a prior stillbirth (Mangesi, 2015).

Delivery at 39 weeks' gestation is recommended. Labor induction is suitable, and cesarean delivery is elected for those with a contraindication to induction. This timing minimizes fetal mortality rates, although the degree of risk reduction may be greater for older women (Page, 2013).

CHANGES IN STILLBIRTH RATES

Following declines between 2000 and 2006, the United States fetal mortality rate has been relatively unchanged since 2006 (MacDorman, 2015). Interpretation of these fetal mortality rates in the context of changing national healthcare strategies has spawned considerable debate. One example is the effort to prevent non-medically indicated deliveries before 39 weeks and its subsequent effect on term stillbirth rates. The value of this practice for neonatal outcome is described in Chapter 26 (Techniques). To analyze whether implementation of this "39-week rule" has altered the term stillbirth rate, Nicholson and coworkers (2016) examined data from 45 states and the District of Columbia during a 7-year period. The proportion of births before 39 weeks progressively declined from 2007 and 2013, but the term stillbirth rate rose. This suggested that the 39-week rule may cause unintended harm. MacDorman and associates (2015) also evaluated trends in stillbirth rates by gestational ages in the United States between 2006 and 2012. They used a "traditional stillbirth rate," which was calculated using a denominator composed of the live-birth number *plus* the stillbirth number at a given gestational age. They found increased rates at 24 to 27, 34 to 36, and 38 weeks' gestation. Alternatively, no

differences were found in “prospective stillbirth rates.” These rates were calculated using a denominator composed of the number of women who are pregnant at a given gestational age for weeks 21 through 42. The discrepancies in stillbirth rates appear to be primarily due to the decline in the number of births in the preterm and early-term gestational ages.

To summarize, implementation of the 39-week rule has reduced the number of elective births before 39 weeks’ gestation, although an unintended consequence may be an increase in term stillbirths—especially among women with medical complications. The importance of induction at less than 39 weeks in pregnant women with complications to prevent stillbirth is underscored by Little and colleagues (2015). These authors performed a retrospective multistate analysis of early-term deliveries ($37^{0/7}$ to $38^{6/7}$ weeks) from 2005 to 2011. They noted a decline in the number of early-term deliveries during this time but not a significant change in the term stillbirth rates. There was, however, a 25-percent rise in the rate of term, singleton stillbirths among women with diabetes, and this was attributed to clinicians misapplying early-term delivery policies to high-risk women. Undoubtedly, continued surveillance of stillbirth rates is warranted for both high- and low-risk pregnancies at a state and national level.

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CHAPTER 36: The Puerperium

Although the changes occurring during the puerperium are considered as physiological, they border very closely upon the pathological, in as much as under no other circumstances does such marked and rapid tissue metabolism occur without a departure from a condition of health.

—J. Whitridge Williams (1903)

INTRODUCTION

The word *puerperium* is derived from Latin—*puer,* child + *parus,* bringing forth. Currently, it defines the time following delivery during which pregnancy-induced maternal anatomical and physiological changes return to the nonpregnant state. Its duration is understandably inexact, but is considered to be between 4 and 6 weeks. Although much less complex compared with pregnancy, the puerperium has appreciable changes as stated above by Williams (1903), and some of these may be either bothersome or worrisome for the new mother. Kanotra and colleagues (2007) analyzed challenges that women faced from 2 to 9 months following delivery. The Pregnancy Risk Assessment Surveillance System—PRAMS—of the Centers for Disease Control and Prevention (2016) listed concerns of new mothers that are shown in Table 36-1. At least a third of these women felt the need for social support, and 25 percent had concerns with breastfeeding.

TABLE 36-1

Pregnancy Risk Assessment Surveillance System—PRAMS[a] Concerns Raised by Women in the First 2–9 Months Postpartum

Concerns	Percent
Need for social support	32
Breastfeeding issues	24
Inadequate education about newborn care	21
Help with postpartum depression	10
Perceived need for extended hospital stay	8
Need for maternal insurance coverage postpartum	6

[a]Centers for Disease Control and Prevention, 2016.

Data from Kanotra S, D'Angelo D, Phares TM, et al: Challenges faced by new mothers in the early postpartum period: an analysis of comment data from the 2000 Pregnancy Risk Assessment Monitoring System (PRAMS) survey. Matern Child Health J 11(6):549, 2007.

REPRODUCTIVE TRACT INVOLUTION

Birth Canal

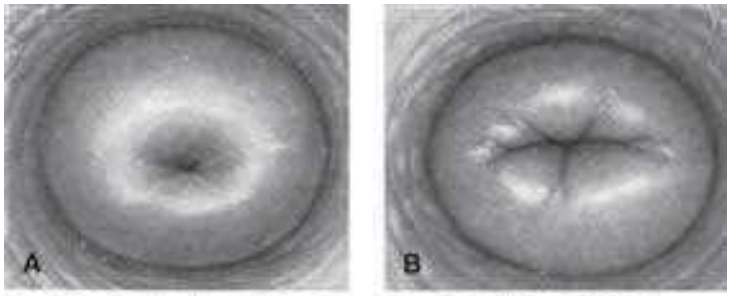
Return of the tissues in the birth canal to the nonpregnant state begins soon after delivery. The vagina and its outlet gradually diminish in size but rarely regain their nulliparous dimensions. Rugae begin to reappear by the third week but are less prominent than before. The hymen is represented by several small tags of tissue, which scar to form the *myrtiform caruncles.* The vaginal epithelium reflects the hypoestrogenic state, and it does not begin to proliferate until 4 to 6 weeks. This timing is usually coincidental with resumed ovarian estrogen production. Lacerations or stretching of the perineum during delivery can lead to vaginal outlet relaxation. Some damage to the pelvic floor may be inevitable, and parturition predisposes to urinary incontinence and pelvic organ prolapse.

Uterus

The massively increased uterine blood flow necessary to maintain pregnancy is made possible by significant hypertrophy and remodeling of pelvic vessels. After delivery, their caliber gradually diminishes to approximately that of the prepregnant state. Within the puerperal uterus, larger blood vessels become obliterated by hyaline changes. They are gradually resorbed and replaced by smaller ones. Minor vestiges of the larger vessels, however, may persist for years.

During labor, the margin of the dilated cervix, which corresponds to the external os, may be lacerated. The cervical opening contracts slowly, and for a few days immediately after labor, it readily admits two fingers. By the end of the first week, this opening narrows, the cervix thickens, and the endocervical canal re-forms. The external os does not completely resume its pregravid appearance. It remains somewhat wider, and typically, ectocervical depressions at the site of lacerations become permanent. These changes are characteristic of a parous cervix (Fig. 36-1). Cervical epithelium also undergoes considerable remodeling. This actually may be salutary because almost half of women have regression of high-grade dysplasia following delivery (Ahdoot, 1998; Kaneshiro, 2005).

FIGURE 36-1
Common appearance of nulliparous **(A)** and parous **(B)** cervices.



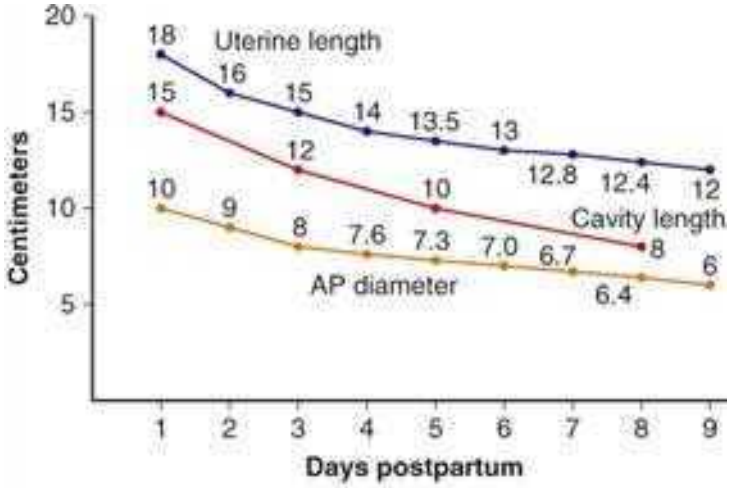
After delivery, the fundus of the contracted uterus lies slightly below the umbilicus. It consists mostly of myometrium covered by serosa and internally lined by decidua. The markedly attenuated lower uterine segment contracts and retracts, but not as forcefully as the uterine corpus. During the next few weeks, the lower segment is converted from a clearly distinct substructure large enough to accommodate the fetal head to a barely discernible uterine isthmus located between the corpus and internal cervical os. Immediately postpartum, the anterior and posterior walls, which lie in close apposition, are each 4 to 5 cm thick (Buhimschi, 2003). At this time, the uterus weighs approximately 1000 g.

Myometrial involution is a truly remarkable feat of destruction or deconstruction that begins as soon as 2 days after delivery (Williams, 1931). The total number of myocytes does not decrease appreciably—rather, their size decreases markedly. As emphasized by Hytten (1995), the quality of studies that describe the degree of decreasing uterine weight postpartum are poor. Best estimates show that the uterus weighs approximately 500 g by 1 week postpartum, about 300 g by 2 weeks, and at 4 weeks, involution is complete and the uterus weighs approximately 100 g. After each successive delivery, the uterus is usually slightly larger than before the most recent pregnancy.

Sonographic Findings

Uterine involution and rapid dissipation of size progresses in the first week (Fig. 36-2). Sonographically, the uterus and endometrium return to pregravid size by 8 weeks postpartum (Bae, 2012; Steinkeler, 2012). In a study of 42 normal puerperas, Tekay and Jouppila (1993) identified fluid in the endometrial cavity in 78 percent of women at 2 weeks, 52 percent at 3 weeks, 30 percent at 4 weeks, and 10 percent at 5 weeks. Belachew and coworkers (2012) used three-dimensional sonography and visualized intracavitary tissue matter in a third on day 1, in 95 percent on day 7, in 87 percent on day 14, and in 28 percent on day 28. By day 56, the small cavity was empty. Sohn and associates (1988) described Doppler ultrasound results showing continuously increasing uterine artery vascular resistance during the first 5 days postpartum. Weintraub and colleagues (2013) posited that uterine involution may be different in preeclamptic women because they more likely had early diastolic notches seen on uterine artery velocimetry.

FIGURE 36-2
Sonographic measurements of uterine involution during the first 9 days postpartum. AP = anteroposterior. (Data from Hytten F: The Clinical Physiology of the Puerperium. London, Farrand Press, 1995.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Decidua and Endometrial Regeneration

Because separation of the placenta and membranes involves the spongy layer, the decidua basalis is not sloughed. The in situ decidua varies markedly in thickness, it has an irregular jagged border, and it is infiltrated with blood, especially at the placental site. Within 2 or 3 days after delivery, the remaining decidua becomes differentiated into two layers. The superficial layer becomes necrotic and is sloughed in the lochia. The basal layer adjacent to the myometrium remains intact and is the source of new endometrium.

Endometrial regeneration is rapid, except at the placental site. Within a week or so, the free surface becomes covered by epithelium, and Sharman (1953) identified fully restored endometrium in all biopsy specimens obtained from the 16th day onward. Histological endometritis is part of the normal reparative process. Moreover, microscopic inflammatory changes characteristic of acute salpingitis are seen in almost half of women between 5 and 15 days, however, these findings are not thought to reflect infection (Andrews, 1951).

Clinical Aspects

Afterpains

Several clinical findings arise with uterine involution. In primiparas, the uterus tends to remain tonically contracted following delivery. In multiparas, it often contracts vigorously at intervals and gives rise to *afterpains*, which are similar to but milder than labor contractions. These are more pronounced as parity increases and worsen when the newborn suckles, likely because of oxytocin release (Holdcroft, 2003). Usually, afterpains decrease in intensity and become mild by the third day. We have encountered unusually severe and persistent afterpains in women with postpartum uterine infections.

Lochia

Early in the puerperium, sloughing of decidual tissue results in a vaginal discharge of variable quantity. The discharge is termed *lochia* and contains erythrocytes, shredded decidua, epithelial cells, and bacteria. For the first few days after delivery, there is blood sufficient to color it red—*lochia rubra.* After 3 or 4 days, lochia becomes progressively pale in color—*lochia serosa.* After approximately the 10th day, because of an admixture of leukocytes and reduced fluid content, lochia assumes a white or yellow-white color—*lochia alba.* The average duration of lochial discharge ranges from 24 to 36 days (Fletcher, 2012). Because of this expected leukocyte component, saline preparations of lochia for microscopic evaluation in cases of suspected puerperal metritis are typically uninformative and not recommended.

Placental Site Involution

Complete extrusion of the placental site takes up to 6 weeks. Immediately after delivery, the placental site is approximately palm-sized. Within hours of delivery, it normally contains many thrombosed vessels that ultimately undergo organization. By the end of the second week, it is 3 to 4 cm in diameter.

Placental site involution is an exfoliation process, which is prompted in great part by undermining of the implantation site by new endometrial proliferation (Williams, 1931). Thus, involution is not simply absorption in situ. Exfoliation consists of both extension and “downgrowth” of endometrium from the margins of the placental site, as well as development of endometrial tissue from the glands and stroma left deep in the decidua basalis after placental separation. Anderson and Davis (1968) concluded that placental site exfoliation results from sloughing of infarcted and necrotic superficial tissues followed by a remodeling process.

Subinvolution

In some cases, uterine involution is hindered because of infection, retained placental fragments, or other causes. Such subinvolution is accompanied by varied intervals of prolonged lochia as well as irregular or excessive uterine bleeding. During bimanual examination, the uterus is larger and softer than would be expected. With bleeding, pelvic sonography may help exclude retained placenta or, less-commonly, vascular malformations as the source (Iraha, 2017). Methylergonovine (Methergine), 0.2 mg orally every 3 to 4 hours for 24 to 48 hours, is recommended by many, but its efficacy is questionable. If there is infection, antimicrobial therapy usually leads to a good response. In an earlier study, Wager and coworkers (1980) reported that a third of these late cases of postpartum metritis are caused by *Chlamydia trachomatis.* For mild infection, empirical therapy with azithromycin or doxycycline usually

prompts resolution regardless of bacterial etiology. At our institution, common oral options taken for 7 to 10 days include doxycycline, 100 mg twice daily; azithromycin, 500 mg twice daily; or ampicillin-clavulanate (Augmentin), 875 mg twice daily. Serious metritis is treated with intravenous broad-spectrum antibiotics listed in Table 37-2.

Another cause of subinvolution is incompletely remodeled uteroplacental arteries (Andrew, 1989; Kavalar, 2012). These noninvoluted vessels are filled with thromboses and lack an endothelial lining. Perivascular trophoblasts are also identified in the vessel walls, which suggests an aberrant interaction between uterine cells and trophoblasts.

Late Postpartum Hemorrhage

Secondary postpartum hemorrhage is defined as bleeding 24 hours to 12 weeks after delivery. Clinically worrisome uterine hemorrhage develops within 1 to 2 weeks in perhaps 1 percent of women. Such bleeding most often is the result of abnormal involution of the placental site. It occasionally is caused by retention of a placental fragment or by a uterine artery pseudoaneurysm. Usually, retained products undergo necrosis with fibrin deposition and may eventually form a so-called *placental polyp.* As the eschar of the polyp detaches from the myometrium, hemorrhage may be brisk. As discussed in Chapter 56 (Von Willebrand Disease), delayed postpartum hemorrhage may also be caused by von Willebrand disease or other inherited coagulopathies (Lipe, 2011).

In our experiences, few women with delayed hemorrhage are found to have retained placental fragments. Thus, we and others do not routinely perform curettage (Lee, 1981). Another concern is that curettage may worsen bleeding by avulsing part of the implantation site. Thus, in a stable patient, if sonographic examination shows an empty cavity, then oxytocin, methylergonovine, or a prostaglandin analogue is given. Suitable dosing is found in Table 20-2. Antimicrobials are added if uterine infection is suspected. If large clots are seen in the uterine cavity with sonography, then *gentle* suction curettage is considered. Otherwise curettage is carried out only if appreciable bleeding persists or recurs after medical management.

URINARY TRACT

Normal pregnancy-induced glomerular hyperfiltration persists during the puerperium but returns to prepregnancy baseline by 2 weeks (Hladunewich, 2004). Dilated ureters and renal pelves return to their prepregnant state by 2 to 8 weeks postpartum. Because of this dilated collecting system, coupled with residual urine and bacteriuria in a traumatized bladder, symptomatic urinary tract infection remains a concern in the puerperium.

Funnell and colleagues (1954) used cystoscopy immediately postpartum and described varying degrees of submucosal hemorrhage and edema. Bladder trauma is associated most closely with labor length and thus to some degree is a normal accompaniment of vaginal delivery. Postpartum, the bladder has an increased capacity and a relative insensitivity to intravesical pressure. Thus, overdistention, incomplete emptying, and excessive residual urine are frequent (Buchanan, 2014; Mulder, 2014). Acute urinary retention is also more common with narcotic analgesia (Kandadai, 2014). Their management is discussed in Perineal Care.

It is unusual for urinary incontinence to manifest during the puerperium. That said, much attention has been given to the potential for subsequent development of urinary incontinence and other pelvic floor disorders in the years following delivery. A more detailed discussion is found in Chapter 30 (Cesarean Delivery Risks).

PERITONEUM AND ABDOMINAL WALL

The broad and round ligaments require considerable time to recover from stretching and loosening during pregnancy. As a result of ruptured elastic fibers in the skin and prolonged distention by the pregnant uterus, the abdominal wall remains soft and flaccid. If the abdomen is unusually flabby or pendulous, an ordinary girdle is often satisfactory. An abdominal binder is another temporary measure. Several weeks are required for these structures to return to normal, and recovery is aided by exercise. These may be started anytime following vaginal delivery. After cesarean delivery, a 6-week interval to allow fascia to heal and abdominal soreness to diminish is reasonable. Silvery abdominal striae commonly develop as *striae gravidarum* (Chap. 4, Breasts). Except for these, the abdominal wall usually resumes its prepregnancy appearance. When muscles remain atonic, however, the abdominal wall also remains lax. Marked separation of the rectus abdominis muscles—*diastasis recti*—may result.

BLOOD AND BLOOD VOLUME

Hematological and Coagulation Changes

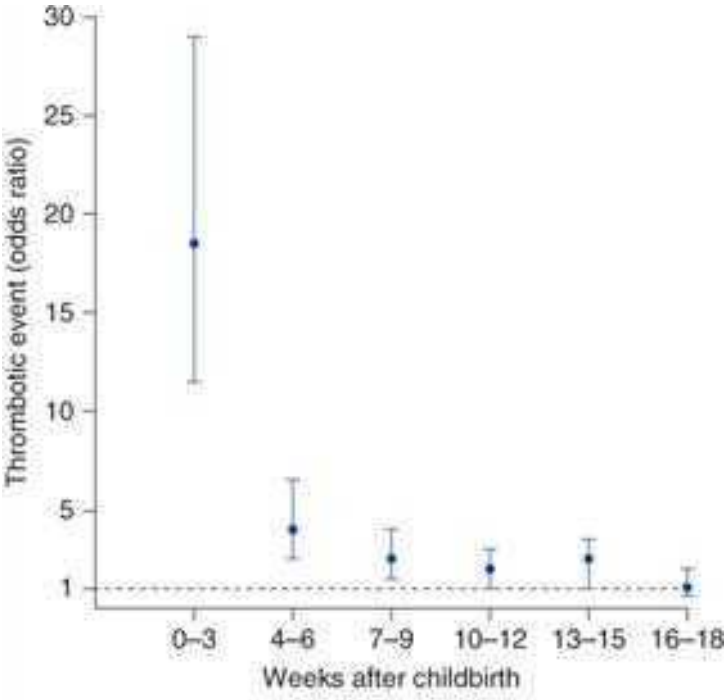
Marked leukocytosis and thrombocytosis may occur during and after labor. The white blood cell count sometimes reaches 30,000/µL, with the increase predominantly due to granulocytes. There is a relative lymphopenia and an absolute eosinopenia. Normally, during the first few postpartum days, hemoglobin concentration and hematocrit fluctuate moderately. We routinely check these on the first postpartum day or earlier if indicated. If they fall much below the levels present just before labor, a considerable amount of blood has been lost.

By the end of pregnancy, laboratory values that assess coagulation are altered (Kenny, 2014). These changes are discussed in Chapter 4 (Leukocytes and Lymphocytes) and listed in the Appendix (Serum and Blood Constituents). Many persist variably in the puerperium. For example, a markedly increased plasma fibrinogen level is maintained at least through the first week and hence so is an elevated sedimentation rate. Hypercoagulability appears to be

greater and is reflected by the likelihood of deep-vein thrombosis and pulmonary embolism in the 12 weeks following childbirth (Kamel, 2014). This is depicted in Figure 36-3 and is discussed further in Chapter 52 (Pathophysiology).

FIGURE 36-3

Risk of deep-vein thrombosis or pulmonary embolism following childbirth. (Data from Kamel H, Navi B, Sriram N, et al: Risk of a Thrombotic Event after the 6-week postpartum period. N Engl J Med 370:1307, 2014.)

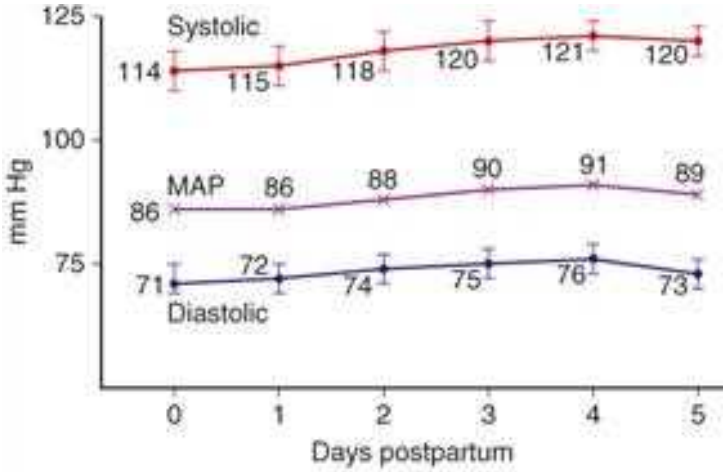


Pregnancy-Induced Hypervolemia

When the amount of blood attained by normal pregnancy hypervolemia is lost as postpartum hemorrhage, the woman almost immediately regains her nonpregnant blood volume (Chap. 41, Definition and Incidence). If less has been lost at delivery, blood volume generally nearly returns to its nonpregnant level by 1 week after delivery. Cardiac output usually remains elevated for 24 to 48 hours postpartum and declines to nonpregnant values by 10 days (Robson, 1987). Heart rate changes follow this pattern, and blood pressure similarly returns to nonpregnant values (Fig. 36-4). Correspondingly, systemic vascular resistance remains in the lower range characteristic of pregnancy for 2 days postpartum and then begins to steadily increase to normal nonpregnant values (Hibbard, 2014). Despite this, Morris and coworkers (2015) found that reduced arterial stiffness persists following pregnancy. They suggest a significant favorable effect of pregnancy on maternal cardiovascular remodeling, which may represent a mechanism by which preeclampsia risk is reduced in subsequent pregnancies.

FIGURE 36-4

During the early puerperium, blood pressure normally rises toward nonpregnant values. MAP = mean arterial pressure.



Postpartum Diuresis

Normal pregnancy is associated with an appreciable increase in extracellular sodium and water retention, and postpartum diuresis is a physiological reversal of this process. Chesley and coworkers (1959) demonstrated a decrease in sodium space of approximately 2 L during the first week postpartum. This also corresponds with loss of residual pregnancy hypervolemia. In preeclampsia, pathological retention of fluid antepartum and its diuresis postpartum may be prodigious (Chap. 40, Long-Term Consequences).

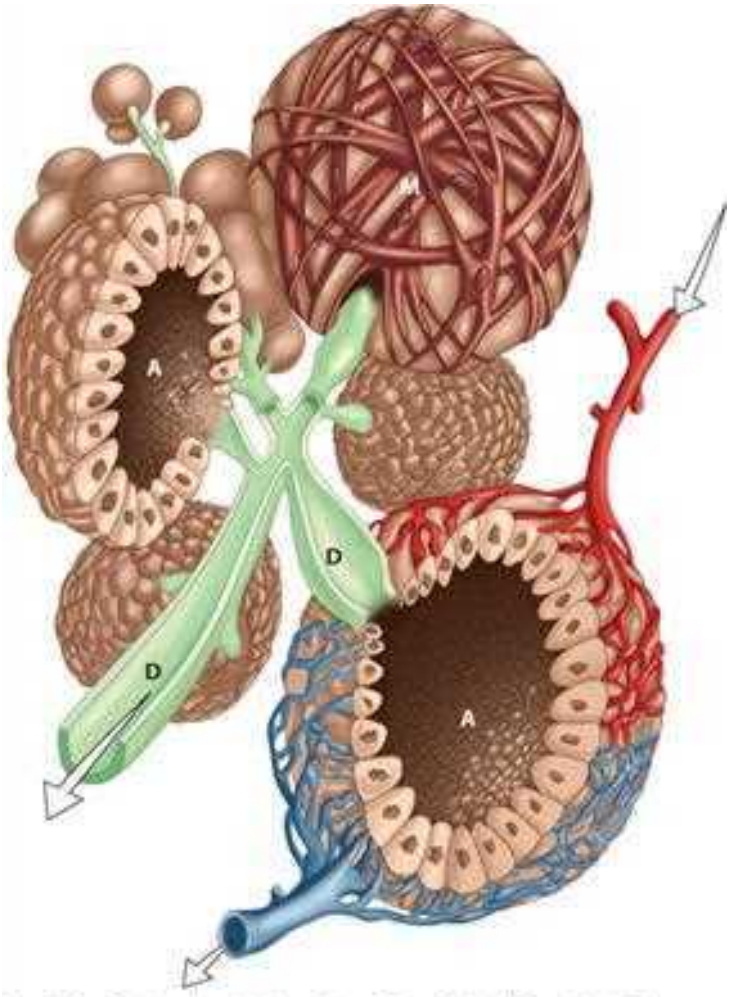
Postpartum diuresis results in relatively rapid weight loss of 2 to 3 kg, which is additive to the 5 to 6 kg incurred by delivery and normal blood loss. Weight loss from pregnancy itself is likely to be maximal by the end of the second week postpartum. It follows that any residual increased weight compared with prepregnancy values probably represents fat stores that will persist. According to Schauberger and associates (1992), women approach their self-reported prepregnancy weight 6 months after delivery but still retain an average surplus of 1.4 kg (3 lb).

LACTATION AND BREASTFEEDING

Breast Anatomy and Secretory Products

Each mature mammary gland or breast is composed of 15 to 25 lobes. They are arranged radially and are separated from one another by varying amounts of fat. Each lobe consists of several lobules, which in turn are composed of numerous alveoli. Each alveolus is provided with a small duct that joins others to form a single larger duct for each lobe as shown in Figure 36-5. These *lactiferous ducts* open separately on the nipple, where they may be distinguished as minute but distinct orifices. The alveolar secretory epithelium synthesizes the various milk constituents.

FIGURE 36-5
Schematic of the alveolar and ductal system during lactation. Note the myoepithelial fibers (*M*) that surround the outside of the uppermost alveolus. The secretions from the glandular elements are extruded into the lumen of the alveoli (*A*) and ejected by the myoepithelial cells into the ductal system (*D*), which empties through the nipple. Arterial blood supply to the alveolus is identified by the upper right arrow and venous drainage by the arrow beneath.



After delivery, the breasts begin to secrete *colostrum*, which is a deep lemon-yellow liquid. It usually can be expressed from the nipples by the second postpartum day. Compared with mature milk, colostrum is rich in immunological components and contains more minerals and amino acids (Ballard,

2013). It also has more protein, much of which is globulin, but less sugar and fat. Secretion persists for 5 days to 2 weeks, with gradual conversion from "transitional" to mature milk by 4 to 6 weeks. The colostrum content of immunoglobulin A (IgA) offers the newborn protection against enteric pathogens. Other host resistance factors found in colostrum and milk include complement, macrophages, lymphocytes, lactoferrin, lactoperoxidase, and lysozymes.

Mature milk is a complex and dynamic biological fluid that includes fat, proteins, carbohydrates, bioactive factors, minerals, vitamins, hormones, and many cellular products (Table 36-2). The concentrations and contents of human milk change even during a single feed and are influenced by maternal diet and by newborn age, health, and needs. A nursing mother easily produces 600 mL of milk daily, and maternal gestational weight gain has little impact on its quantity or quality. Milk is isotonic with plasma, and lactose accounts for half of the osmotic pressure. Essential amino acids are derived from blood, and nonessential amino acids are derived in part from blood or synthesized in the mammary gland. Most milk proteins are unique and include alpha-lactalbumin, beta-lactoglobulin, and casein. Fatty acids are synthesized in the alveoli from glucose and are secreted by an apocrine-like process. Most vitamins are found in human milk, but in variable amounts. Vitamin K is virtually absent, and thus, an intramuscular dose is given to the newborn (Chap. 33, Polycythemia and Hyperviscosity). Vitamin D content is low— 22 IU/mL, and newborn supplementation is also recommended by the American Academy of Pediatrics (Wagner, 2008).

TABLE 36-2

Average Composition of Human Breast Milk

Fat	g/100 mL
Total	4.2
Fatty Acids	Trace
PUFA	0.6
Cholesterol	0.016
Protein	g/100 mL
Total	1.1
Casein	0.3
α-Lactalbumin	0.3
Lactoferrin	0.2
Carbohydrate	g/100 mL
Lactose	7
Oligosaccharides	0.5

PUFA = Polyunsaturated fatty acids.

Whey is milk serum and has been shown to contain large amounts of interleukin-6 (Saito, 1991). Human milk has a whey-to-casein ratio of 60:40, considered ideal for absorption. *Prolactin* appears to be actively secreted into breast milk. *Epidermal growth factor (EGF)* has been identified, and because it is not destroyed by gastric proteolytic enzymes, it may be absorbed to promote growth and maturation of newborn intestinal mucosa (McCleary, 1991). Other critical components in human milk include lactoferrin, melatonin, oligosaccharides, and essential fatty acids.

Endocrinology of Lactation

The precise humoral and neural mechanisms involved in lactation are complex. Progesterone, estrogen, and placental lactogen, as well as prolactin, cortisol, and insulin, appear to act in concert to stimulate the growth and development of the milk-secreting apparatus (Stuebe, 2014). With delivery, the maternal serum levels of progesterone and estrogen decline abruptly and profoundly. This drop removes the inhibitory influence of progesterone on alpha-lactalbumin production and stimulates lactose synthase to increase milk lactose. Progesterone withdrawal also allows prolactin to act unopposed in its stimulation of alpha-lactalbumin production. Activation of calcium-sensing receptors (CaSR) in mammary epithelial cells downregulates parathyroid hormone-related protein (PTHrP) and increases calcium transport into milk (Vanhouten, 2013). Serotonin is also produced in mammary epithelial cells and has a role in maintaining milk production (Collier, 2012).

The intensity and duration of subsequent lactation are controlled, in large part, by the repetitive stimulus of nursing and emptying of milk from the breast. Prolactin is essential for lactation, and women with extensive pituitary necrosis— *Sheehan syndrome*—do not lactate (Chap. 58, Acromegaly). Although plasma prolactin levels fall after delivery to levels lower than during pregnancy, each act of suckling triggers a rise in levels (Pang, 2007). Presumably a stimulus from the breast curtails the release of dopamine, also known as *prolactin-inhibiting factor*, from the hypothalamus. In turn, this transiently induces increased prolactin secretion.

The posterior pituitary secretes oxytocin in pulsatile fashion. This stimulates milk expression from a lactating breast by causing contraction of myoepithelial cells in the alveoli and small milk ducts (see Fig. 36-5). Milk ejection, or *letting down*, is a reflex initiated especially by suckling, which

stimulates the posterior pituitary to liberate oxytocin. The reflex may even be provoked by an infant cry and can be inhibited by maternal fright or stress (Stuebe, 2014).

Immunological Consequences of Breastfeeding

Human milk contains several protective immunological substances, including secretory IgA and growth factors. The antibodies in human milk are specifically directed against maternal environmental antigens such as *Escherichia coli* (Iyengar, 2012). According to the Centers for Disease Control and Prevention (Perrine, 2015), breastfeeding decreases the incidence of ear, respiratory, and gastrointestinal infections; necrotizing enterocolitis; and sudden infant death syndrome.

Much attention has been directed to the role of maternal breast milk lymphocytes in neonatal immunological processes. Milk contains both T and B lymphocytes, but the T lymphocytes appear to differ from those found in blood. Specifically, milk T lymphocytes are almost exclusively composed of cells that exhibit specific membrane antigens. These memory T cells appear to be an avenue for the neonate to benefit from the maternal immunological experience.

Nursing

Human milk is ideal food for newborns in that it provides age-specific nutrients, immunological factors, and antibacterial substances. Milk also contains factors that act as biological signals for promoting cellular growth and differentiation. A list of the advantages of breastfeeding is shown in Table 36-3. For both mother and infant, the benefits of breastfeeding are long-term. For example, women who breastfeed have a lower risk of breast and reproductive cancer, and their children have increased adult intelligence independent of a wide range of possible confounding factors (Jong, 2012; Kramer, 2008). Breastfeeding is associated with decreased postpartum weight retention (Baker, 2008). In addition, rates of sudden-infant-death syndrome are significantly lower among breastfed infants. Bartek and colleagues (2013) estimate that a 90-percent breastfeeding rate for 12 months would save more than $3 billion annually in excess infant and maternal morbidity costs. For all these reasons, the American Academy of Pediatrics (2017) and American College of Obstetricians and Gynecologists (2016a, 2017b) supports the World Health Organization (2011) recommendations of exclusive breastfeeding for up to 6 months.

TABLE 36-3

Advantages of Breastfeeding

Nutritional
Immunological
Developmental
Psychological
Social
Economical
Environmental
Optimal growth and development
Decrease risks for acute and chronic diseases

Data from American Academy of Pediatrics and the American College of Obstetricians and Gynecologists: Guidelines for Perinatal Care, 8th ed, Elk Grove Village, AAP, 2017.

The Surgeon General of the U.S. Department of Health and Human Services (2011) lists some barriers to breastfeeding and suggests practical means of overcoming them. Educational initiatives that include father and peer counseling may improve these rates (Pisacane, 2005; Wolfberg, 2004). The *Baby Friendly Hospital Initiative* is an international program to increase rates of exclusive breastfeeding and to extend its duration. It is based on the World Health Organization (1989) *Ten Steps to Successful Breastfeeding* (Table 36-4). Worldwide, almost 20,000 hospitals are designated as “baby-friendly,” however, only 10 to 15 percent of hospitals in the United States are so designated (Centers for Disease Control and Prevention, 2014; Perrine, 2015). Forrester-Knauss and coworkers (2013) described successful trends toward exclusive breastfeeding in Switzerland during 9 years in which a Baby-Friendly Hospital Initiative was implemented. In a large population-based study done in the United States, fewer than two thirds of term neonates were exclusively breastfed at the time of discharge (McDonald, 2012).

TABLE 36-4

Ten Steps to Successful Breastfeeding

1. Have a written breastfeeding policy that is regularly communicated to all health-care staff
2. Train all staff in skills necessary to implement this policy
3. Inform all pregnant women about the benefits and management of breastfeeding
4. Help mothers initiate breastfeeding within an hour of birth
5. Show mothers how to breastfeed and how to sustain lactation, even if they should be separated from their infants
6. Feed newborns nothing but breast milk, unless medically indicated, and under no circumstances provide breast milk substitutes, feeding bottles, or pacifiers free of charge or at low cost
7. Practice rooming-in, which allows mothers and newborns to remain together 24 hours a day
8. Encourage breastfeeding on demand
9. Give no artificial pacifiers to breastfeeding newborns
10. Help start breastfeeding support groups and refer mothers to them

Adapted with permission from World Health Organization: Protecting, promoting and supporting breast-feeding: the special role of maternity services. Geneva, World Health Organization, 1989.

Various individual resources available are available for breastfeeding mothers that include online information from the American Academy of Pediatrics (http://www.aap.org) and La Leche League International (http://www.llli.org).

Care of Breasts

The nipples require little attention other than cleanliness and attention to skin fissures. Fissured nipples render nursing painful, and they may have a deleterious influence on milk production. These cracks also provide a portal of entry for pyogenic bacteria. Because dried milk is likely to accumulate and irritate the nipples, washing the areola with water and mild soap is helpful before and after nursing. When the nipples are irritated or fissured, some recommend topical lanolin and a nipple shield for 24 hours or longer. Although specific evidence supporting this practice is lacking, nipple pain usually subsides by 10 days (Dennis, 2014). If fissuring is severe, the newborn should not be permitted to nurse on the affected side. Instead, the breast is emptied regularly with a pump until the lesions are healed. Poor latching of the neonate to the breast can create such fissures. For example, the newborn may take into its mouth only the nipple, which is then is forced against the hard palate during suckling. Ideally, the nipple and areola are both taken in to evenly distribute suckling forces. Moreover, the force of the hard palate against the lactiferous sinuses aids their efficient emptying, while the nipple is thereby positioned closer to the soft palate.

Contraindications to Breastfeeding

Nursing is contraindicated in women who take street drugs or do not control their alcohol use; have an infant with galactosemia; have human immunodeficiency virus (HIV) infection; have active, untreated tuberculosis; take certain medications; or are undergoing breast cancer treatment (American Academy of Pediatrics, 2017; Faupel-Badger, 2013). Breastfeeding has been recognized for some time as a mode of HIV transmission and is proscribed in developed countries in which adequate nutrition is otherwise available. Other viral infections do not contraindicate breastfeeding. For example, with maternal cytomegalovirus infection, both virus and antibodies are present in breast milk. And, although hepatitis B virus is excreted in milk, breastfeeding is not contraindicated if hepatitis B immune globulin is given to the newborns of affected mothers. Maternal hepatitis C infection is not a contraindication because breastfeeding has not been shown to transmit infection (Society for Maternal-Fetal Medicine, 2017). Women with active herpes simplex virus may suckle their infants if there are no breast lesions and if particular care is directed to hand washing before nursing.

Drugs Secreted in Milk

Most drugs given to the mother are secreted in breast milk, although the amount ingested by the infant typically is small. Many factors influence drug excretion and include plasma concentration, degree of protein binding, plasma and milk pH, degree of ionization, lipid solubility, and molecular weight (Rowe, 2013). The ratio of drug concentration in breast milk to that in maternal plasma is the *milk-to-plasma drug-concentration ratio*. Ideally, to minimize infant exposure, medication selection should favor drugs with a shorter half-life, poorer oral absorption, and lower lipid solubility. If multiple daily drug doses are required, then each is taken by the mother *after* the closest feed. Single daily-dosed drugs may be taken just before the longest infant sleep interval—usually at bedtime (Spencer, 2002).

Only a few drugs are absolutely contraindicated while breastfeeding (Berlin, 2013; Bertino, 2012). Cytotoxic drugs may interfere with cellular metabolism and potentially cause immune suppression or neutropenia, affect growth, and at least theoretically, increase the risk of childhood cancer. Examples include cyclophosphamide, cyclosporine, doxorubicin, methotrexate, and mycophenolate. If a medication presents a concern, then the importance of therapy should be ascertained. It should be determined whether there is a safer alternative or whether neonatal exposure can be minimized if the

medication dose is taken immediately after each breastfeeding (American Academy of Pediatrics, 2017). Finally, recreational drugs such as marijuana and alcohol should be avoided (American College of Obstetricians and Gynecologists, 2017a). Data on individual drugs are available through the National Institutes of Health website, LactMed, which can be found at toxnet.nlm.nih.gov.

Radioactive isotopes of copper, gallium, indium, iodine, sodium, and technetium rapidly appear in breast milk. Consultation with a nuclear medicine specialist is recommended before performing a diagnostic study with these isotopes (Chap. 46, Radiographic Contrast Agents). The goal is to use a radionuclide with the shortest excretion time in breast milk. The mother should pump her breasts before the study and store enough milk in a freezer to feed the infant. After the study, she should pump her breasts to maintain milk flow but discard all milk produced during the time that radioactivity is present. This ranges from 15 hours to 2 weeks, depending on the isotope used. Importantly, radioactive iodine concentrates and persists in the thyroid. Its special considerations are discussed in Chapter 63 (Thyroid Cancer).

Breast Engorgement

This is common in women who do not breastfeed. It is typified by milk leakage and breast pain, which peak 3 to 5 days after delivery (Spitz, 1998). Up to half of affected women require analgesia for breast pain relief, and as many as 10 percent report severe pain for up to 14 days.

Evidence is insufficient to firmly support any specific treatment (Mangesi, 2016). That said, breasts can be supported with a well-fitting brassiere, breast binder, or sports bra. Cool packs and oral analgesics for 12 to 24 hours aid discomfort. Pharmacological or hormonal agents are in general not recommended to suppress lactation.

Fever caused by breast engorgement was common before the renaissance of breastfeeding. In one study, Almeida and Kitay (1986) reported that 13 percent of puerperas had fever from engorgement that ranged from 37.8 to 39°C. Fever seldom persists for longer than 4 to 16 hours. The incidence and severity of engorgement and of the fever associated with it are much lower if women breastfeed. Other causes of fever, especially those due to infection, must be excluded. Of these, *mastitis* is infection of the mammary parenchyma. It is relatively common in lactating women and is discussed in Chapter 37 (Breast Infections).

Other Issues with Lactation

With *inverted nipples*, lactiferous ducts open directly into a depression at the center of the areola. With these depressed nipples, nursing is difficult. If the depression is not deep, milk sometimes can be drawn out by a breast pump. If instead the nipple is greatly inverted, daily attempts are made during the last few months of pregnancy to draw or “tease” the nipple out with the fingers.

Extra breasts—*polymastia*, or extra nipples—*polythelia*, may develop along the former embryonic mammary ridge. Also termed the *milk line*, this line extends from the axilla to the groin bilaterally. In some women, rests of accessory breast tissue can be found in the mons pubis or vulva (Wagner, 2013). In the general population, the incidence of accessory breast tissue ranges from 0.22 to 6 percent (Loukas, 2007). These breasts may be so small as to be mistaken for pigmented moles, or if without a nipple, for lymphadenopathy or lipoma. Polymastia has no obstetrical significance, although occasionally enlargement of these accessory breasts during pregnancy or engorgement postpartum may result in patient discomfort and anxiety.

Galactocele is a milk duct that becomes obstructed by inspissated secretions. The amount is ordinarily limited, but an excess may form a fluctuant mass—a galactocele—that may cause pressure symptoms and have the appearance of an abscess. It may resolve spontaneously or require aspiration.

Among individuals, the volume of milk secreted varies markedly. This depends not on general maternal health but on breast glandular development. Rarely, there is complete lack of mammary secretion—*agalactia*. Occasionally, mammary secretion is excessive—*polygalactia*.

HOSPITAL CARE

For 2 hours after delivery, blood pressure and pulse are taken every 15 minutes, or more frequently if indicated. Temperature is assessed every 4 hours for the first 8 hours and then at least every 8 hours subsequently (American Academy of Pediatrics, 2017). The amount of vaginal bleeding is monitored, and the fundus palpated to ensure that it is well contracted. If relaxation is detected, the uterus should be massaged through the abdominal wall until it remains contracted. Uterotonics are also sometimes required. Blood can accumulate within the uterus without external bleeding. This may be detected early by uterine enlargement during fundal palpation in the first postdelivery hours. Because the likelihood of significant hemorrhage is greatest immediately postpartum, even in normal births, the uterus is closely monitored for at least 1 hour after delivery. Postpartum hemorrhage is discussed in Chapter 41 (Uterine Atony). If regional analgesia or general anesthesia was used for labor or delivery, the mother should be observed in an appropriately equipped and staffed recovery area.

Women are out of bed within a few hours after delivery. An attendant should be present for at least the first time, in case the woman becomes syncopal. The many confirmed advantages of early ambulation include fewer bladder complications, less frequent constipation, and reduced rates of puerperal venous thromboembolism. As discussed in Peritoneum and Abdominal Wall, deep-vein thrombosis and pulmonary embolism are common in the puerperium (see Fig. 36-3). In an audit of puerperal women at Parkland Hospital, the frequency of venous thromboembolism was found to be 0.008

percent after a vaginal birth and 0.04 percent following cesarean delivery. We attribute this low incidence to early ambulation. Risk factors and other measures to diminish the frequency of thromboembolism are discussed in Chapter 52 (Pathophysiology).

There are no dietary restrictions for women who have been delivered vaginally. Two hours after uncomplicated vaginal delivery, a woman is allowed to eat. With breastfeeding, the level of calories and protein consumed during pregnancy are increased slightly as recommended by the Food and Nutrition Board of the National Research Council (Chap. 9, Dietary Reference Intakes—Recommended Allowances). If the mother does not breastfeed, dietary requirements are the same as for a nonpregnant woman. We recommend oral iron supplementation for at least 3 months after delivery and hematocrit evaluation at the first postpartum visit.

As noted earlier, profound drops in estrogen levels follow removal of the placenta. Reminiscent of the menopause, postpartum women may experience hot flushes, especially at night. Importantly, the patient's temperature is assessed to differentiate these physiological vasomotor events from infection.

In women with migraines, dramatic hypoestrogenism may trigger headaches. Importantly, severe headaches should be differentiated from spinal headache or hypertensive complications. Care varies depending on migraine severity. Mild headaches may respond to analgesics such as ibuprofen or acetaminophen. Alternatively, Midrin combines isometheptene mucate, which is a sympathomimetic agent; dichloralphenazone, which is a mild sedative; and acetaminophen and is compatible with breastfeeding. For more severe headaches, oral or systemic narcotics can be used. Instead of Midrin, a triptan, such as sumatriptan (Imitrex), can effectively relieve headaches by causing intracranial vasoconstriction.

Perineal Care

The woman is instructed to clean the vulva from anterior to posterior—the vulva toward the anus. A cool pack applied to the perineum may help reduce edema and discomfort during the first 24 hours if there is a perineal laceration or an episiotomy. Most women also appear to obtain a measure of relief from the periodic application of a local anesthetic spray. *Severe perineal, vaginal, or rectal pain always warrants careful inspection and palpation*. Severe discomfort usually indicates a problem, such as a hematoma within the first day or so and infection after the third or fourth day (Chap. 37, Perineal Infections and Chap. 41, Puerperal Hematomas). Beginning approximately 24 hours after delivery, moist heat as provided by warm sitz baths can be used to reduce local discomfort. Tub bathing after uncomplicated delivery is allowed. The episiotomy incision normally is firmly healed and nearly asymptomatic by the third week.

Rarely, the cervix, and occasionally a portion of the uterine body, may protrude from the vulva following delivery. This is accompanied by variable degrees of anterior and posterior vaginal wall prolapse. Symptoms include a palpable mass at or past the introitus, voiding difficulties, or pressure. Puerperal procidentia typically improves with time as the weight of the uterus lessens with involution. As a temporizing measure in those with pronounced prolapse, the uterus can be replaced and held in position with a suitable pessary.

Hemorrhoidal veins are often congested at term. Thrombosis is common and may be promoted by second-stage pushing. Treatment includes topically applied anesthetics, warm soaks, and stool-softening agents. Nonprescription topical preparations containing corticosteroids, astringents, or phenylephrine are often used, but no randomized studies support their efficacy compared with conservative management.

Bladder Function

In most delivery units, intravenous fluids are infused during labor and for an hour or so after delivery. Oxytocin, in doses that have an antidiuretic effect, is typically infused postpartum, and rapid bladder filling is common. Moreover, both bladder sensation and capability to empty spontaneously may be diminished by local or conduction analgesia, by trauma to the bladder, by episiotomy or lacerations, or by operative vaginal delivery. Thus, urinary retention and bladder overdistention is common in the early puerperium. The incidence in more than 5500 women studied with a bladder scanner was 5.1 percent (Buchanan, 2014). In another study, Musselwhite and coworkers (2007) reported retention in 4.7 percent of women who had labor epidural analgesia. Risk factors that increased the likelihood of retention were primiparity, cesarean delivery, perineal laceration, oxytocin-induced or augmented labor, operative vaginal delivery, catheterization during labor, and labor duration >10 hours.

Prevention of bladder overdistention demands observation after delivery to ensure that the bladder does not overfill and that it empties adequately with each voiding. The enlarged bladder can be palpated suprapubically, or it is evident abdominally indirectly as it elevates the fundus above the umbilicus. The use of an automated bladder scanner sonography system has been studied to detect high bladder volumes and thus postpartum urinary retention (Buchanan, 2014; Van Os, 2006).

If a woman has not voided within 4 hours after delivery, it is likely that she cannot. If she has trouble voiding initially, she also is likely to have further trouble. An examination for perineal and genital-tract hematomas is completed. With an overdistended bladder, an indwelling catheter should be left in place until the factors causing retention have abated. Even without a demonstrable cause, it usually is best to leave the catheter in place for at least 24 hours. This prevents recurrence and allows recovery of normal bladder tone and sensation.

When the catheter is removed, a voiding trial is completed to demonstrate an ability to void appropriately. If a woman cannot void after 4 hours, she should be catheterized and the urine volume measured. If more than 200 mL, the bladder is not functioning appropriately, and the catheter is left for

another 24 hours. Although rare, if retention persists after a second voiding trial, an indwelling catheter and leg bag can be elected, and the patient returns in 1 week for an outpatient voiding trial. Intermittent self-catheterization is another option (Mulder, 2017).

During a voiding trial, if less than 200 mL of urine is obtained, the catheter can be removed and the bladder subsequently monitored clinically as described earlier. Harris and coworkers (1977) reported that 40 percent of such women develop bacteriuria, and thus a single dose or short course of antimicrobial therapy against uropathogens is reasonable after the catheter is removed.

Pain, Mood, and Cognition

Discomfort and its causes following cesarean delivery are considered in Chapter 30 (Postoperative Care). During the first few days after vaginal delivery, the mother may be uncomfortable because of afterpains, episiotomy and lacerations, breast engorgement, and at times, postdural puncture headache. Mild analgesics containing codeine, aspirin, or acetaminophen, preferably in combinations, are given as frequently as every 4 hours during the first few days.

It is important to screen the postpartum woman for depression (American College of Obstetricians and Gynecologists, 2016b). It is fairly common for a mother to exhibit some degree of depressed mood a few days after delivery. Termed *postpartum blues,* this likely is the consequence of several factors. These include emotional letdown that follows the excitement and fears experienced during pregnancy and delivery, discomforts of the early puerperium, fatigue from sleep deprivation, anxiety over the ability to provide appropriate newborn care, and body image concerns. In most women, effective treatment includes anticipation, recognition, and reassurance. This disorder is usually mild and self-limited to 2 to 3 days, although it sometimes lasts for up to 10 days. Should these moods persist or worsen, an evaluation for symptoms of major depression is done (Chap. 61, Postpartum Depression). Suicidal or infanticidal ideation is dealt with emergently. Because major postpartum depression recurs in at least a fourth of women in subsequent pregnancies, some recommend pharmacological prophylaxis beginning in late pregnancy or immediately postpartum.

Last, postpartum hormonal changes in some women may affect brain function. Bannbers and colleagues (2013) compared a measure of executive function in postpartum women and controls and observed a functional decline in postpartum subjects.

Neuromusculoskeletal Problems

Obstetrical Neuropathies

Pressure on branches of the lumbosacral nerve plexus during labor may manifest as complaints of intense neuralgia or cramp- like pains extending down one or both legs as soon as the head descends into the pelvis. If the nerve is injured, pain may continue after delivery, and variable degrees of sensory loss or muscle paralysis can result. In some cases, there is footdrop, which can be secondary to injury at the level of the lumbosacral plexus, sciatic nerve, or common fibular (peroneal) nerve (Bunch, 2014). Components of the lumbosacral plexus cross the pelvic brim and can be compressed by the fetal head or by forceps. The common fibular nerves may be externally compressed when the legs are positioned in stirrups, especially during prolonged second-stage labor.

Obstetrical neuropathy is relatively infrequent. Wong and associates (2003) evaluated more than 6000 puerperas and found that approximately 1 percent had a confirmed nerve injury. Lateral femoral cutaneous neuropathies were the most common (24 percent), followed by femoral neuropathies (14 percent). A motor deficit accompanied a third of injuries. Nulliparity, prolonged second-stage labor, and pushing for a long duration in the semi-Fowler position were risk factors. The median duration of symptoms was 2 months, and the range was 2 weeks to 18 months.

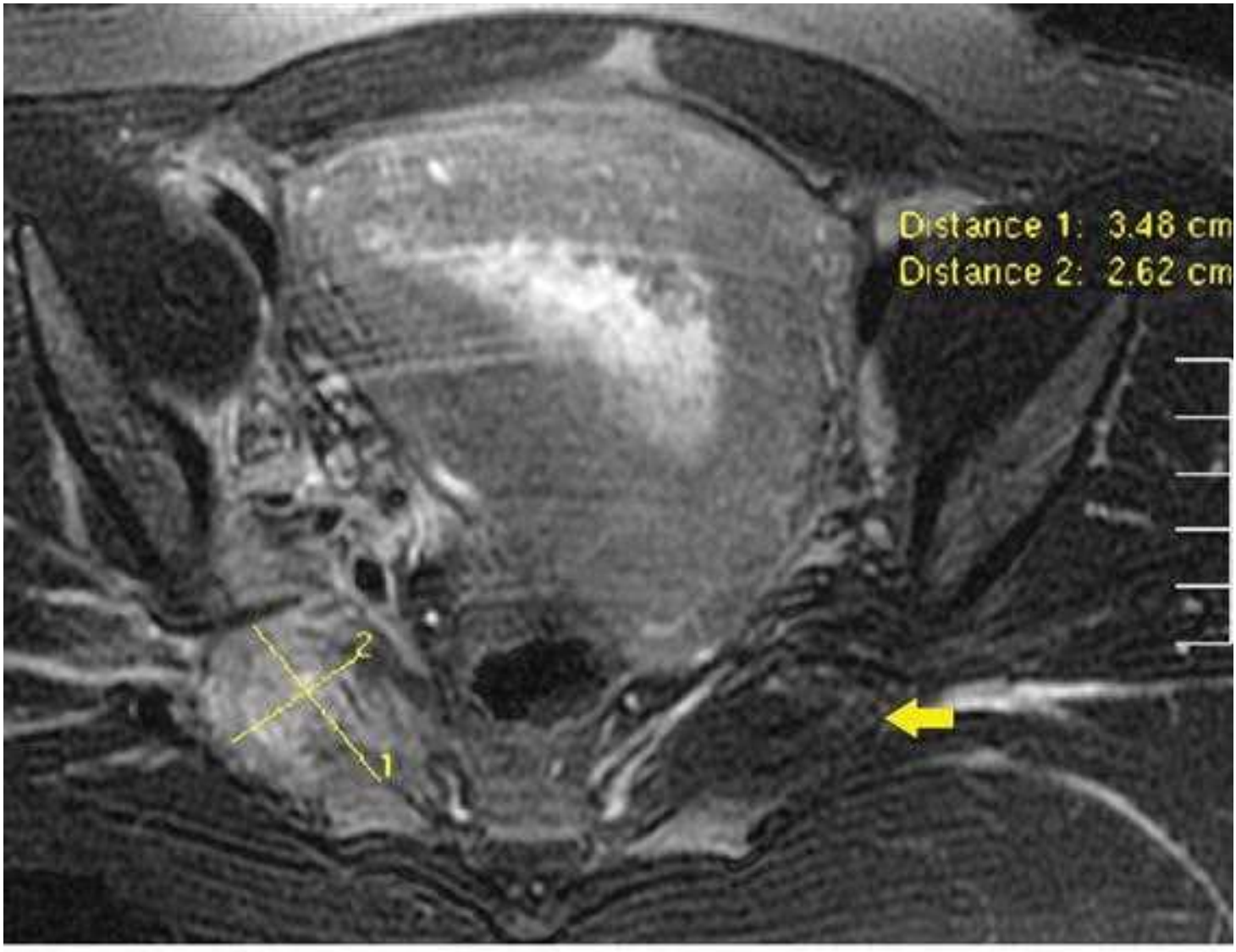
Nerve injuries with cesarean delivery include the iliohypogastric and ilioinguinal nerves (Rahn, 2010). These are discussed further in Chapter 2 (Innervation).

Musculoskeletal Injuries

Pain in the pelvic girdle, hips, or lower extremities may follow stretching or tearing injuries sustained at normal or difficult delivery. Magnetic resonance (MR) imaging is often informative (Miller, 2015). One example is the piriformis muscle hematoma shown in Figure 36-6. Most injuries resolve with antiinflammatory agents and physical therapy. Rarely, there may be septic pyomyositis such as with iliopsoas muscle abscess (Nelson, 2010; Young, 2010).

FIGURE 36-6

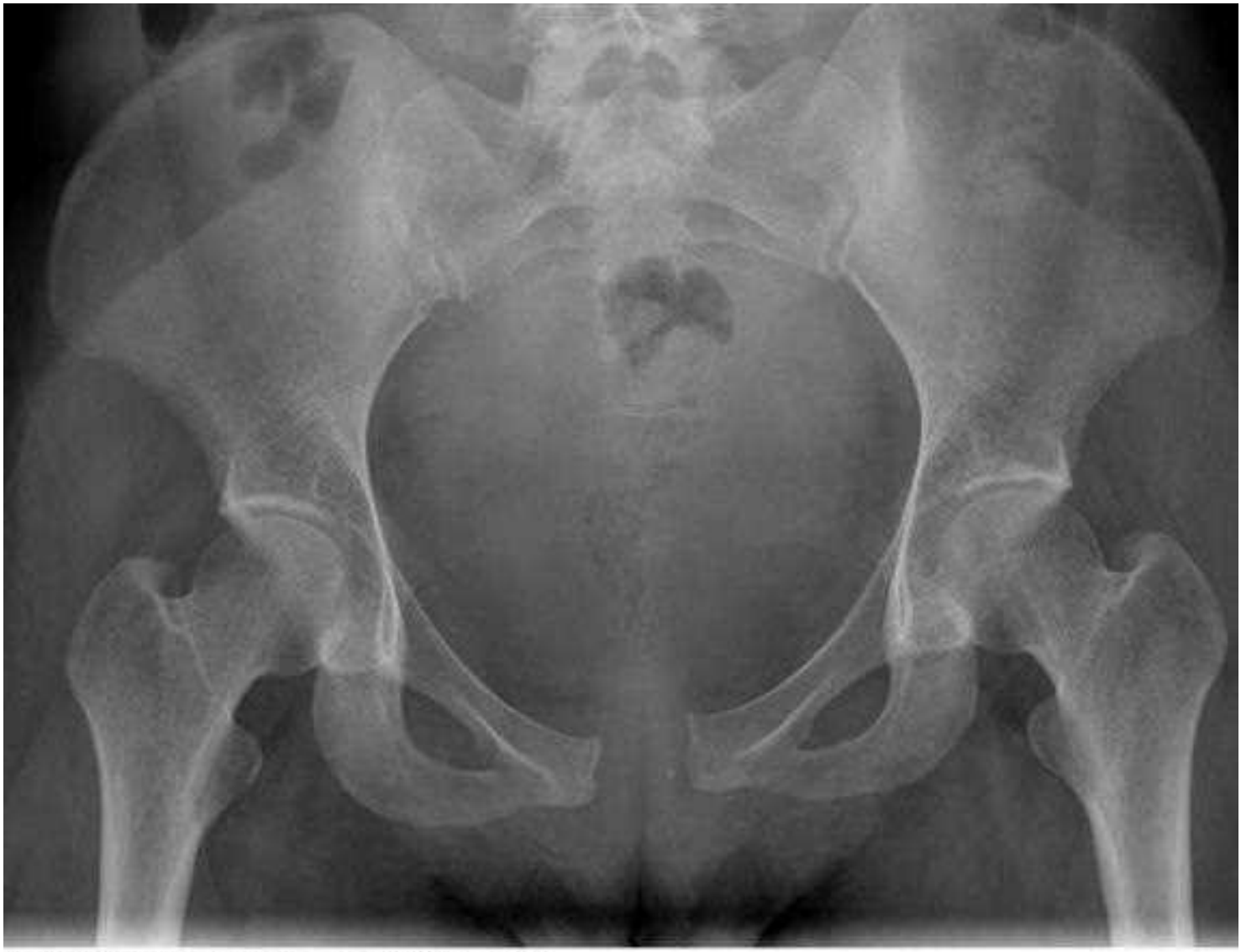
Inhomogeneous mass of the right piriformis muscle consistent with a hematoma (*yellow cursor measurements*) is compared with the normal-appearing left piriformis muscle (*yellow arrow*).



Separation of the symphysis pubis or one of the sacroiliac synchondroses during labor leads to pain and marked interference with locomotion (Fig. 36-7). Estimates of the frequency of this event vary widely from 1 in 600 to 1 in 30,000 deliveries (Reis, 1932; Taylor, 1986). In our experiences, symptomatic separations are uncommon. Their onset of pain is often acute during delivery, but symptoms may manifest either antepartum or up to 48 hours postpartum (Snow, 1997). In suspected cases, radiography is typically selected. The normal distance of the symphyseal joint is 0.4 to 0.5 cm, and symphyseal separation >1 cm is diagnostic for diastasis. Treatment is generally conservative, with rest in a lateral decubitus position and an appropriately fitted pelvic binder (Lasbleiz, 2017). Surgery is occasionally necessary in some symphyseal separations of more than 4 cm (Kharrazi, 1997). The recurrence risk is high in subsequent pregnancy, and Culligan and coworkers (2002) recommend consideration for cesarean delivery.

FIGURE 36-7

Pubic symphyseal separation found on the first postpartum day following vaginal delivery of a 2840-g newborn. The patient had pain over the pubic bone and pain with ambulation. A shuffling gait was noted, and she had difficulty with leg elevation when supine. The patient was treated with physical therapy and analgesics. A pelvic binder was applied, and a rolling walker was provided. She improved quickly and was discharged home on postoperative day 5.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

In rare cases, fractures of the sacrum or pubic ramus are caused by even uncomplicated deliveries (Alonso-Burgos, 2007; Speziali, 2015). As discussed in Chapter 58 (Hypoparathyroidism), the latter are more likely with osteoporosis associated with heparin or corticosteroid therapy (Cunningham, 2005). In rare but serious cases, bacterial osteomyelitis—*osteitis pubis*—can be devastating. Lawford and coworkers (2010) reported such a case that caused massive vulvar edema.

Immunizations

The D-negative woman who is not isoimmunized and whose newborn is D-positive is given 300 µg of anti-D immune globulin shortly after delivery (Chap. 15, Prevention of Anti-D Alloimmunization). Women who are not already immune to rubella or varicella are excellent candidates for vaccination before discharge (Swamy, 2015). Those who have not received a tetanus/diphtheria or influenza vaccine should be given these (American College of Obstetricians and Gynecologists, 2017c). Morgan and colleagues (2015) reported that implementation of a best-practices alert in the electronic medical record was associated with a tetanus/diphtheria immunization rate of 97 percent at Parkland Hospital. Vaccination is also discussed in Chapter 9 (Automobile and Air Travel).

Hospital Discharge

Following uncomplicated vaginal delivery, hospitalization is seldom warranted for more than 48 hours. A woman should receive instructions concerning anticipated normal physiological puerperal changes, including lochia patterns, weight loss from diuresis, and milk let-down. She also should receive instructions concerning fever, excessive vaginal bleeding, or leg pain, swelling, or tenderness. Persistent headaches, shortness of breath, or chest pain warrant immediate concern.

Hospital-stay length following labor and delivery is now regulated by federal law (Chap. 32, Rooming In and Hospital Discharge). Currently, the norms are hospital stays up to 48 hours following uncomplicated vaginal delivery and up to 96 hours following uncomplicated cesarean delivery (American Academy

of Pediatrics, 2017; Blumenfield, 2015). Earlier hospital discharge is acceptable for appropriately selected women if they desire it.

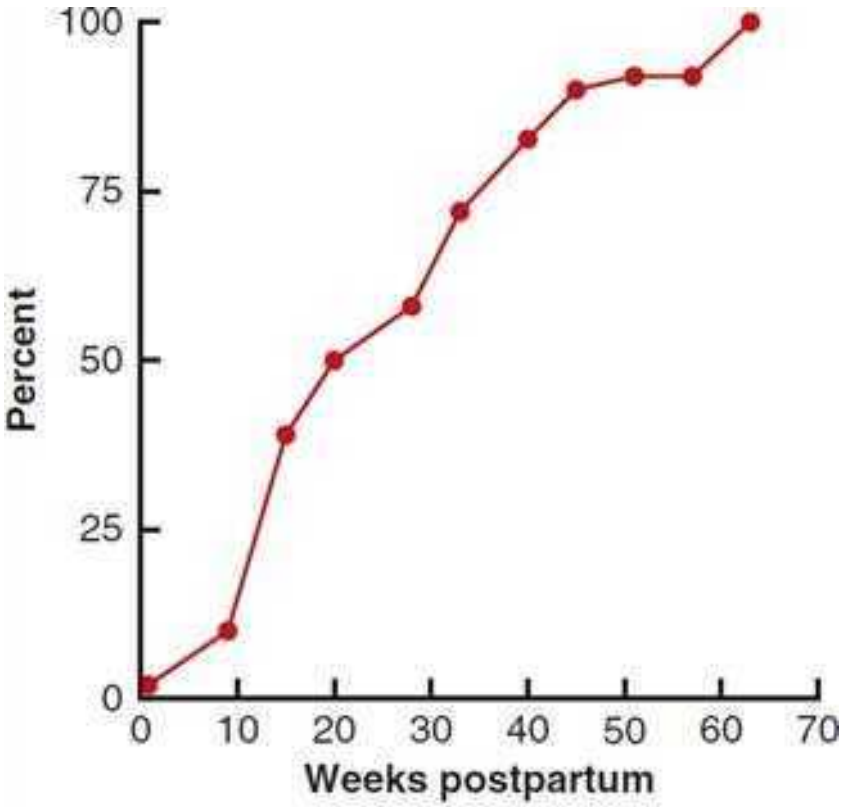
Contraception

During the hospital stay, a concerted effort is made to provide family planning education. Various forms of contraception are discussed throughout Chapter 38 and sterilization procedures in Chapter 39.

Women not breastfeeding have return of menses usually within 6 to 8 weeks. At times, however, it is difficult clinically to assign a specific date to the first menstrual period after delivery. A minority of women bleed small to moderate amounts intermittently, starting soon after delivery. Ovulation occurs at a mean of 7 weeks, but ranges from 5 to 11 weeks (Perez, 1972). That said, ovulation before 28 days has been described (Hytten, 1995). Thus, conception is possible during the artificially defined 6-week puerperium. *Women who become sexually active during the puerperium, and who do not desire to conceive, should initiate contraception*. Kelly and associates (2005) reported that by the third month postpartum, 58 percent of adolescents had resumed sexual intercourse, but only 80 percent of these were using contraception. Because of this, many recommend long-acting reversible contraceptives—LARC (Baldwin, 2013).

Women who breastfeed ovulate much less frequently compared with those who do not, but variation is great. Timing of ovulation depends on individual biological variation and the intensity of breastfeeding. Lactating women may first menstruate as early as the second or as late as the 18th month after delivery. Campbell and Gray (1993) analyzed daily urine specimens to determine the time of ovulation in 92 lactating women. As shown in Figure 36-8, breastfeeding in general delays resumption of ovulation, although as already emphasized, it does not invariably forestall it. Other findings in their study included the following:

FIGURE 36-8
Cumulative proportion of breastfeeding women who ovulated during the first 70 weeks following delivery. (Data from Campbell OM, Gray RH: Characteristics and determinants of postpartum ovarian function in women in the United States. Am J Obstet Gynecol 169:55, 1993.)



1. Resumption of ovulation was frequently marked by return of normal menstrual bleeding.
2. Breastfeeding episodes lasting 15 minutes seven times daily delayed ovulation resumption.
3. Ovulation can occur without bleeding.
4. Bleeding can be anovulatory.
5. The risk of pregnancy in breastfeeding women was approximately 4 percent per year.

For the breastfeeding woman, progestin-only contraceptives, such as progestin pills, depot medroxyprogesterone, or progestin implants, do not affect the quality or quantity of milk. Success with the progesterone-releasing vaginal ring has also been described (Carr, 2016). These may be initiated any time during the puerperium. Estrogen-progestin contraceptives likely reduce the quantity of breast milk, but under the proper circumstances, they too can be used by breastfeeding women. These hormonal methods are discussed in Chapter 38.

HOME CARE

Coitus

No evidence-based data guide resumption of coitus after delivery, and practices are individualized (Minig, 2009). After 2 weeks, coitus may be resumed *based on desire and comfort.* Barrett and colleagues (2000) reported that almost 90 percent of 484 primiparous women resumed sexual activity by 6 months. And although 65 percent of these reported problems, only 15 percent discussed them with a health-care provider.

Intercourse too soon may be unpleasant, if not frankly painful, and this may be related to episiotomy incisions or severe lacerations. In a study of women without an episiotomy, only 0.4 percent of those with a first- or second-degree tear had dyspareunia (Ventolini, 2014). Conversely, in primiparas with an episiotomy, 67 percent had sexual dysfunction at 3 months, 31 percent at 6 months, and 15 percent at 12 months (Chayachinda, 2015). Dyspareunia was also common following cesarean delivery (McDonald, 2015).

Postpartum, the vulvovaginal epithelium is thin, and very little lubrication follows sexual stimulation. This stems from the hypoestrogenic state following delivery, which lasts until ovulation resumes. It may be particularly problematic in breastfeeding women who are hypoestrogenic for many months postpartum (Palmer, 2003). For treatment, small amounts of topical estrogen cream can be applied daily for several weeks to vulvar tissues. Additionally, vaginal lubricants may be used with coitus.

This same thinning of the vulvovaginal epithelium can lead to dysuria. Topical estrogen can again be offered once cystitis is excluded.

Late Maternal Morbidity

Taken together, major and minor maternal morbidity are surprisingly common in the months following childbirth. In a survey of 1249 British mothers followed for up to 18 months, 3 percent required hospital readmission within 8 weeks (Glazener, 1995; Thompson, 2002). Milder health problems during the first 8 weeks were reported by 87 percent (Table 36-5). Moreover, almost three fourths continued to have various problems for up to 18 months. Practitioners should be aware of these potential issues in their convalescing patients.

TABLE 36-5

Puerperal Morbidity Reported by 8 Weeks

Morbidity	Percent[a]
Fatigue	59
Breast problems	36
Anemia	25
Backache	24
Hemorrhoids	23
Headache	22
“Blues”	21
Constipation	20
Suture breakdown	16
Vaginal discharge	15

[a]In 87 percent of all women, at least one symptom was reported.

Data from Glazener CM, Abdalla M, Stroud P, et al: Postnatal maternal morbidity: extent, causes, prevention and treatment. BJOG 102:282, 1995.

Follow-Up Care

By discharge, women who had an uncomplicated vaginal delivery can resume most activities, including bathing, driving, and household functions. Jimenez and Newton (1979) tabulated cross-cultural information on 202 societies from various international geographical regions. Following childbirth, most societies did not restrict work activity, and approximately half expected a return to full duties within 2 weeks. Wallace and coworkers (2013) reported that 80 percent of women who worked during pregnancy resume work by 1 year after delivery. Despite this, Tulman and Fawcett (1988) reported that only half of mothers regained their usual level of energy by 6 weeks. Women who delivered vaginally were twice as likely to have normal energy levels at this time compared with those with a cesarean delivery. Ideally, the care and nurturing of the infant should be provided by the mother with ample help from the father.

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend a postpartum visit between 4 and 6 weeks. This has proven quite satisfactory to identify abnormalities beyond the immediate puerperium and to initiate contraceptive practices.

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CHAPTER 37: Puerperal Complications

One cannot fail to be impressed with the very large proportion of patients whose troubles have originated from febrile affections during the puerperium, which in many cases were clearly due to the neglect of aseptic precautions on the part of the obstetrician or midwife.

—J. Whitridge Williams (1903)

INTRODUCTION

Although the woman who recently gave birth is susceptible to several potentially serious complications, pelvic infection continues to be the most important source of maternal morbidity and mortality. Other infections include mastitis and breast abscesses. That said, puerperal complications include many of those encountered during pregnancy. For example, as discussed in Chapter 52 (Pathophysiology), venous thromboembolism during the short 6-week puerperium is as frequent as during all 40 antepartum weeks. Other puerperal issues and care are discussed in Chapter 36.

PUERPERAL PELVIC INFECTION

Traditionally, the term *puerperal infection* describes any bacterial infection of the genital tract after delivery. These infections as well as preeclampsia and obstetrical hemorrhage formed the lethal triad of maternal death causes before and during the 20th century. Fortunately, because of effective antimicrobials, maternal mortality from infection has become uncommon. Creanga and associates (2017) reported results from the Pregnancy Mortality Surveillance System, which contained 2009 pregnancy-related maternal deaths in the United States from 2011 through 2013. Infection caused 12.7 percent of pregnancy-related deaths and was the second leading cause. In a similar analysis of the North Carolina population from 1991 through 1999, Berg and colleagues (2005) reported that 40 percent of infection-related maternal deaths were preventable.

Puerperal Fever

Several infective and noninfective factors can cause puerperal fever—a temperature of 38.0°C (100.4°F) or higher. *Most persistent fevers after childbirth are caused by genital tract infection.* Using this conservative definition of fever, Filker and Monif (1979) reported that only about 20 percent of women febrile within the first 24 hours after vaginal delivery were subsequently diagnosed with pelvic infection. This was in contrast to 70 percent of those after cesarean delivery. It must be emphasized that spiking fevers of 39°C or higher that develop within the first 24 hours postpartum may be associated with virulent pelvic infection caused by group A streptococcus, discussed in Uterine Infection.

Other causes of puerperal fever include breast engorgement; infections of the urinary tract, of perineal lacerations, and of episiotomy or abdominal incisions; and respiratory complications after cesarean delivery (Maharaj, 2007). Approximately 15 percent of women who do not breastfeed develop postpartum fever from *breast engorgement*. As discussed in Chapter 36 (Hospital Care), the incidence of fever is lower in breastfeeding women. “Breast fever” rarely exceeds 39°C in the first few postpartum days and usually lasts <24 hours. *Urinary infections* are uncommon postpartum because of the normal diuresis encountered then. *Acute pyelonephritis* has a variable clinical picture. The first sign of renal infection may be fever, followed later by costovertebral angle tenderness, nausea, and vomiting. *Atelectasis* following abdominal delivery is caused by hypoventilation and is best prevented by coughing and deep breathing on a fixed schedule following surgery. Fever associated with atelectasis is thought to stem from normal flora that proliferate distal to obstructing mucus plugs.

Uterine Infection

Postpartum uterine infection or puerperal sepsis has been called variously *endometritis, endomyometritis,* and *endoparametritis.* Because infection involves not only the decidua but also the myometrium and parametrial tissues, we prefer the inclusive term *metritis with pelvic cellulitis.*

Predisposing Factors

The route of delivery is the single most significant risk factor for the development of uterine infection (Burrows, 2004; Koroukian, 2004). In the French Confidential Enquiry on Maternal Deaths, Deneux-Tharaux and coworkers (2006) cited a nearly 25-fold increased infection-related mortality rate with cesarean versus vaginal delivery. Rehospitalization rates for wound complications and metritis were increased significantly in women undergoing a planned primary cesarean delivery compared with those having a planned vaginal birth (Declercq, 2007).

Women delivered vaginally at Parkland Hospital have a 1- to 2-percent incidence of metritis. For women at high risk for infection because of membrane rupture, prolonged labor, and multiple cervical examinations, the frequency of metritis after vaginal delivery is 5 to 6 percent. If intrapartum chorioamnionitis is present, the risk of persistent uterine infection increases to 13 percent (Maberry, 1991). These figures are similar to those reported from a cohort of more than 115,000 women by the Maternal Fetal Medicine Units Network in whom the overall pelvic infection rate approximated 5 percent (Grobman, 2015).

Because of the significant morbidity following hysterotomy, single-dose perioperative antimicrobial prophylaxis is recommended for all women undergoing cesarean delivery (American College of Obstetricians and Gynecologists, 2016b). Antimicrobial prophylaxis has done more to decrease the incidence and severity of

postcesarean delivery infections than any other intervention in the past 30 years. Such practices decrease the puerperal pelvic infection risk by 65 to 75 percent (Smaill, 2010).

The magnitude of the risk is exemplified from earlier reports that predate antimicrobial prophylaxis. Cunningham and associates (1978) described an overall incidence of 50 percent in all women undergoing cesarean delivery at Parkland Hospital. Important risk factors for infection following surgery included prolonged labor, membrane rupture, multiple cervical examinations, and internal fetal monitoring. Women with all these factors who were not given perioperative prophylaxis had a 90-percent serious postcesarean delivery pelvic infection rate (DePalma, 1982).

It is generally accepted that pelvic infection is more frequent in women of lower socioeconomic status (Maharaj, 2007). Except in extreme cases usually not seen in this country, it is likely uncommon that anemia or poor nutrition predispose to infection. *Bacterial colonization* of the lower genital tract with certain microorganisms—for example, group B streptococcus, *Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum*, and *Gardnerella vaginalis*—has been associated with an increased postpartum infection risk (Andrews, 1995; Jacobsson, 2002; Watts, 1990). Other factors associated with an increased infection risk include general anesthesia, cesarean delivery for multifetal gestation, young maternal age and nulliparity, prolonged labor induction, obesity, and meconium-stained amnionic fluid (Acosta, 2012; Leth, 2011; Siriwachirachai, 2014; Tsai, 2011).

Microbiology

Most female pelvic infections are caused by bacteria indigenous to the genital tract. Over the past 25 years, there have been reports of group A β-hemolytic streptococcus causing toxic shock-like syndrome and life-threatening infection (Castagnola, 2008; Nathan, 1994). Prematurely ruptured membranes are a prominent risk factor in these infections (Anteby, 1999). In reviews by Crum (2002) and Udagawa (1999) and their colleagues, women in whom group A streptococcal infection was manifested before, during, or within 12 hours of delivery had a maternal mortality rate of almost 90 percent and fetal mortality rate >50 percent. In the past 10 years, skin and soft-tissue infections due to community-acquired methicillin-resistant *Staphylococcus aureus (CA-MRSA)* have become common (Chap. 64, Listeriosis). Although this variant is not a frequent cause of puerperal metritis, it is often implicated in abdominal incisional infections (Anderson, 2007; Patel, 2007). Rotas and coworkers (2007) reported a woman with episiotomy cellulitis from CA-MRSA and hematogenously spread necrotizing pneumonia.

Common Pathogens

Bacteria responsible for most female genital tract infections are listed in Table 37-1. Most of these infections are polymicrobial, which enhances bacterial synergy. Other factors that promote virulence are hematomas and devitalized tissue. Although the cervix and vagina routinely harbor such bacteria, the uterine cavity is usually sterile before rupture of the amnionic sac. As the consequence of labor and delivery and associated manipulations, the amnionic fluid and uterus become contaminated with anaerobic and aerobic bacteria. Intraamnionic cytokines and C-reactive protein are also markers of infection (Combs, 2013; Marchocki, 2013). In studies done before the use of antimicrobial prophylaxis, Gilstrap and Cunningham (1979) cultured amnionic fluid obtained at cesarean delivery in women in labor with membranes ruptured more than 6 hours. All had bacterial growth, and on average, each specimen contained 2.5 organisms. Anaerobic and aerobic organisms were identified in 63 percent, anaerobes alone in 30 percent, and aerobes alone in only 7 percent. Anaerobes included *Peptostreptococcus* and *Peptococcus* species in 45 percent, *Bacteroides* species in 9 percent, and *Clostridium* species in 3 percent. Aerobes included *Enterococcus* in 14 percent, group B streptococcus in 8 percent, and *Escherichia coli* in 9 percent of isolates. Sherman and coworkers (1999) later showed that bacterial isolates at cesarean delivery correlated with those taken from women with metritis at 3 days postpartum. Group B streptococci, *E coli*, and enterococci are some of the more common blood culture isolates with metritis (Cape, 2013; O'Higgins, 2014). Although important because of the severity of infections they cause, clostridial species rarely cause puerperal infections (Chong, 2016).

TABLE 37-1

Bacteria Commonly Responsible for Female Genital Infections

Aerobes
Gram-positive cocci—group A, B, and D streptococci, enterococcus, *Staphylococcus aureus, Staphylococcus epidermidis*
Gram-negative bacteria—*Escherichia coli, Klebsiella, Proteus*
Gram-variable—*Gardnerella vaginalis*
Others
Mycoplasma and *Chlamydia, Neisseria gonorrhoeae*
Anaerobes
Cocci—*Peptostreptococcus* and *Peptococcus* species
Others—*Clostridium, Bacteroides, Fusobacterium, Mobiluncus*

The role of other organisms in the etiology of these infections is unclear. Observations of Chaim and colleagues (2003) suggest that when cervical colonization of *U urealyticum* is heavy, it may contribute to the development of metritis. To add evidence to these observations, Tita and associates (2016) recently reported that azithromycin-based extended-spectrum antimicrobial prophylaxis reduced postoperative cesarean delivery infections from 12 to 6 percent compared with β-lactam

agents given alone. Chlamydial infections have been implicated in late-onset, indolent metritis (Ismail, 1985). Finally, Jacobsson and associates (2002) reported a threefold risk of puerperal infection in a group of Swedish women in whom bacterial vaginosis was identified in early pregnancy (Chap. 65, Vaginitis).

Bacterial Cultures

Routine genital tract cultures obtained before treatment serve little clinical use and add significant costs. Similarly, routine blood cultures seldom modify care. In two earlier studies done before perioperative prophylaxis was used, blood cultures were positive in 13 percent of women with postcesarean metritis at Parkland Hospital and 24 percent in those at Los Angeles County Hospital (Cunningham, 1978; DiZerega, 1979). In a later Finnish study, Kankuri and associates (2003) identified bacteremia in only 5 percent of almost 800 women with puerperal sepsis. Blood cultures might be reasonable in women with exceedingly high temperature spikes that may signify virulent infection with group A streptococci.

Pathogenesis and Clinical Course

Puerperal infection following vaginal delivery primarily involves the placental implantation site, decidua and adjacent myometrium, or cervicovaginal lacerations. The pathogenesis of uterine infection following cesarean delivery is that of an infected surgical incision. Bacteria that colonize the cervix and vagina gain access to amnionic fluid during labor. Postpartum, they invade devitalized uterine tissue. Parametrial cellulitis next follows with infection of the pelvic retroperitoneal fibroareolar connective tissue. With early treatment, infection is contained within the parametrial and paravaginal tissue, but it may extend deeply into the pelvis.

Fever is the most important criterion for the diagnosis of postpartum metritis. Intuitively, the degree of fever is believed proportional to the extent of infection and sepsis syndrome. Temperatures commonly are 38 to 39°C. Chills that accompany fever suggest bacteremia or endotoxemia. Women usually complain of abdominal pain, and parametrial tenderness is elicited on abdominal and bimanual examination. Leukocytosis may range from 15,000 to 30,000 cells/μL, but recall that delivery itself increases the leukocyte count (Hartmann, 2000). Although an offensive odor may develop, many women have foul-smelling lochia without evidence for infection, and vice versa. Some other infections, notably those caused by group A β-hemolytic streptococci, may be associated with scant, odorless lochia (Anderson, 2014).

Treatment

If nonsevere metritis develops following vaginal delivery, then treatment with an oral or intramuscular antimicrobial agent may be sufficient (Meaney-Delman, 2015). For moderate to severe infections, however, intravenous therapy with a broad-spectrum antimicrobial regimen is indicated. Improvement follows in 48 to 72 hours in nearly 90 percent of women treated with one of several regimens discussed below. Persistent fever after this interval mandates a careful search for causes of refractory pelvic infection. These include a parametrial phlegmon—an area of intense cellulitis; an abdominal incisional or pelvic abscess or infected hematoma; and septic pelvic thrombophlebitis. In our experience, persistent fever is seldom due to antimicrobial-resistant bacteria or due to drug side effects. The woman may be discharged home after she has been afebrile for at least 24 hours, and further oral antimicrobial therapy is not needed (French, 2004; Mackeen, 2015).

Choice of Antimicrobials

Although therapy is empirical, initial treatment following cesarean delivery is directed against elements of the mixed flora shown in Table 37-1. For infections following vaginal delivery, as many as 90 percent of women respond to regimens such as ampicillin plus gentamicin. In contrast, anaerobic coverage is included for infections following cesarean delivery (Table 37-2).

TABLE 37-2

Antimicrobial Regimens for Pelvic Infections Following Cesarean Delivery

Regimen	Comments
Clindamycin + gentamicin	"Gold standard," 90–97% efficacy, once-daily gentamicin dosing acceptable ***PLUS*** Ampicillin added to regimen with sepsis syndrome or suspected enterococcal infection
Clindamycin + aztreonam	Gentamicin substitute for renal insufficiency
Extended-spectrum penicillins	Piperacillin, piperacillin tazobactam, ampicillin/sulbactam, ticarcillin/clavulanate
Cephalosporins	Cefotetan, cefoxitin, cefotaxime
Vancomycin	Added to other regimens for suspected *Staphylococcus aureus* infections
Metronidazole + ampicillin + gentamicin	Metronidazole has excellent anaerobic coverage
Carbapenems	Imipenem/cilastatin, meropenem, ertapenem reserved for special indications

In 1979, DiZerega and colleagues compared the effectiveness of clindamycin plus gentamicin with that of penicillin G plus gentamicin for treatment of pelvic infections following cesarean delivery. Women given the clindamycin-gentamicin regimen had a 95-percent response rate, and this regimen is still considered by most to be the standard by which others are measured (French, 2004; Mackeen, 2015). Because enterococcal cultures may be persistently positive despite this standard therapy, some add ampicillin to the clindamycin-gentamicin regimen, either initially or if there is no response by 48 to 72 hours (Brumfield, 2000).

Many authorities recommend that serum gentamicin levels be periodically monitored. At Parkland Hospital, we do not routinely do so if the woman has normal renal function. Once-daily dosing and multiple-dosing with gentamicin both provide adequate serum levels, and either method has similar cure rates (Livingston, 2003). Because of potential nephrotoxicity and ototoxicity with gentamicin in the event of diminished glomerular filtration, some have recommended a combination of clindamycin and a second-generation cephalosporin to treat such women. Others recommend a combination of clindamycin and aztreonam, which is a monobactam compound with activity similar to the aminoglycosides.

The spectra of *β-lactam antimicrobials* include activity against many anaerobic pathogens. Some examples include cephalosporins such as cefoxitin, cefotetan, cefotaxime, and ceftriaxone, as well as extended-spectrum penicillins such as piperacillin, ticarcillin, and mezlocillin. β-Lactam antimicrobials are inherently safe and, except for allergic reactions, are free of major toxicity. The *β-lactamase inhibitors* clavulanic acid, sulbactam, and tazobactam have been combined with ampicillin, amoxicillin, ticarcillin, and piperacillin to extend their spectra. *Metronidazole* has superior in vitro activity against most anaerobes. This agent given with ampicillin and an aminoglycoside provides coverage against most organisms encountered in serious pelvic infections. Metronidazole is also used to treat *Clostridium difficile* colitis.

Imipenem and similar antimicrobials are in the carbapenem family. These offer broad-spectrum coverage against most organisms associated with metritis. Imipenem is used in combination with *cilastatin*, which inhibits its renal metabolism. Preliminary findings with *ertapenem* indicated suboptimal outcomes (Brown, 2012). It seems reasonable from both a medical and an economic standpoint to reserve these drugs for serious nonobstetrical infections.

Vancomycin is a glycopeptide antimicrobial active against gram-positive bacteria. It is used in lieu of β-lactam therapy for a patient with a type 1 allergic reaction and given for suspected infections due to *Staphylococcus aureus* and to treat *C difficile* colitis (Chap. 54, Inflammatory Bowel Disease).

Perioperative Prophylaxis

The use of periprocedural antimicrobial prophylaxis is common in obstetrics. Even so, no rigorous studies have evaluated providing prophylaxis following operative vaginal delivery or manual removal of the placenta (Chongsomchai, 2014; Liabsuetrakul, 2017). But, as discussed, antimicrobial prophylaxis at the time of cesarean delivery has remarkably reduced the postoperative pelvic and wound infection rates. Numerous studies have shown that prophylactic antimicrobials reduce the pelvic infection rate by 70 to 80 percent (Chelmow, 2001; Dinsmoor, 2009; Smaill, 2014). The observed benefit applies to both elective and nonelective cesarean delivery and also includes a reduction in abdominal incision infection rates.

Single-dose prophylaxis with a 2-g dose of ampicillin or a first-generation cephalosporin is ideal. Both equal the efficacy of broad-spectrum agents or multiple-dose regimens (American College of Obstetricians and Gynecologists, 2016b). For obese women, evidence supports a 3-g dose of cefazolin to reach optimal tissue concentrations (Swank, 2015). Extended-spectrum prophylaxis with azithromycin added to standard single-dose prophylaxis further reduced postcesarean metritis rates (Sutton, 2015; Ward, 2016). As noted earlier, Tita and colleagues (2016) reported that postoperative uterine infection was decreased from 12 to 6 percent with the addition of azithromycin to cefazolin. Women known to be colonized with MRSA are given vancomycin in addition to a cephalosporin (Chap. 64, Listeriosis).

It is controversial whether the infection rate is lowered further if the antimicrobial is given before the skin incision compared with after umbilical cord clamping (Baaqeel, 2013; Macones, 2012; Sun, 2013). The American College of Obstetricians and Gynecologists (2016b) has concluded that the evidence favors predelivery administration. Abdominal preoperative skin preparation with chlorhexidine-alcohol is superior to iodine-alcohol for preventing surgical-site infections (Tuuli, 2016). Additive salutary effects may be gained by preoperative vaginal cleansing with povidone-iodine rinse or application of metronidazole gel (Haas, 2014; Reid, 2011; Yildirim, 2012).

Other Methods of Prophylaxis

Several studies have addressed the value of prenatal cervicovaginal cultures. These are obtained in the hope of identifying pathogens that might be eradicated to decrease incidences of preterm labor, chorioamnionitis, and puerperal infections. Unfortunately, treatment of asymptomatic vaginal infections has not been shown to prevent these complications. Carey and coworkers (2000) reported no beneficial effects for women treated for asymptomatic bacterial vaginosis. Klebanoff and colleagues (2001) reported a similar postpartum infection rate in women treated for second-trimester asymptomatic *Trichomonas vaginalis* infection compared with that of placebo-treated women.

Technical maneuvers done to alter the postpartum infection rate have been studied with cesarean delivery. For example, allowing the placenta to separate spontaneously compared with removing it manually lowers the infection risk. However, changing gloves by the surgical team after placental delivery does not (Atkinson, 1996). Exteriorizing the uterus to close the hysterotomy may decrease febrile morbidity (Jacobs-Jokhan, 2004). Postdelivery mechanical lower segment and cervical dilatation has not been shown to be effective (Liabsuetrakul, 2011). No differences were found in postoperative infection rates when single- and two-layer uterine closures were compared (Hauth, 1992). Similarly, infection rates are not appreciatively affected by closure versus nonclosure of the peritoneum (Bamigboye, 2014; Tulandi, 2003). Importantly, although closure of subcutaneous tissue in obese women does not lower the wound infection rate, it does decrease the wound separation incidence (Chelmow, 2004). Similarly, skin closure with staples versus suture has a higher incidence of noninfectious skin separation (Mackeen, 2012; Tuuli, 2011).

Complications of Uterine and Pelvic Infections

In more than 90 percent of women, metritis responds to antimicrobial treatment within 48 to 72 hours. In some of the remainder, any of several complications may arise. These include wound infections, complex pelvic infections such as phlegmons or abscesses, and septic pelvic thrombophlebitis (Jaiyeoba, 2012). As with other aspects of puerperal infections, the incidence and severity of these complications are remarkably decreased by perioperative antimicrobial prophylaxis.

Abdominal Incisional Infections

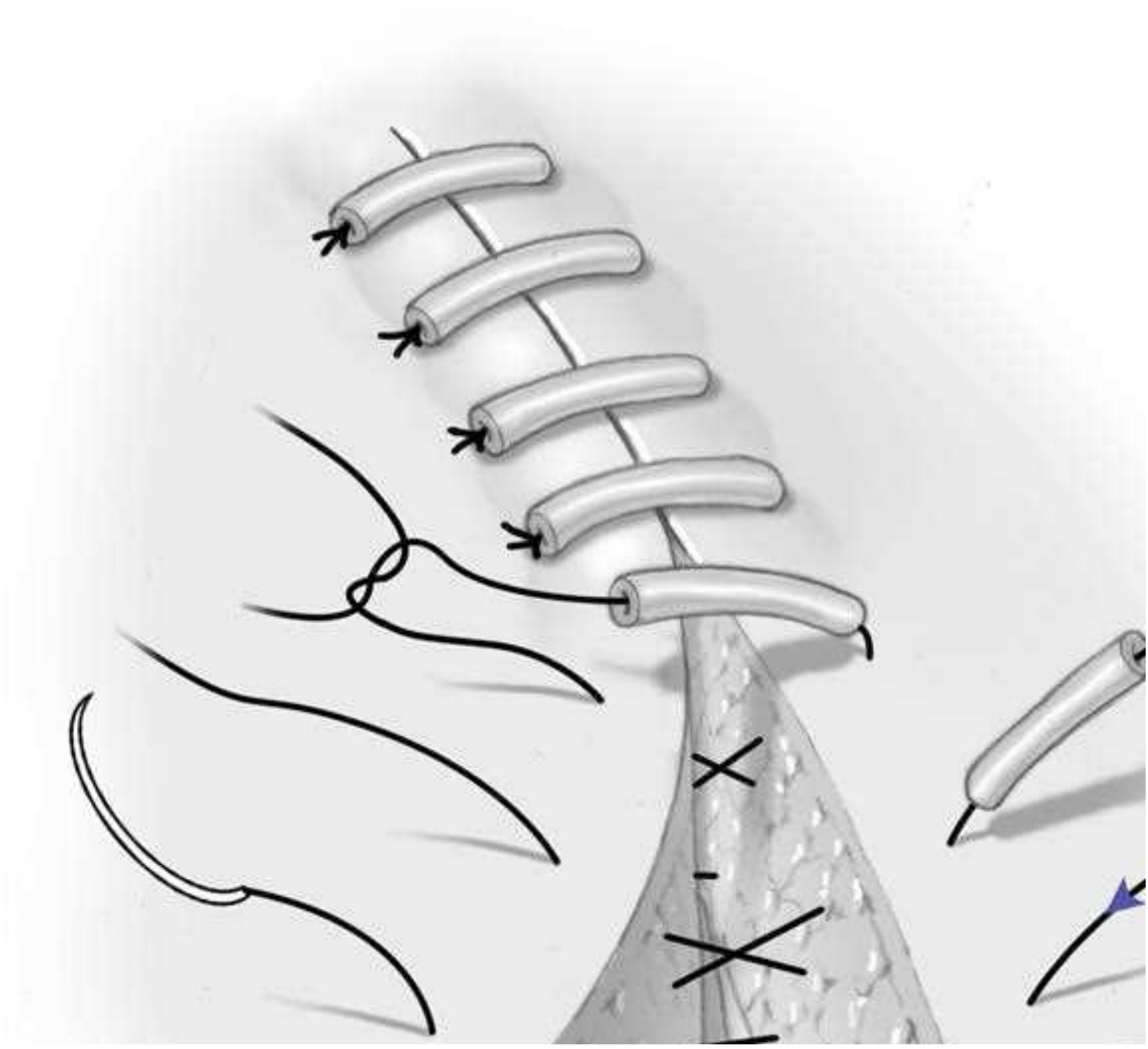
Wound infection is a common cause of persistent fever in women treated for metritis. Incisional infection risk factors include obesity, diabetes, corticosteroid therapy, immunosuppression, anemia, hypertension, and inadequate hemostasis with hematoma formation. If prophylactic antimicrobials are given, the incidence of abdominal wound infection following cesarean delivery ranges from 2 to 10 percent depending on risk factors (Andrews, 2003; Chaim, 2000). From our experiences at Parkland Hospital, the incidence is closer to 2 percent.

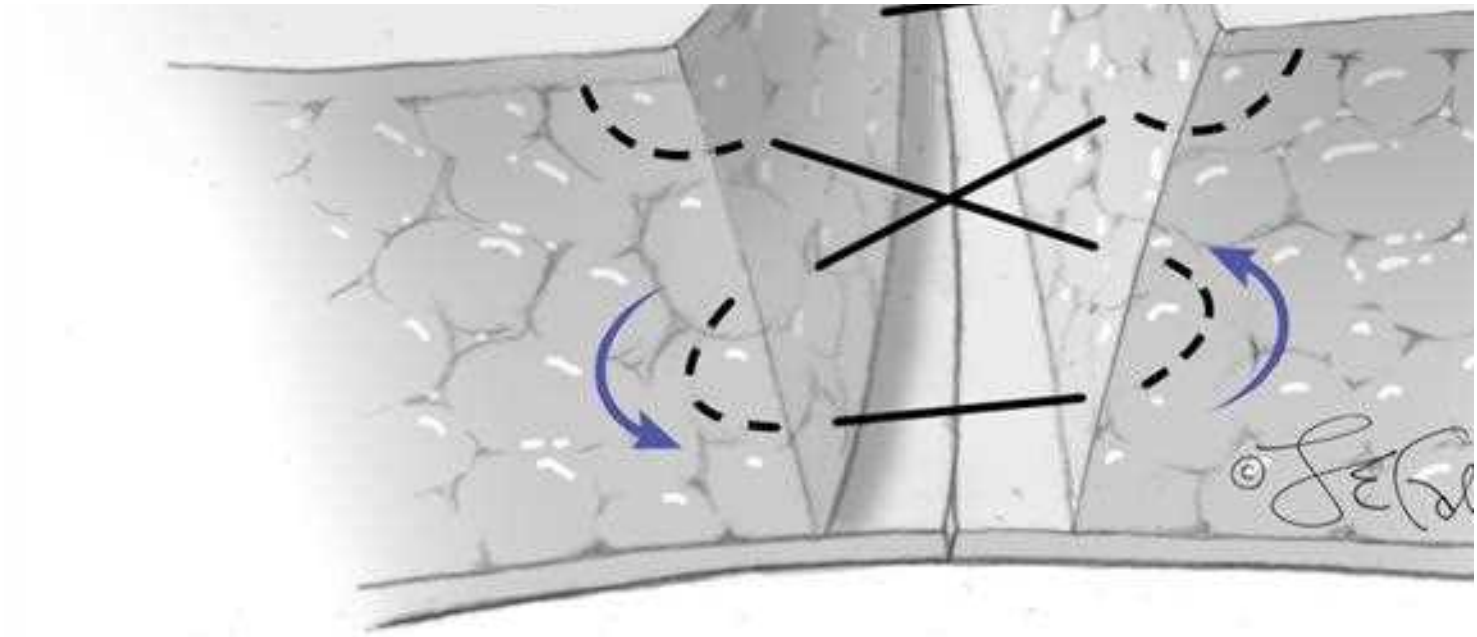
Incisional abscesses that develop following cesarean delivery usually cause persistent fever or fever that begins on about the fourth day. In many cases, antimicrobials had been given to treat pelvic infection, yet fever persisted. The wound is erythematous and drains pus. Although organisms that cause wound infections are generally the same as those isolated from amnionic fluid at cesarean delivery, hospital-acquired pathogens may also be causative (Owen, 1994).

Treatment includes antimicrobials and surgical drainage and debridement of devitalized tissue. This typically requires spinal analgesia or general anesthesia. The fascia is carefully inspected to document integrity. Local wound care thereafter is completed twice daily. Before each dressing change, procedural analgesia is tailored to wound size and location, and oral, intramuscular, or intravenous dosage routes are suitable. Topical lidocaine may also be added. Necrotic tissue is removed, and the wound is repacked with moist gauze. At 4 to 6 days, healthy granulation tissue is typically present, and secondary en bloc closure of the open layers can usually be accomplished (Wechter, 2005). As shown in Figure 37-1, a polypropylene or nylon suture of appropriate gauge enters 2 to 3 cm from one wound edge. It crosses the wound to incorporate the full wound thickness and emerges 3 cm from the other wound edge. These are placed in series to close the opening. In most cases, sutures may be removed on postprocedural day 10.

FIGURE 37-1

Secondary abdominal wound closure technique. (From Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw Hill Education, 2017.)





Vacuum-Assisted Wound Closure

This system was designed to apply negative pressure to a foam-wound interface that would promote wound healing. The technique is variably referred to as *vacuum-assisted closure—VAC; topical negative pressure—TNP*; and *negative-pressure wound therapy—NPWT*. Several systems are available and widely accepted despite meager formal evidence for clinical efficacy (Echebiri, 2015; Rouse, 2015; Swift, 2015). In obstetrics, disrupted and infected abdominal wounds are a major indication for vacuum-assisted closure. Closure of perineal wounds resulting from infected episiotomies, hematomas, or abscesses is another (Aviki, 2015). These devices are also used for the "open surgical abdomen," which is occasionally encountered in obstetrics. Negative-pressure wound therapy has also been used to prevent wound infections in those closed to heal by primary intention.

Very few randomized trials have compared vacuum-assisted wound closure with conventional wound care (Semsarzadeh, 2015). Likewise, its cost effectiveness has not been thoroughly studied, although provider time is decreased substantially (Lewis, 2014). From their review, Mouës and colleagues (2011) are more circumspect about its use for disrupted abdominal wounds because of scarce data. Other reviewers conclude that vacuum therapy is the most efficient method of temporary abdominal closure for patients with open abdominal wounds (Bruhin, 2014; Quyn, 2012).

Wound Dehiscence

Wound disruption or dehiscence refers to separation of the fascial layer. This is a serious complication and requires secondary closure of the incision in the operating room. McNeeley and associates (1998) reported a fascial dehiscence rate of approximately 1 per 300 operations in almost 9000 women undergoing cesarean delivery. Other than wound infection, obesity may be a risk factor (Subramaniam, 2014). Most disruptions manifested on about the fifth postoperative day and were accompanied by a serosanguinous discharge. Two thirds of 27 fascial dehiscences identified in this study were associated with concurrent fascial infection and tissue necrosis.

Necrotizing Fasciitis

This uncommon, severe wound infection is associated with high mortality rates. In obstetrics, necrotizing fasciitis may involve abdominal incisions, or it may complicate episiotomy or other perineal lacerations. As the name implies, tissue necrosis is significant. Of the risk factors for fasciitis summarized by Owen and Andrews (1994), three of these—diabetes, obesity, and hypertension—are relatively common in gravidas. Like pelvic infections, these wound complications usually are polymicrobial and are caused by organisms that make up the normal vaginal flora. In some cases, however, infection is caused by a single virulent bacterial species such as group A β-hemolytic streptococcus (Anderson, 2014; Rimawi, 2012). Occasionally, necrotizing infections are caused by rarely encountered pathogens (Chong, 2016; Swartz, 2004).

Goepfert and coworkers (1997) reviewed their experiences with necrotizing fasciitis. Nine cases complicated more than 5000 cesarean deliveries, a frequency of 1.8 per 1000. In two women, the infection was fatal. In another report, Schorge and colleagues (1998) described five women with fasciitis following cesarean delivery. None of these women had predisposing risk factors, and none died.

Infection may involve skin, superficial and deep subcutaneous tissues, and any of the abdominopelvic fascial layers (Fig. 37-2). In some cases, muscle is also involved —*myofasciitis*. Although some virulent infections—for example, those caused by group A β-hemolytic streptococci—develop early postpartum, most of these necrotizing infections do not cause symptoms until 3 to 5 days after delivery. Clinical findings vary, and it is frequently difficult to differentiate more innocuous superficial wound infections from an ominous deep fascial one. A high index of suspicion, with surgical exploration if the diagnosis is uncertain, may be lifesaving (Goh, 2014). We aggressively pursue early exploration. Certainly, if myofasciitis progresses, the woman may become ill from septicemia (Chap. 47, Sepsis Syndrome).

FIGURE 37-2

Necrotizing fasciitis involving the abdominal wall and Pfannenstiel incision. The skin rapidly became dusky and gangrenous, and pus is seen exuding from the left angle of the incision. Extensive debridement and supportive therapy were lifesaving.

Early diagnosis, surgical debridement, antimicrobials, and intensive care are paramount to successfully treat necrotizing soft-tissue infections (Gallup, 2002; Goh, 2014). Surgery includes extensive debridement of all infected tissue, leaving wide margins of healthy bleeding tissue. This may include extensive abdominal or vulvar debridement with unroofing and excision of abdominal, thigh, or buttock fascia. Death is virtually universal without surgical treatment, and rates approach 25 percent even if extensive debridement is performed. With extensive resection, synthetic mesh may ultimately be required later to close the fascial incision (Gallup, 2002; McNeeley, 1998).

Adnexal Abscesses and Peritonitis

An *ovarian abscess* rarely develops in the puerperium. These are presumably caused by bacterial invasion through a rent in the ovarian capsule (Wetchler, 1985). The abscess is usually unilateral, and women typically present 1 to 2 weeks after delivery. Rupture is common, and peritonitis may be severe.

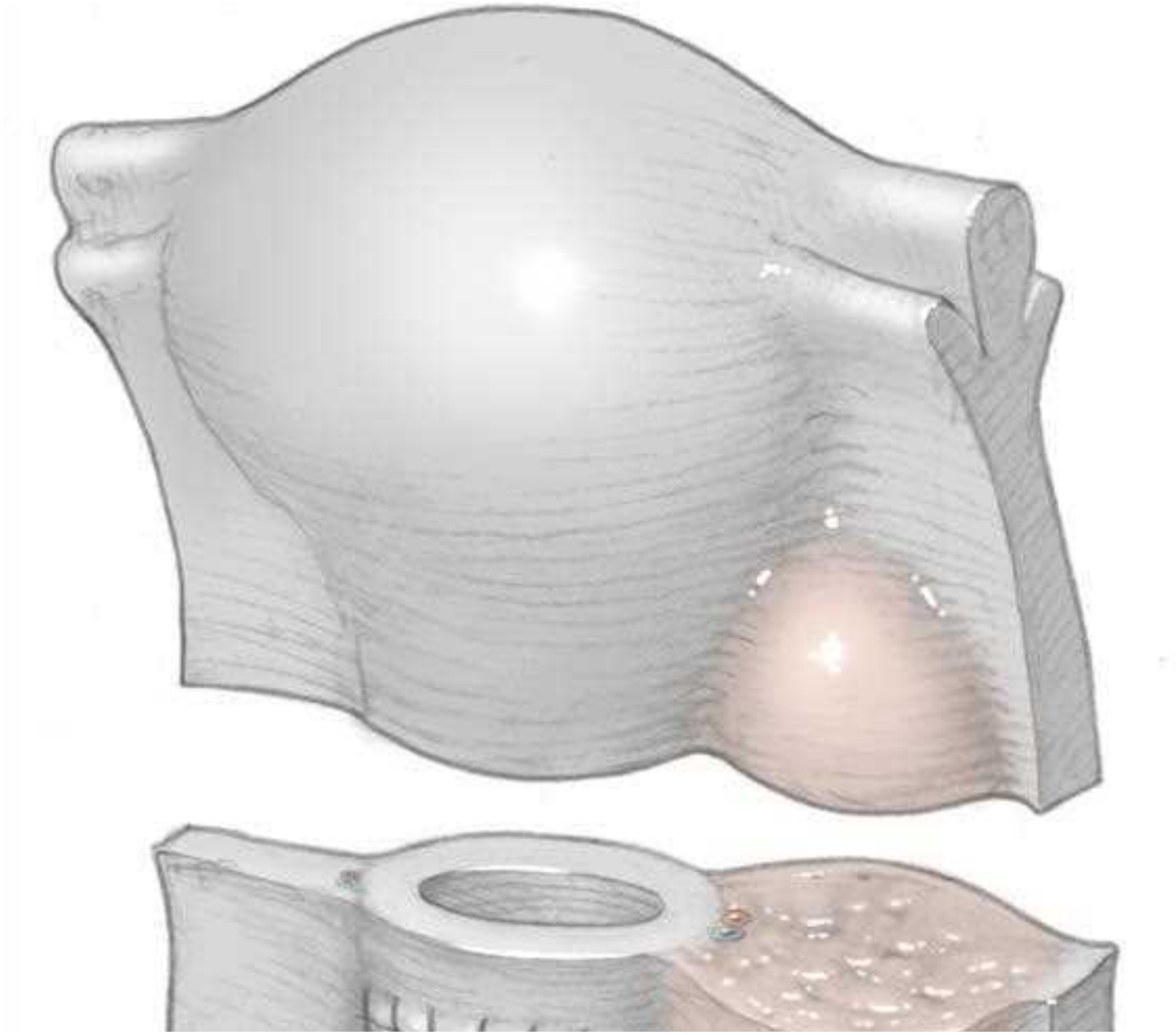
Peritonitis is infrequent following cesarean delivery. It almost invariably is preceded by metritis, especially cases with uterine incisional necrosis and dehiscence. However, it may stem from a ruptured adnexal abscess or an inadvertent intraoperative bowel injury.

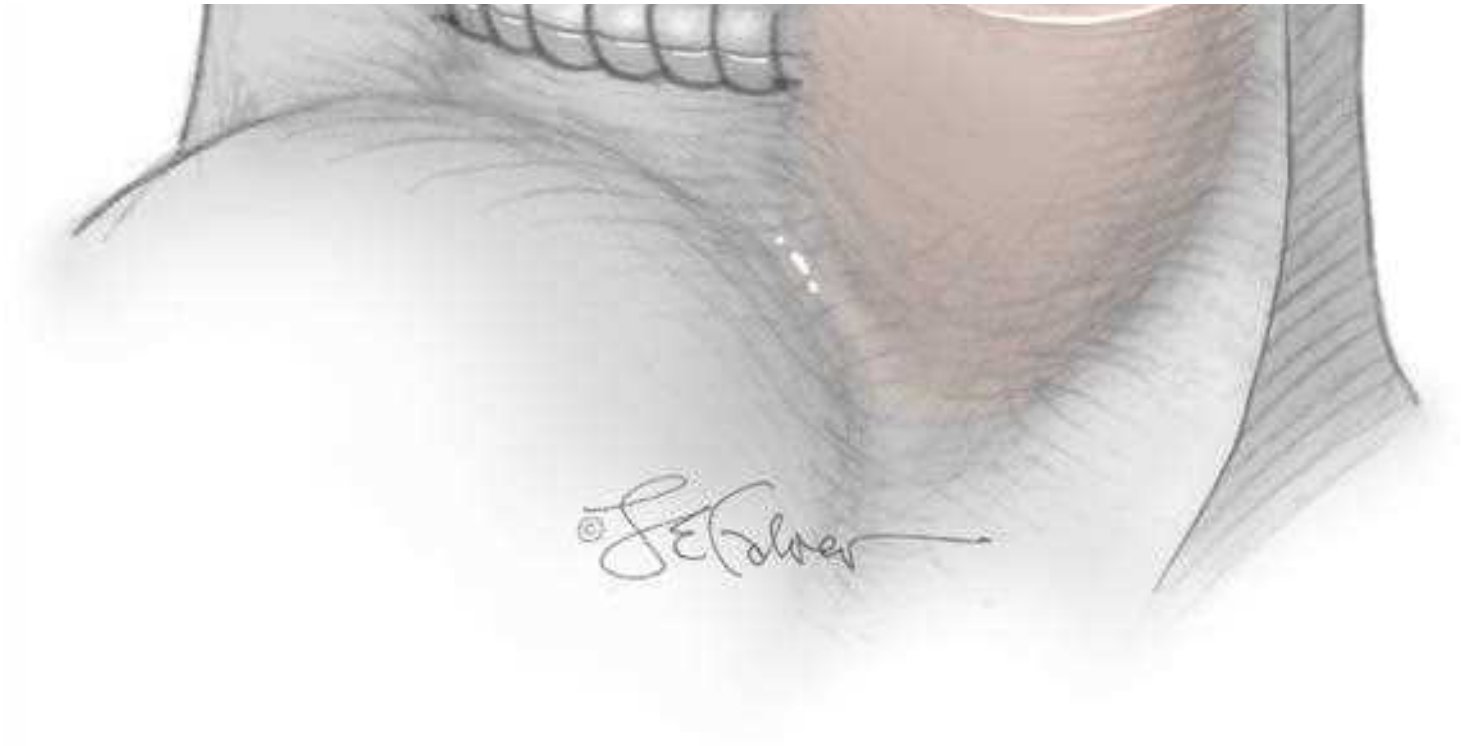
Peritonitis is rarely encountered after vaginal delivery, and many such cases are due to virulent strains of group A β-hemolytic streptococci or similar organisms. Importantly in postpartum women, abdominal rigidity may not be prominent with puerperal peritonitis because of physiological abdominal wall laxity from pregnancy. Pain may be severe, but frequently, the first symptoms of peritonitis are those of *adynamic ileus.* Marked bowel distention may develop, which is unusual after uncomplicated cesarean delivery. If the infection begins in an intact uterus and extends into the peritoneum, antimicrobial treatment alone usually suffices. Conversely, peritonitis caused by uterine incisional necrosis as discussed subsequently, or from bowel perforation, must be treated promptly with surgical intervention.

Parametrial Phlegmon

For some women in whom metritis develops following cesarean delivery, parametrial cellulitis is intensive and forms an area of induration—a *phlegmon*—within the leaves of the broad ligament (Fig. 37-3). These infections are considered when fever persists longer than 72 hours despite intravenous antimicrobial therapy (Brown, 1999; DePalma, 1982).

FIGURE 37-3
Left-sided parametrial phlegmon: cellulitis causes induration in the parametrium adjacent to the hysterotomy incision. (From Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw Hill Education, 2017.)

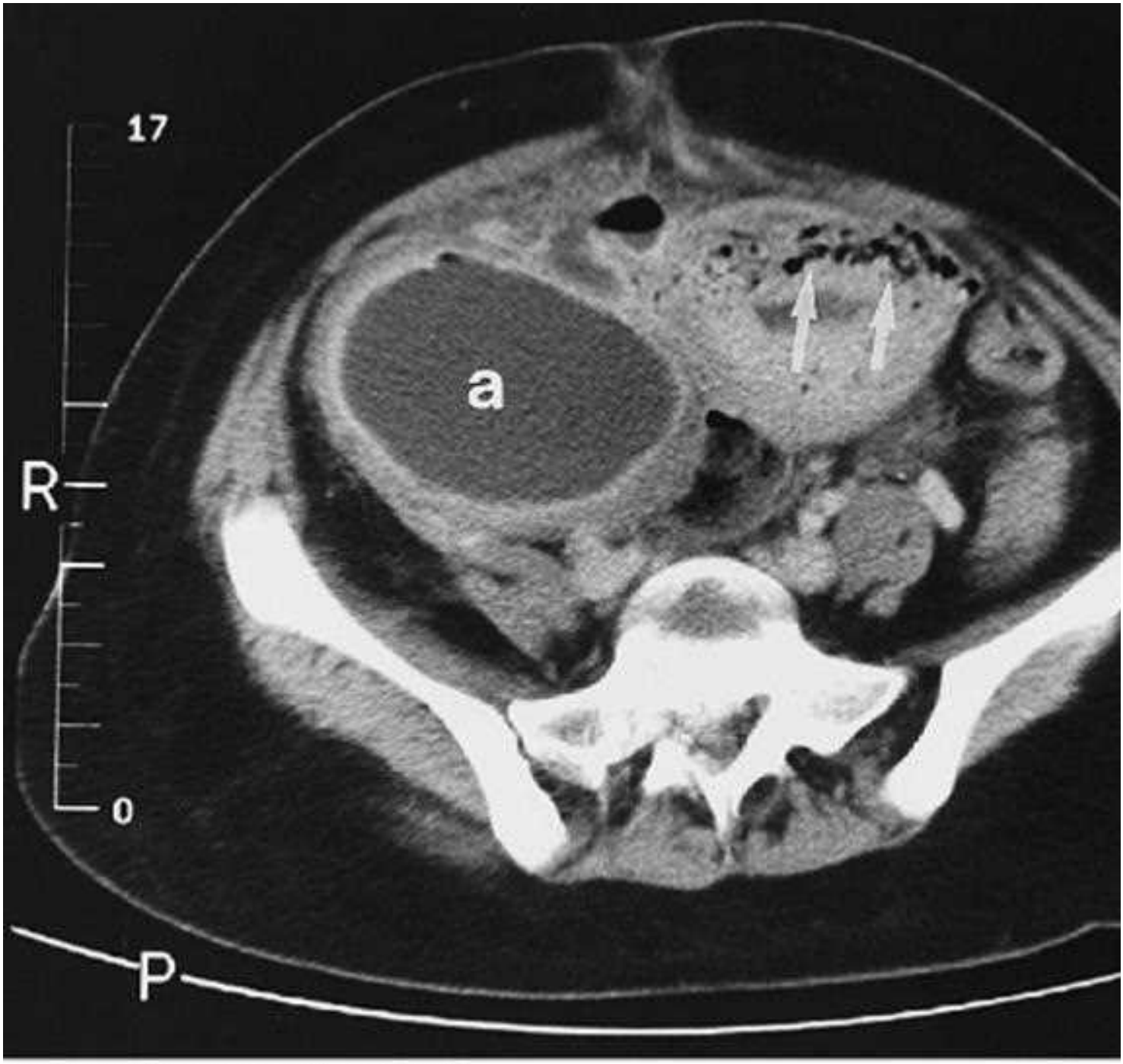




Phlegmons are usually unilateral, and they frequently are limited to the parametrium at the base of the broad ligament. If the inflammatory reaction is more intense, cellulitis extends along natural lines of cleavage. The most common form of extension is laterally along the broad ligament, with a tendency to extend to the pelvic sidewall. Occasionally, posterior extension may involve the rectovaginal septum, producing a firm mass posterior to the cervix. In most women with a phlegmon, clinical improvement follows continued treatment with a broad-spectrum antimicrobial regimen. Typically, fever resolves in 5 to 7 days, but in some cases, it persists longer. Absorption of the induration may require several days to weeks.

In some women, severe cellulitis of the uterine incision may ultimately lead to necrosis and separation (Treszezamsky, 2011). Extrusion of purulent material as shown in Figure 37-4 causes intraabdominal abscess formation and peritonitis as described above. Surgery is reserved for women in whom uterine incisional necrosis is suspected because of ileus and peritonitis. For most, hysterectomy and surgical debridement are needed and are predictably difficult because the cervix and lower uterine segment are involved with an intense inflammatory process that extends to the pelvic sidewall. The adnexa are seldom involved, and one or both ovaries can usually be conserved. Blood loss is often appreciable, and transfusion is usually necessary.

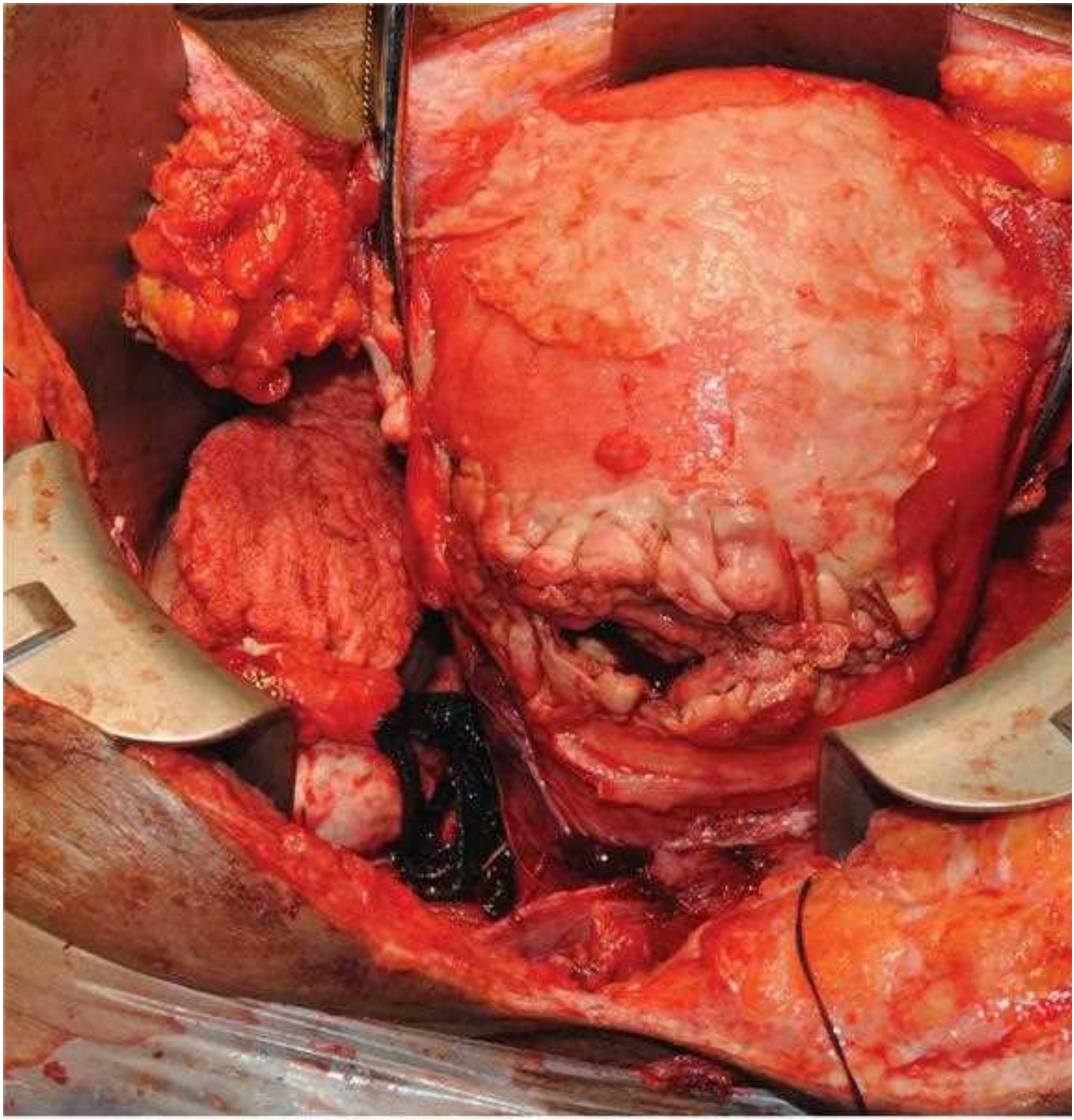
FIGURE 37-4
Pelvic computed tomography scan showing necrosis of the uterine incision with gas in the myometrium (*arrows*). There is also a large right-sided parametrial abscess (*a*).



Imaging Studies

Persistent puerperal infections can be evaluated using computed tomography (CT) or magnetic resonance (MR) imaging. Brown and associates (1991) used CT imaging in 74 women in whom pelvic infection was refractory to antimicrobial therapy given for 5 days. They found at least one abnormal radiological finding in 75 percent of these women, and in most, these were nonsurgical lesions. In most cases, imaging can be used to dissuade surgical exploration. Uterine incisional dehiscence such as shown in Figure 37-4 can sometimes be confirmed based on CT scanning images. These findings must be interpreted within the clinical context because apparent uterine incisional defects thought to represent edema can be seen even after uncomplicated cesarean delivery (Twickler, 1991). Shown in Figure 37-5 is a necrotic hysterotomy incision that leaked into the peritoneal cavity.

FIGURE 37-5
Necrotic hysterotomy infection. Severe cellulitis of the uterine incision resulted in dehiscence with subsequent leakage into the peritoneal cavity. Hysterectomy was required for sufficient debridement of necrotic tissue.



Occasionally, a parametrial phlegmon may suppurate, forming a fluctuant broad ligament mass that may point above the inguinal ligament. These abscesses can dissect anteriorly as shown in Figure 37-4 and be amenable to CT-directed needle drainage. Occasionally they dissect posteriorly to the rectovaginal septum, where surgical drainage is easily effected by colpotomy. A *psoas abscess* is rare, and despite antimicrobial therapy, percutaneous drainage may be required to effectively treat it (Shahabi, 2002; Swanson, 2008).

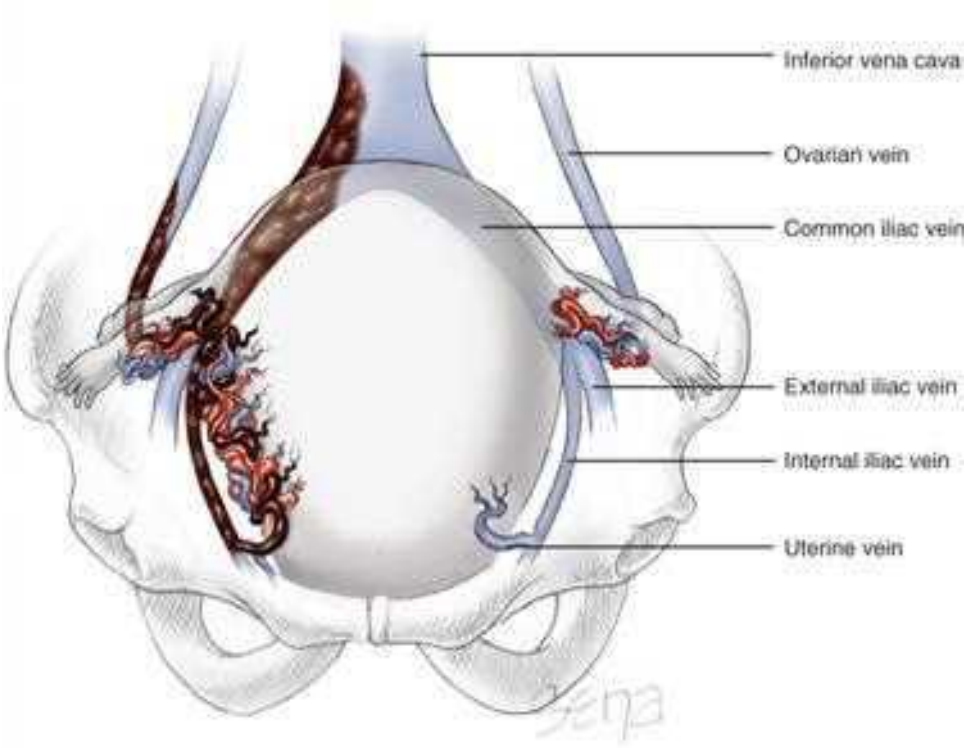
Septic Pelvic Thrombophlebitis

Suppurative thrombophlebitis was a frequent complication in the preantibiotic era, and septic embolization was common. However, with the advent of antimicrobial therapy, the mortality rate and need for surgical therapy for these infections diminished. Septic phlebitis arises as an extension along venous routes and may cause thrombosis as shown in Figure 37-6. Lymphangitis often coexists. The ovarian veins may then become involved because they drain the upper uterus and therefore the placental implantation site. The experiences of Witlin and Sibai (1995) and Brown and coworkers (1999) suggest that puerperal septic

thrombophlebitis is likely to involve one or both ovarian venous plexuses. In a fourth of women, the clot extends into the inferior vena cava and occasionally to the renal vein.

FIGURE 37-6

Septic pelvic thrombophlebitis: uterine and parametrial infection may extend to any pelvic vessel as well as the inferior vena cava. The clot in the right common iliac vein extends from the uterine and internal iliac veins and into the inferior vena cava. The ovarian vein septic thrombosis extends halfway to the vena cava.

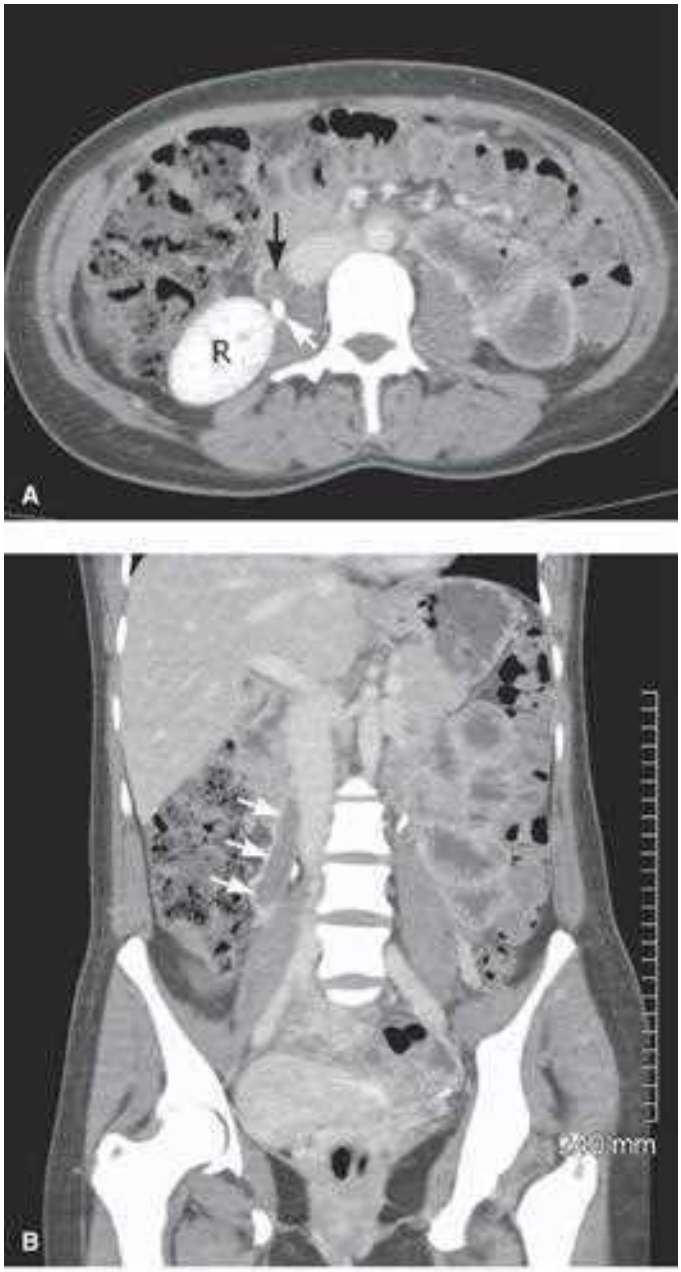


The incidence of septic phlebitis has varied in several reports. In a 5-year survey of 45,000 women who were delivered at Parkland Hospital, Brown and associates (1999) found an incidence of septic pelvic thrombophlebitis in 1 per 9000 gravidas following vaginal delivery and 1 per 800 after cesarean delivery. The overall incidence of 1 per 3000 deliveries was similar to the 1 per 2000 reported by Dunnihoo and colleagues (1991). In large studies of women with cesarean delivery, the incidence was 1 in 400 to 1 in 1000 surgeries (Dotters-Katz, 2017; Rouse 2004). Chorioamnionitis, endometritis, and wound complications were other risks.

Women with septic thrombophlebitis usually have symptomatic improvement with antimicrobial treatment, however, they continue to have fever. Although pain occasionally is noted in one or both lower quadrants, patients are usually asymptomatic except for chills. As shown in Figure 37-7, the diagnosis can be confirmed by pelvic CT or MR imaging (Klima, 2008). Using either, Brown and colleagues (1999) found that 20 percent of 69 women with metritis who had fever despite >5 days of appropriate antimicrobial therapy had septic pelvic thrombophlebitis.

FIGURE 37-7

Septic ovarian vein thrombosis—contrast-enhanced computed tomography scan. **A.** Enlarged right ovarian vein filled with low-density thrombus (*black arrow*). Contrast is seen in ureter (*white arrow*). *R* = lower pole, right kidney. **B.** Coronal image demonstrates enlarged right ovarian vein filled with low-density thrombus (*arrows*). (From Worley KC: Postoperative complications. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw Hill Education, 2017.)



It has been disproven that intravenous heparin causes fever to dissipate with septic phlebitis (Brown, 1986; Witlin, 1995). And although Garcia and coworkers (2006) and Klima and Snyder (2008) advocate heparin therapy, we do not recommend anticoagulation. In a randomized study of 14 women by Brown and associates (1999), the addition of heparin to antimicrobial therapy for septic pelvic thrombophlebitis did not hasten recovery or improve outcome. Certainly, no evidence supports long-term anticoagulation.

Perineal Infections

Episiotomy infections are not common because the operation is performed much less frequently now than in the past (American College of Obstetricians and Gynecologists, 2016a). Reasons for this are discussed further in Chapter 27 (Indications). In an older study, Owen and Hauth (1990) described only 10 episiotomy infections in 20,000 women delivered vaginally. With infection, however, dehiscence is a concern. Ramin and colleagues (1992) reported an episiotomy dehiscence rate of 0.5 percent at Parkland Hospital—80 percent of these were infected. Uygur and associates (2004) reported a 1-percent dehiscence rate and attributed two thirds to infection. No data suggest that dehiscence is related to faulty repair.

When the anal sphincter is disrupted at delivery, the subsequent infection rate is higher and is likely influenced by intrapartum antimicrobial treatment (Buppasiri, 2014; Stock, 2013). Lewicky-Gaupp and colleagues (2015) reported a 20-percent infection rate. Infection of a fourth-degree laceration can be even more serious. Goldaber and coworkers (1993) described fourth-degree lacerations in 390 parturients, of whom 5.4 percent had morbidity. In these women, 2.8 percent had infection and dehiscence, 1.8 percent had only dehiscence, and 0.8 percent only infection. Although life-threatening septic shock is rare, it may still occur as a result of an infected episiotomy. Occasionally also, necrotizing fasciitis develops as discussed in Necrotizing Fasciitis.

Pathogenesis and Clinical Course

Episiotomy dehiscence is most commonly associated with infection. Other factors include coagulation disorders, smoking, and human papillomavirus infection (Ramin, 1994). Local pain and dysuria, with or without urinary retention, are frequent symptoms. Ramin and colleagues (1992), evaluating a series of 34 women with episiotomy dehiscence, reported that the most common findings were pain in 65 percent, purulent discharge in 65 percent, and fever in 44 percent. In extreme cases, the entire vulva may become edematous, ulcerated, and covered with exudate.

Vaginal lacerations may also become infected directly or by extension from the perineum. The epithelium becomes red and swollen and may then become necrotic and slough. Parametrial extension can lead to lymphangitis. Cervical lacerations are common but seldom are noticeably infected, which may manifest as metritis. Deep lacerations that extend directly into the base of the broad ligament may become infected and cause lymphangitis, parametritis, and bacteremia.

Treatment

Infected episiotomies are managed similar to other infected surgical wounds. Drainage is established, and in most cases, sutures are removed and the infected wound debrided. In women with obvious cellulitis but no purulence, close observation and broad-spectrum antimicrobial therapy alone may be appropriate. With dehiscence, local wound care is continued along with intravenous antimicrobials.

Early Repair of Infected Episiotomy

Hauth and colleagues (1986) were the first to advocate early episiotomy repair after infection subsided, and other studies have confirmed the efficacy of this approach. Hankins and coworkers (1990) described early repair in 31 women with an average duration of 6 days from dehiscence to repair. All but two had a successful repair. Each of the two women with failures developed a pinpoint rectovaginal fistula that was treated successfully with a small rectal flap. With episiotomy dehiscence due to infection, Ramin and coworkers (1992) reported successful early repair in 32 of 34 women (94 percent), and Uygur and colleagues (2004) noted a similarly high percentage. Rarely, intestinal diversion may be required to allow healing (Rose, 2005).

Before performing early repair, diligent preparation is essential as outlined in Table 37-3. The surgical wound must be properly cleaned and cleared of infection. Once the surface of the episiotomy wound is free of infection and exudate and covered by pink granulation tissue, secondary repair can be accomplished. The tissue must be adequately mobilized, with special attention to identify and mobilize the anal sphincter muscle. Secondary closure of the episiotomy is accomplished in layers, as described for primary episiotomy closure (Chap. 27, Laceration and Episiotomy Repairs). Postoperative care includes local wound care, stool softeners, and nothing per vagina or rectum until healed.

TABLE 37-3

Preoperative Protocol for Early Repair of Episiotomy Dehiscence

Open wound, remove sutures, begin intravenous antimicrobials
Wound care
Sitz bath several times daily or hydrotherapy
Adequate analgesia or anesthesia—regional analgesia or general anesthesia may be necessary for the first few debridements
Scrub wound twice daily with a povidone-iodine solution
Debride necrotic tissue
Closure when afebrile and pink, healthy granulation tissue predominates
Bowel preparation for fourth-degree repair

Toxic Shock Syndrome

This acute febrile illness with severe multisystem derangement has a case-fatality rate of 10 to 15 percent. Fever, headache, mental confusion, diffuse macular erythematous rash, subcutaneous edema, nausea, vomiting, watery diarrhea, and marked hemoconcentration are usual findings. Renal failure followed by hepatic failure, disseminated intravascular coagulopathy, and circulatory collapse may follow in rapid sequence. During recovery, the rash-covered areas undergo desquamation. For some time, *Staphylococcus aureus* was recovered from almost all afflicted persons. Specifically, a staphylococcal exotoxin, termed *toxic shock syndrome toxin-1* (*TSST-1*), was found to cause the clinical manifestations by provoking profound endothelial injury. A very small amount of TSST-1 has been shown to activate T cells to create a “cytokine storm” as described by Que (2005) and Heying (2007) and their coworkers.

During the 1990s, sporadic reports of virulent group A β-hemolytic streptococcal infection began to appear (Anderson, 2014). Heavy colonization or infection is complicated in some cases by *streptococcal toxic shock syndrome,* which is produced when pyrogenic exotoxin is elaborated. Serotypes M1 and M3 are particularly virulent (Beres, 2004; Okumura, 2004). Finally, almost identical findings of toxic shock were reported by Robbie and associates (2000) in women with *Clostridium sordellii* colonization.

Thus, in some cases of toxic shock syndrome, infection is not apparent and colonization of a mucosal surface is the presumed source. At least 10 to 20 percent of pregnant women have vaginal colonization with *S aureus.* And *Clostridium perfringens* and *sordellii* are cultured from 3 to 10 percent of asymptomatic women (Chong, 2016). Thus, it is not surprising that the disease develops in postpartum women when growth of vaginal bacteria is luxuriant (Chen, 2006; Guerinot, 1982).

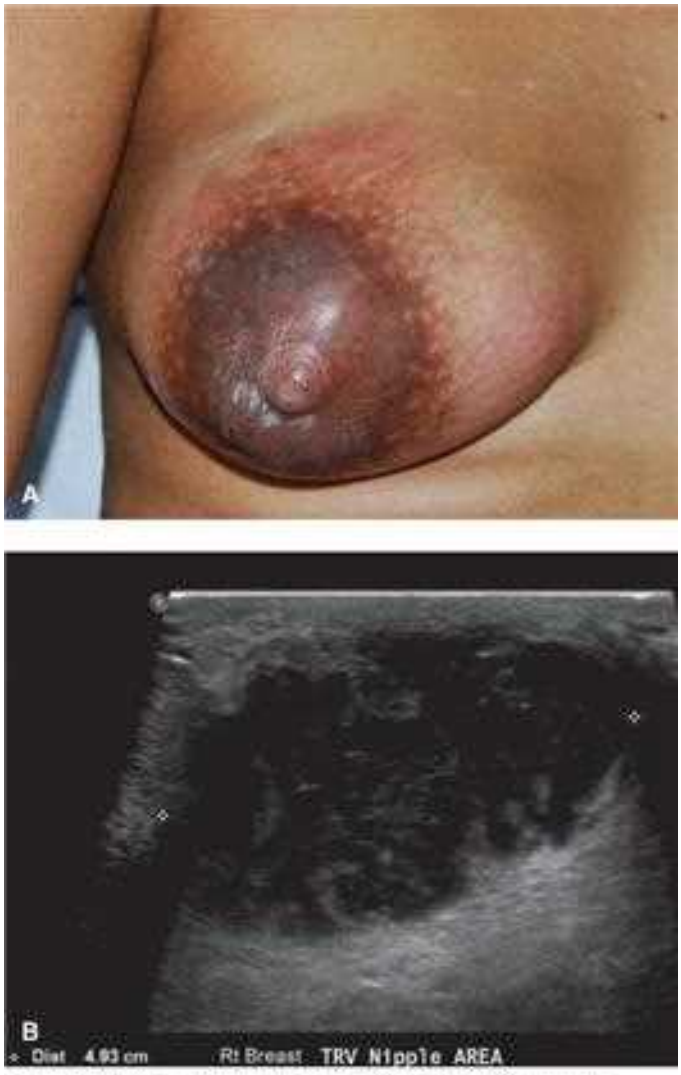
Delayed diagnosis and treatment may be associated with maternal mortality (Schummer, 2002). Crum and colleagues (2002) described a neonatal death following antenatal toxic shock syndrome. Principal therapy is supportive, while allowing reversal of capillary endothelial injury. Antimicrobial therapy that includes staphylococcal and streptococcal coverage is given. With evidence of pelvic infection, antimicrobial therapy must also include agents used for polymicrobial infections. Women with these infections may require extensive wound debridement and possibly hysterectomy. Because the toxin is so potent, the mortality rate is correspondingly high (Hotchkiss, 2003).

BREAST INFECTIONS

Parenchymal infection of the mammary glands is a rare antepartum complication but is estimated to develop in up to a third of breastfeeding women (Barbosa-Cesnik, 2003). Excluding breast engorgement, in our experiences, as well as that of Lee and associates (2010), the incidence of mastitis is much lower and probably approximates 3 percent. No evidence supports any of several prophylactic measures to prevent breast infection (Crepinsek, 2012). Risk factors include difficulties in nursing, cracked nipples, and oral antibiotic therapy (Branch-Elliman, 2012; Mediano, 2014). Symptoms of suppurative mastitis seldom appear before the end of the first week postpartum and, as a rule, not until the third or fourth week. Infection almost invariably is unilateral, and marked engorgement usually precedes inflammation. Symptoms include chills or actual rigors, which are soon followed by fever and tachycardia. Pain is severe, and the breast(s) becomes hard and red (Fig. 37-8). Approximately 10 percent of women with mastitis develop an abscess. Detection of fluctuation may be difficult, and sonography is usually diagnostic.

FIGURE 37-8

Puerperal mastitis with breast abscess. **A.** Photograph shows indurated, erythematous skin overlying area of right breast infection. **B.** Sonographic picture of this 5-cm abscess. (Used with permission from Dr. Emily Adhikari.)



Etiology

Staphylococcus aureus, especially MRSA, is the most commonly isolated organism in breast infections. Matheson and coworkers (1988) found it in 40 percent of women with mastitis. Other commonly isolated organisms are coagulase-negative staphylococci and viridans streptococci. The immediate source of organisms that cause mastitis is almost always the infant's nose and throat. Bacteria enter the breast through the nipple at fissures or small abrasions. The infecting organism can usually be cultured from milk. Toxic shock syndrome from mastitis caused by *S aureus* has been reported (Demey, 1989; Fujiwara, 2001).

At times, suppurative mastitis reaches epidemic levels among nursing mothers. Such outbreaks most often coincide with the appearance of a new strain of antibiotic-resistant staphylococcus. A contemporaneous example is CA-MRSA, which has rapidly become the most commonly isolated staphylococcal species in some areas (Berens, 2010; Klevens, 2007). At Parkland Hospital from 2000 to 2004, Laibl and associates (2005) reported that a fourth of CA-MRSA isolates were from pregnant or postpartum women with puerperal mastitis. Hospital-acquired MRSA may cause mastitis when the newborn becomes colonized after contact with nursery personnel who are colonized (Centers for Disease Control and Prevention, 2006). Stafford and colleagues (2008) found a higher incidence of recurrent abscess in those with CA-MRSA-associated mastitis.

Management

Provided that appropriate therapy for mastitis is started before suppuration begins, the infection usually resolves within 48 hours. As discussed, abscess formation is more common with *S aureus* infection (Matheson, 1988). Most recommend that milk be expressed from the affected breast onto a swab and cultured before therapy is begun. Bacterial identification and antimicrobial sensitivities provide information mandatory for a successful program of nosocomial infection surveillance (Lee, 2010).

The most effective treatment has not been reported (Jahanfar, 2013). Thus, the initial antimicrobial choice is influenced by the current experience with staphylococcal infections at a given institution. Dicloxacillin, 500 mg orally four times daily, may be started empirically. Erythromycin is given to women who are penicillin sensitive. If the infection is caused by resistant, penicillinase-producing staphylococci or if resistant organisms are suspected while awaiting the culture results, then vancomycin, clindamycin, or trimethoprim-sulfamethoxazole is given (Sheffield, 2013). Although clinical response may be prompt, treatment is recommended for 10 to 14 days.

Marshall and coworkers (1975) demonstrated the importance of continued breastfeeding. They reported that of 65 women with mastitis, the only three who developed abscesses were among the 15 women who quit breastfeeding. Vigorous milk expression may be sufficient treatment alone (Thomsen, 1984). Sometimes the infant will not nurse on the inflamed breast. This probably is not related to any changes in the milk taste but is secondary to engorgement and edema, which can make the areola harder to grip. Pumping can alleviate this. When nursing bilaterally, it is best to begin suckling on the uninvolved breast. This allows let-down to commence before moving to the tender breast.

In resource-poor countries, breastfeeding in women infected with the human immunodeficiency virus (HIV) is not contraindicated. In the setting of mastitis or breast abscess, it is recommended to stop feeding from the infected breast. This is because HIV RNA levels increase in affected breast milk. These levels return to baseline after symptoms resolve (Semrau, 2013).

Breast Abscess

In a population-based study of nearly 1.5 million Swedish women, the incidence of breast abscess was 0.1 percent (Kvist, 2005). An abscess should be suspected when defervescence does not follow within 48 to 72 hours of mastitis treatment or when a mass is palpable. Again, sonographic imaging is valuable. Breast abscesses can be large, and in one case report, 2 L of pus were released (Martic, 2012). Traditional therapy is surgical drainage, which usually requires general anesthesia. The incision ideally is placed along Langer skin lines for a cosmetic result (Stehman, 1990). In early cases, a single incision over the most dependent portion of fluctuation is usually sufficient. Multiple abscesses, however, require several incisions and disruption of loculations. The resulting cavity is loosely packed with gauze, which should be replaced at the end of 24 hours by a smaller pack.

A more recently used technique that is less invasive is sonographically guided needle aspiration using local analgesia. This has an 80- to 90-percent success rate (Geiss, 2014; Schwarz, 2001). In a randomized trial, Naeem and colleagues (2012) compared surgical drainage and aspiration. They found aspiration resulted in quicker healing at 8 weeks, 77 versus 93 percent, respectively.

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CHAPTER 38: Contraception

From the evidence available, it appears to be tolerably satisfactorily demonstrated that in women who copulate at frequent intervals the tube must be regarded as a species of receptaculum seminis, in which spermatozoa are always present and waiting for the ovum, and that fertilization usually occurs in the tubes and only rarely in the uterus.

—J. Whitridge Williams (1903)

INTRODUCTION

Nearly half of all pregnancies each year in the United States are unintended (Finer, 2016). These may follow contraceptive method failure or stem from lack of contraceptive use. In 2011 to 2013, 7 percent of sexually active fertile women in the United States not pursuing pregnancy did not use any birth control method (Daniels, 2015).

For those seeking contraception, effective contraceptive methods are available and variably selected (Table 38-1). With these methods, estimated failure rates of perfect and typical use during the first year differ widely. To reflect these failure rates, the World Health Organization (WHO) has grouped methods into efficacy tiers (see Table 38-1). Implants and intrauterine devices are found in the top tier. They effectively lower unintended pregnancy rates and are considered long-acting reversible contraception (LARC). The American College of Obstetricians and Gynecologists (2017c) recognizes these tiers, recommends counseling on *all* options, and encourages highly effective LARC for appropriate candidates.

TABLE 38-1

Contraceptive Failure Rates During the First Year of Method Use in Women in the United States

Method[a]	Perfect Use	Typical Use
Top Tier: Most Effective		
Intrauterine devices:		
Levonorgestrel system	0.2	0.2
T 380A copper	0.6	0.8
Levonorgestrel implants	0.05	0.05
Female sterilization	0.5	0.5
Male sterilization	0.1	0.15
Second Tier: Very Effective		
Combination pill	0.3	9
Vaginal ring	0.3	9
Patch	0.3	9
DMPA	0.2	6
Progestin-only pill	0.3	9
Third Tier: Effective		
Condom		
Male	2	18
Female	5	21
Diaphragm with spermicides	6	12
Fertility-awareness		24
Standard days	5	
Two day	4	
Ovulation	3	
Symptothermal	0.4	
Fourth Tier: Least Effective		
Spermicides	18	28
Sponge		
Parous women	20	24
Nulliparous women	9	12
No WHO Category		

Method[a]	Perfect Use	Typical Use
Withdrawal	4	22
No contraception	85	85

[a]Methods organized according to tiers of efficacy.

DMPA = depot medroxyprogesterone acetate; WHO = World Health Organization.

Data from Trussell, 2011a.

No contraceptive method is completely without side effects, but contraception usually poses less risk than pregnancy. However, some disorders or medications can raise the risks from certain contraceptives. The World Health Organization (2015) has provided and updated evidence-based guidelines, termed *Medical Eligibility Criteria*, for the use of all highly effective reversible contraceptive methods by women with various health conditions. Individual countries have subsequently modified these guidelines. The *United States Medical Eligibility Criteria (US MEC)* was updated in 2016 by the Centers for Disease Control and Prevention (Curtis, 2016b). These documents are available at: http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Contraception_Guidance.htm.

In the United States MEC, reversible contraceptive methods are organized into six groups by their similarity: combination hormonal contraceptives (CHCs), progestin-only pills (POPs), depot medroxyprogesterone acetate (DMPA), implants, levonorgestrel-releasing intrauterine system (LNG-IUS), and copper intrauterine devices (Cu-IUDs). For a given health condition, each method is categorized 1 through 4 (Table 38-2). The score describes the safety profile for a typical woman with that condition: (1) no restriction of method use, (2) method advantages outweigh risks, (3) method risks outweigh advantages, and (4) method poses an unacceptably high health risk.

TABLE 38-2

Contraindications and Cautions with Specific Contraceptive Methods

1 = no method restrictions
2 = method benefits outweigh risks
3 = method risks outweigh benefits
4 = method poses an unacceptably high health risk

In this table, a blank space indicates the method is category 1 or 2

Condition	CHC[a]	POP	DMPA	Implants	LNG-IUS	Cu-IUD
Postpartum <21 d/<30 d	4/3					
21–42 d	2/3[b]					
Postpregnancy infection					4	4
Smoking & age ≥35 yr	3/4[c]					
Active breast cancer	4	4	4	4	4	
Breast cancer disease free ≥5 yr	3	3	3	3	3	
Multiple cardiovascular risks	3/4[d]		3			
Well-controlled or mild CHTN	3					
Systolic BP ≥160 or diastolic BP ≥100	4		3			
Vascular disease	4		3			
Complicated heart valve disease	4					
Peripartum cardiomyopathy	3/4[d]					
Acute or prior VTE[e]	3/4[d]					
Thrombophilia	4					
Surgery with long immobilization	4					
MS with immobilization	3					
DM >20 yr or vascular disease	3/4[d]		3			
DM with end-organ disease	3/4[d]		3			
Malabsorptive bariatric surgery	3[f]	3				
Inflammatory bowel disease	2/3[d]					
Cirrhosis (severe, decompensated)	4	3	3	3	3	
Liver tumors[g]	4	3	3	3	3	
Symptomatic gallbladder disease	3					
CHC-related cholestasis	3					
At risk for GC/CT					3	3

Distorted uterine cavity					4	4
GTD surveillance					4	4
Fosamprenavir	3					
Enzyme-inducing anticonvulsants[h]	3	3				
Lamotrigine	3					
Rifampin/rifabutin	3	3				
	Start/Continue (S/C)[i]					
Condition	**S/C**	**S/C**	**S/C**	**S/C**	**S/C**	**S/C**
Current or history of ISHD	4	2/3	3	2/3	2/3	
Stroke	4	2/3	3	2/3		
Migraine with aura	4	2/3	2/3	2/3	2/3	
Unexplained vaginal bleeding[j]			3	3	4/2	4/2
Cervical cancer before treatment					4/2	4/2
GTD surveillance					4/2	4/2
Current PID or cervicitis					4/2	4/2
Rheumatoid arthritis			2/3[k]			
Acute viral hepatitis	4/2					
Pelvic tuberculosis					4/3	4/3
SLE & positive or unknown APAs	4	3	3	3	3	
SLE & severe thrombocytopenia			3			3/2
Complicated solid-organ transplant	4				3/2	3/2

[a]Combination hormone contraception (CHC) group includes pills, vaginal ring, and patch.

[b]Associated risks that increase category score include: age ≥35, transfusion at delivery, BMI ≥30, postpartum hemorrhage, cesarean delivery, smoking, preeclampsia.

[c]Smoking ≥15 cigarettes/day increases risk category to 4 in this age group.

[d]Risk category score is modified by associated risk factors and disease severity.

[e]Including superficial thrombosis.

[f]Oral agents only. Ring and patch are category 1.

[g]Benign hepatic adenoma or hepatocellular cancer. Focal nodular hyperplasia compatible with hormone use.

[h]These include phenytoin, barbiturates, carbamazepine, oxcarbazepine, primidone, topiramate.

[i]In those methods under Start/Continue columns, the first US MEC number refers to whether a method may be initiated in an affected patient. For patients who initially develop the condition while using a specific method, the second number refers to risks for continuing that method.

[j]Prior to evaluation.

[k]Those on chronic corticosteroids and at risk for bone fracture.

AIDS = acquired immunodeficiency syndrome; APA = antiphospholipid antibodies; ARV = antiretroviral; BP = blood pressure; BMI = body mass index; CHTN = chronic hypertension; Cu-IUD = copper intrauterine device; DM = diabetes mellitus; DMPA = depot medroxyprogesterone acetate; GC/CT = gonorrhea/chlamydial infection; GTD = gestational trophoblastic disease; ISHD = ischemic heart disease; LNG-IUS = levonorgestrel-releasing intrauterine system; MS = multiple sclerosis; PI = protease inhibitor; PID = pelvic inflammatory disease; POP = progestin-only pills; SLE = system lupus erythematosus; VTE = venous thromboembolism.

Compiled from Curtis, 2016b; Merck, 2015; Teva Women's Health, 2014.

Alternatively, depending on the underlying disorder or patient desire, male or female sterilization may be a preferred or recommended permanent contraceptive method (American College of Obstetricians and Gynecologists, 2017b). These options are fully discussed in Chapter 39.

INTRAUTERINE DEVICES

Globally, 14 percent of reproductive-aged women use intrauterine contraception, and in the United States, 10 percent of contracepting women use this method (Buhling, 2014; Daniels, 2015). The five intrauterine devices (IUDs) currently approved for use in the United States are *chemically active* and continually elute either copper or levonorgestrel. These all have a T-shaped frame of polyethylene that is compounded with barium to render them radiopaque. Of devices, *Mirena* and *Liletta* both measure 32 × 32 mm and contain a 52-mg levonorgestrel-releasing cylinder reservoir in the stem of the T (Fig. 38-1). Two trailing strings that are tan (*Mirena*) or blue (*Liletta*) are attached to the distal stem to aid eventual device removal. *Skyla*—known as *Jaydess* in some countries—contains 13.5 mg of levonorgestrel. It has smaller dimensions—28 × 30 mm—and was sized to more appropriately fit a nulliparous uterus (Gemzell-Danielsson, 2012). *Kyleena* has the same dimensions but contains 19.5 mg of the same progestin. Two trailing strings off *Skyla* are tan, and those off *Kyleena* are blue. *Skyla* and *Kyleena* can be differentiated from *Mirena* and *Liletta* visually and sonographically by a silver ring near the junction of their stem and arms. *Mirena* and *Kyleena* are currently approved for 5 years of use following insertion, whereas *Skyla* and *Liletta* are approved for 3 years.

FIGURE 38-1
Intrauterine devices (IUDs). **A.** *ParaGard T 380A* copper IUD. **B.** *Mirena* levonorgestrel-releasing intrauterine system. (Reproduced with permission from Stuart GS: Contraception and sterilization. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Joanna S. Sheffield: Williams Obstetrics, 25th Edition

The third device, the T380A IUD named *ParaGard,* is wound with copper, and two strings extend from the stem base. Originally blue, the strings are now white. It is currently approved for 10 years of use following insertion (Teva Women's Health, 2014).

In addition to these five currently marketed IUDs, women may retain discontinued brands. A *Lippes Loop* has two "S" shapes stacked one on the other. The *Dalkon Shield* has a crab form, whereas a *Copper 7* mirrors that number. *Progestasert* is an early T-shaped progestin-releasing IUD. Last, various metal-eluting ring devices are common in Asia.

Contraceptive Action

All these IUDs are effective. Failure rates are well below 1 percent and similar overall to those of tubal sterilization (Thonneau, 2008; Trussell, 2011b). Their mechanisms have not been precisely defined, but prevention of fertilization is now favored.

With the LNG-IUS, long-term progestin release leads to endometrial atrophy, which hinders normal implantation (Silverberg, 1986). Moreover, progestins create scant viscous cervical mucus that obstructs sperm motility (Apter, 2014; Moraes, 2016). Within the uterus, an intense local endometrial inflammatory response is induced, especially by copper-containing devices. Cellular and humoral components of this inflammation are expressed in endometrial tissue and in fluid filling the uterine cavity and fallopian tubes. These lead to decreased sperm and egg viability (Ortiz, 2007). Also, in the unlikely event that fertilization does occur, the same inflammatory actions are directed against the blastocyst. Also, with the Cu-IUD specifically, copper levels rise in the cervical mucus of users and act to decrease sperm motility and viability (Jecht, 1973). The above effects are considered primary for contraception because ovulation inhibition is inconsistent with the LNG-IUS and lacking with the Cu-IUD (Nilsson, 1984).

Method-Specific Adverse Effects

Ectopic Pregnancy

Contraindications to IUD use are few and shown in Table 38-2. In the past, IUDs were perceived to increase the risk of ectopic pregnancy, but this has since been clarified. Specifically, IUDs provide effective contraception and lower the absolute number of ectopic pregnancies by half compared with the rate in noncontracepting women (World Health Organization, 1985, 1987). But, the IUD mechanisms of action are more effective in preventing *intrauterine* implantation. Thus, if an IUD fails, a higher proportion of pregnancies are likely to be ectopic (Backman, 2004; Furlong, 2002).

Lost Device

Expulsion of an IUD from the uterus is most common during the first month. Thus, women are examined approximately 1 month following IUD insertion, usually after menses, to identify the tails trailing from the cervix. Following this, a woman is instructed to palpate the strings each month after menses. Regardless of IUD type, the cumulative 3-year expulsion rate approximates 10 percent (Madden, 2014; Simonatto, 2016). This rate is higher in those ≤25 years (Jatlaoui, 2017).

If the tail of an IUD cannot be visualized, the device may have been expelled, may have perforated the uterus, or may be malpositioned. Alternatively, the device may be normally positioned with its tails folded within the endocervical canal or uterine cavity. To investigate, after excluding pregnancy, a cytological brush can be twirled within the endocervical canal to entangle the strings and bring them gently into the vagina. If unsuccessful, the uterine cavity is probed gently with a Randall stone clamp or with a specialized rod with a terminal hook to snare the strings or device.

One should not assume that a device has been expelled unless it was seen. Thus, if tails are not visible and the device is not felt by gentle probing of the uterine cavity, transvaginal sonography can be used to ascertain if the device lies within the uterus. Although traditional sonography will document IUD position adequately in most cases, three-dimensional sonography offers improved visualization, especially with the LNG-IUS (Moschos, 2011). If sonography is inconclusive or if no device is seen, then a plain radiograph of the abdominopelvis is taken. Computed tomography (CT) scanning or, less commonly, magnetic resonance (MR) imaging is an alternative (Boortz, 2012). It is safe to perform MR imaging at 1.5 and 3 Tesla (T) with an IUD in place (Ciet, 2015).

Perforation

During uterine sounding or IUD insertion, the uterus may be perforated, which is identified by the tool traveling farther than the expected uterine length based on initial bimanual examination. Rates approximate 1 per 1000 insertions, and risks include puerperal insertion, lactation, provider inexperience, and extremes of uterine flexion (Harrison-Woolrych, 2003; Heinemann, 2015). Although devices may migrate spontaneously into and through the uterine wall, most perforations occur, or at least begin, at the time of insertion (Ferguson, 2016).

With acute perforation, the fundus is the more common site, and bleeding is typically minimal due to myometrial contraction around the puncture hole. If no brisk or persistent bleeding is noted from the os following instrument or device removal, then patient observation alone is reasonable. Rarely, acute lateral perforations may lacerate the uterine artery, and subsequent brisk bleeding may prompt laparoscopy or laparotomy for control. Following any perforation, although this is not firmly evidence-based, a single dose of broad-spectrum antibiotic may mitigate infection.

With chronic perforation, a device can penetrate the muscular uterine wall to varying degrees. A patient may be asymptomatic but abdominal pain, uterine bleeding, or missing strings can be clues (Kaislasuo, 2013). Those with a predominantly intrauterine location are usually managed by hysteroscopic IUD removal. In contrast, devices that have nearly or completely perforated through the uterine wall are more easily removed laparoscopically. Notably, an extrauterine Cu-IUD frequently induces an intense local inflammatory reaction and adhesions (Kho, 2014). Laparotomy may be necessary, and bowel preparation is considered. Sigmoid and bladder perforations and small-bowel obstruction have been reported remote from insertion (Sano, 2017; Xu, 2015; Zeino, 2011).

Menstrual Changes

Dysmenorrhea and bleeding irregularities can complicate IUD use (Aoun, 2014; Grunloh, 2013). These can be treated with some degree of success by nonsteroidal antiinflammatory drugs (NSAIDs) or tranexamic acid, which is an antifibrinolytic (Godfrey, 2013; Madden, 2012; Sørdal, 2013). Of the two IUDs, heavy bleeding more often complicates Cu-IUD use and may cause iron-deficiency anemia, for which oral iron salts are given. With the LNG-IUS, irregular spotting for up to 6 months after placement often gives way to progressive amenorrhea, which is reported by 30 percent of women after 2 years and by 60 percent after 12 years (Ronnerdag, 1999). This is frequently associated with improved dysmenorrhea.

Infection

The risk of upper genital tract device-related infection is greatest during the first months following IUD insertion (Farley, 1992; Turok, 2016). Pathogens include *Neisseria gonorrhoeae, Chlamydia trachomatis,* and vaginal flora. Women at risk for sexually transmitted diseases (STDs) should be screened either before or at the time of IUD insertion (Centers for Disease Control and Prevention, 2015; Sufrin, 2012). That said, device insertion need not be delayed while awaiting sexually transmitted disease or Pap test results in asymptomatic women (Birgisson, 2015). If these bacteria are subsequently found and the patient is without symptoms, then the IUD may remain and treatment prescribed as detailed in Chapter 65 (Chlamydial Infections). Importantly, *routine* antimicrobial prophylaxis before insertion is not recommended (Grimes, 2012; Walsh, 1998). And the American Heart Association does not recommend bacterial endocarditis prophylaxis with insertion (Nishimura, 2014).

After the first month, infection risk is not increased in IUD users who would otherwise be at low risk of sexually transmitted infections. Correspondingly, IUDs appear to cause little, if any, increase in infertility rates in these low-risk patients (Hubacher, 2001). The American College of Obstetricians and Gynecologists (2015c, 2016a) recommends that women at low risk for STDs, including adolescents, be considered good candidates for IUDs. The IUD is also safe and effective in women infected with human immunodeficiency virus (HIV) and may be used in others who are immunosuppressed (Centers for Disease Control and Prevention, 2015; Tepper, 2016a).

If infection does develop, it may take several forms and typically requires broad-spectrum antimicrobials. *Pelvic inflammatory disease (PID)* without abscess is treated with antibiotics on an outpatient or inpatient basis, depending on infection severity. There are theoretical concerns that a coexistent IUD may worsen the infection or delay resolution. A provider may choose to remove an IUD in this setting, although some evidence supports allowing a device to remain during treatment in those hospitalized with mild or moderate PID (Centers for Disease Control and Prevention, 2015; Tepper, 2013). If infection fails to improve during 48 to 72 hours of treatment, the device is removed. *Tuboovarian abscess* can complicate PID and is treated aggressively with intravenous broad-spectrum antibiotics and IUD removal. Last, *septic abortion* mandates immediate uterine evacuation and antibiotics.

Actinomyces israelii is a gram-positive, slow-growing, anaerobic indigenous vaginal bacterium that rarely causes suppurative infection. Some have found it more frequently in the vaginal flora or on the Pap smears of IUD users (Curtis, 1981; Kim, 2014). Current recommendations advise that an asymptomatic woman may retain her IUD and does not require antibiotic treatment (American College of Obstetricians and Gynecologists, 2017c; Lippes, 1999; Westhoff, 2007a). However, if signs or symptoms of infection develop in a woman who harbors *Actinomyces* species, then the device is removed and antibiotics are given. Early findings with infection include fever, weight loss, abdominal pain, and abnormal uterine bleeding or discharge. *Actinomyces* species are sensitive to antibiotics with gram-positive coverage, notably the penicillins.

Pregnancy with an IUD

For women who conceive while using an IUD, ectopic pregnancy should be excluded. With intrauterine pregnancy, if the tail is seen, it should be grasped and the IUD removed by gentle outward traction. This action reduces complications such as abortion, chorioamnionitis, and preterm birth (Fulkerson Schaeffer, 2017; Kim, 2010). Specifically, in one cohort, a 54-percent abortion rate and 17-percent preterm delivery rate was noted if the device remained in situ. More favorably, rates of 25 percent and 4 percent, respectively, resulted from prompt Cu-IUD removal (Tatum, 1976). Few data guide management with the LNG-IUS, and most practice extrapolates from copper devices.

If the tail is not visible, attempts to locate and remove the device may result in abortion. Although not our practice, some case reports and small series describe sonography or hysteroscopy to assist in difficult device removals (Pérez-Medina, 2014; Schiesser, 2004). After fetal viability is reached, it is unclear whether it is better to remove an IUD whose strings are visible and accessible or to leave it in place. Fetal malformation rates are not greater with a device left in situ (Tatum, 1976; Vessey, 1979).

Second-trimester miscarriage with an IUD in place is more likely to be infected (Vessey, 1974). Sepsis may be fulminant and fatal. Pregnant women with a device in utero who demonstrate any evidence of pelvic infection are treated with broad-spectrum antibiotics and prompt uterine evacuation. Because of these risks, a woman should be given the option of early pregnancy termination if the device cannot be removed early in pregnancy. Last, in women who give birth with a device in place, appropriate steps should be taken at delivery to identify and remove the IUD.

IUD Insertion

Timing

To reduce expulsion rates and perforation risks, IUD insertion has traditionally followed complete uterine involution—at least 6 weeks after delivery. Women delivered at Parkland Hospital are seen 3 weeks postpartum, and IUDs are inserted 6 weeks postpartum or sooner if involution is complete.

Alternatively, immediately after miscarriage, surgical abortion, or delivery, an IUD may be inserted in the absence of overt infection (Lopez, 2015a; Okusanya, 2014). Also, “immediate” insertion 1 week after mifepristone and completed medical abortion has been described (Sääv, 2012; Shimoni, 2011). The risk of IUD expulsion is slightly higher if it is placed immediately following any of these recent pregnancies (Whitaker, 2017). However, in studies, the number of women in immediate-placement groups who ultimately receive and retain an IUD is greater than in groups scheduled for traditionally timed placement, some of whose members do not return for insertion (Bednarek, 2011; Chen, 2010).

With immediate insertion, techniques depend on uterine size. After first-trimester evacuation, the IUD can be placed using the manufacturer’s standard instructions. If the uterine cavity is larger, the IUD can be placed using ring forceps with sonographic guidance (Drey, 2009; Fox, 2011).

Immediately following vaginal or cesarean delivery, an IUD can be placed by a hand, by its inserter tube, or by ring forceps (Levi, 2015; Xu, 1996). With any of these methods, the arms of the IUD need not be folded into the inserter tube prior to insertion. During cesarean delivery placement, the hand or inserter travels through the unsutured open hysterotomy to deposit the device at the fundus. A second hand cupping the outer fundus can provide back pressure and stabilize the uterus during insertion. Strings are then gently directed toward the cervix. For instrumented insertion following vaginal delivery, the clinician resterilizes the vulva and

changes gloves after placental delivery but before perineal repairs. The anterior lip of the floppy cervix is held with ring forceps. A second ring forceps grasp the IUD stem and guides it through the uterine cavity to the fundus. For manual insertion following vaginal delivery, the provider secures the IUD between the index and middle fingers to deposit the device. In either case, back pressure against the fundus by an abdominal hand can guide positioning (Stuart, 2017; The ACQUIRE Project, 2008).

For placement not related to pregnancy, insertion near the end of normal menstruation, when the cervix is usually softer and somewhat more dilated, may be easier and also helps exclude early pregnancy. But, insertion is not limited to this time. For the woman who is sure she is not pregnant and does not want to be pregnant, insertion is done at any time.

Technique

Before insertion, contraindications are sought. Candidates are counseled, and written consent obtained. An oral NSAID, with or without codeine, can be used to allay cramps after insertion (Ngo, 2015). But NSAIDs, misoprostol, or even paracervical blockade do not consistently decrease discomfort experienced during device placement (Bednarek, 2015; Hubacher, 2006; Mody, 2012; Pergialiotis, 2014). Of topical lidocaine products, 2-percent gel is ineffective, but a newer gel and a spray both show promise (Aksoy, 2016; Lopez, 2015b; Tornblom-Paulander, 2015). Bimanual pelvic examination delineates uterine position and size. Abnormalities are evaluated, as they may contraindicate insertion. Mucopurulent cervicitis or significant vaginitis is appropriately treated and resolved before IUD insertion.

The cervical surface is cleansed with an antiseptic solution, and sterile instruments and a sterile IUD are used. A tenaculum is placed on the cervical lip, and the canal and uterine cavity are straightened by applying gentle outward traction. The cavity is then probed by a uterine sound to identify its direction and depth. Specific steps of ParaGard and Mirena insertion are shown in Figures 38-2 and 38-3 and outlined in their respective package inserts.

FIGURE 38-2

Insertion of the *Mirena* intrauterine system. Initially, threads from behind the slider are first released to hang freely. The slider found on the handle should be positioned at the top of the handle nearest the device. The IUD arms are oriented horizontally. A flange on the outside of the inserter tube is positioned from the IUD tip to reflect the depth found with uterine sounding. **A.** As both free threads are pulled, the *Mirena* IUD is drawn into the inserter tube. The threads are then tightly fixed from below into the handle's cleft. In these depictions, the inserter tube has been foreshortened. The inserter tube is gently inserted into the uterus until the flange lies 1.5 to 2 cm from the external cervical os to allow the arms to open. **B.** While holding the inserter steady, the IUD arms are released by pulling the slider back to reach the raised horizontal mark on the handle, but no further. **C.** The inserter is then gently guided into the uterine cavity until its flange touches the cervix. **D.** The device is released by holding the inserter firmly in position and pulling the slider down all the way. The threads will be released automatically from the cleft. The inserter may then be removed, and IUD strings trimmed. (Reproduced with permission from Stuart GS: Contraception and sterilization. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

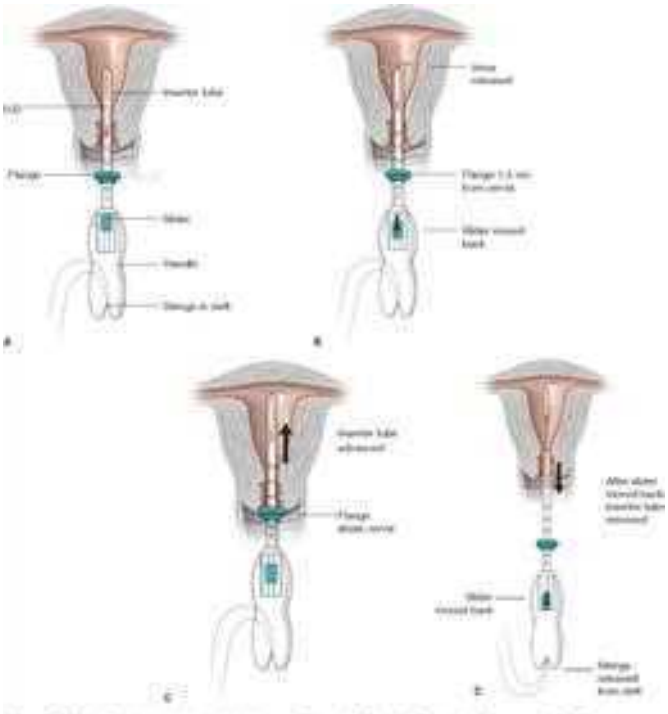
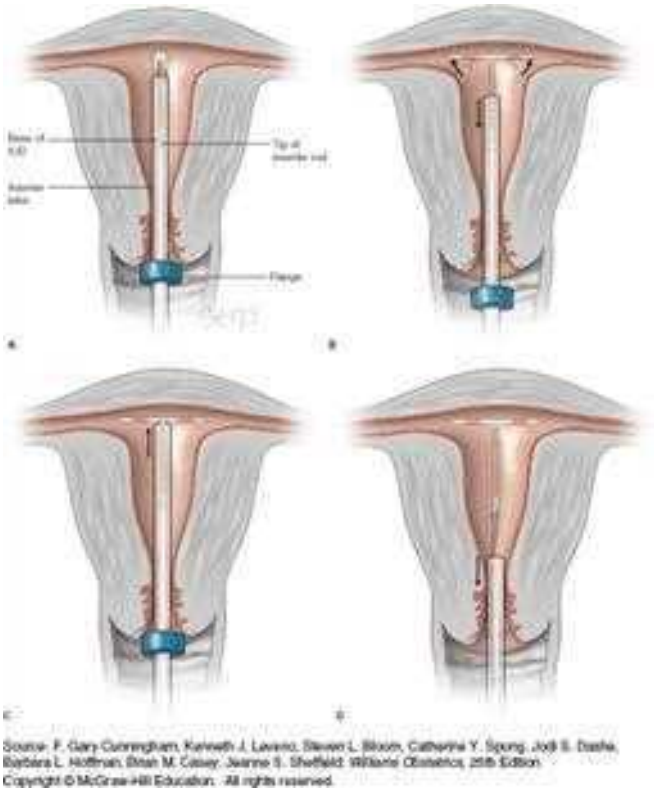


FIGURE 38-3

Insertion of *ParaGard T 380A*. The uterus is sounded, and the IUD is loaded into its inserter tube not more than 5 minutes before insertion. A blue plastic flange on the outside of the inserter tube is positioned from the IUD tip to reflect uterine depth. The IUD arms should lie in the same plane as the flat portion of the oblong blue flange. **A.** The inserter tube, with the IUD loaded, is passed into the endometrial cavity. A long, solid, white inserter rod abuts the base of the IUD. When the blue flange contacts the cervix, insertion stops. **B.** To release the IUD arms, the solid white rod within the inserter tube is held steady, while the inserter tube is withdrawn no more than 1 cm. **C.** The inserter tube, not the inserter rod, is then carefully moved upward toward the top of the uterus until slight resistance is felt. At no time during insertion is the inserter rod advanced forward. **D.** First, the solid white rod and then the inserter tube are withdrawn individually. At completion, only the

threads should be visible protruding from the cervix. These are trimmed to allow 3 to 4 cm to extend into the vagina. (Reproduced with permission from Stuart GS: Contraception and sterilization. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Following insertion, only the threads should be visible trailing from the cervix. These are trimmed to allow 3 to 4 cm to protrude into the vagina, and their length is recorded. If improper device positioning is suspected, placement should be confirmed, using sonography if necessary. If the IUD is not positioned completely within the uterus, it is removed and replaced with a new device. An expelled or partially expelled device should not be reinserted.

PROGESTIN IMPLANTS

Etonogestrel Implant

Contraception can be provided by thin, pliable progestin-containing cylinders that are implanted subdermally and release hormone over many years. One of these, *Nexplanon* is a single-rod implant with 68 mg of etonogestrel covered by an ethylene vinyl acetate copolymer cover. The implant is placed subdermally on the medial surface of the upper arm 8 to 10 cm from the elbow in the biceps groove and is aligned with the long axis of the arm. It may be used as contraception for 3 years, removed, and then replaced at the same site or in the opposite arm (Merck, 2016a).

Nexplanon is radiopaque, and its inserter device is designed to assist with subdermal positioning and avert deeper placement. This device replaced *Implanon*, which is not radiopaque. A misplaced *Implanon* may be identified with sonography using a 10- to 15-MHz linear array transducer (Shulman, 2006). In some cases, MR imaging may be required if supplemental information is needed despite sonography (Correia, 2012). Both implants are similarly shaped and pharmacologically identical. They are highly effective, and the mechanism of action for progestin-only products is described later (Progestin-Only Contraceptives) (Croxatto, 1998; Mommers, 2012). *Implanon* is safe and still approved by the Food and Drug Administration (FDA), but it is no longer distributed by the manufacturer.

Levonorgestrel Implants

The first progestin implants contained levonorgestrel (LNG), and systems are still available outside the United States. *Jadelle*, originally named *Norplant-2*, provides LNG and contraception for 5 years through two subdermally implanted Silastic rods. After this time, rods may be removed and if desired, new rods inserted at the same site (Bayer Group, 2015). *Jadelle* is approved by the FDA, however, it is not marketed or distributed in the United States. Sino-implant II is a two-rod system with the same amount (150 mg) of LNG and same mechanism of action as *Jadelle* but provides 4 years of contraception. Sino-implant II is manufactured in China and approved for use by 20 countries in Asia and Africa (FHI 360, 2012).

Like the etonogestrel implant, these systems are placed subdermally on the inner arm approximately 8 cm from the elbow and have similar removal steps. Implants vary regarding their insertion technique, and manufacturer instructions should be consulted. Both implant systems are highly effective (Sivin, 1998; Steiner, 2010).

The forerunner of these implants was the *Norplant System,* which provided LNG in six Silastic rods implanted subdermally. The manufacturer stopped distributing the system in 2002.

Few data compare the LNG and etonogestrel implants. In one, efficacy and discontinuation rates by 2.5 years of use were similar (Bahamondes, 2015).

Method-Specific Adverse Effects

Unscheduled bleeding is common with progestin-only methods and described in Progestin-Only Contraceptives. Device-specific adverse effects derive mainly from malpositioning. First, branches of the medial antebrachial cutaneous nerve can be injured during implant or needle insertion that is too deep or during exploration for a lost implant. Clinically, numbness and paresthesia over the anteromedial aspect of the forearm are noted (Wechselberger, 2006). Second, nonpalpable devices are not uncommon and require radiological imaging for localization. As an adjunct, one group adopted the hook-wire tagging method used in breast tumor surgery to allow deep-lying implants to be marked prior to extraction (Nouri, 2013). If imaging fails to locate an implant, etonogestrel blood level determination can help verify that the implant is indeed in situ. This special assay must be coordinated with the manufacturer (1–877–467–5266).

Implant Insertion

Timing

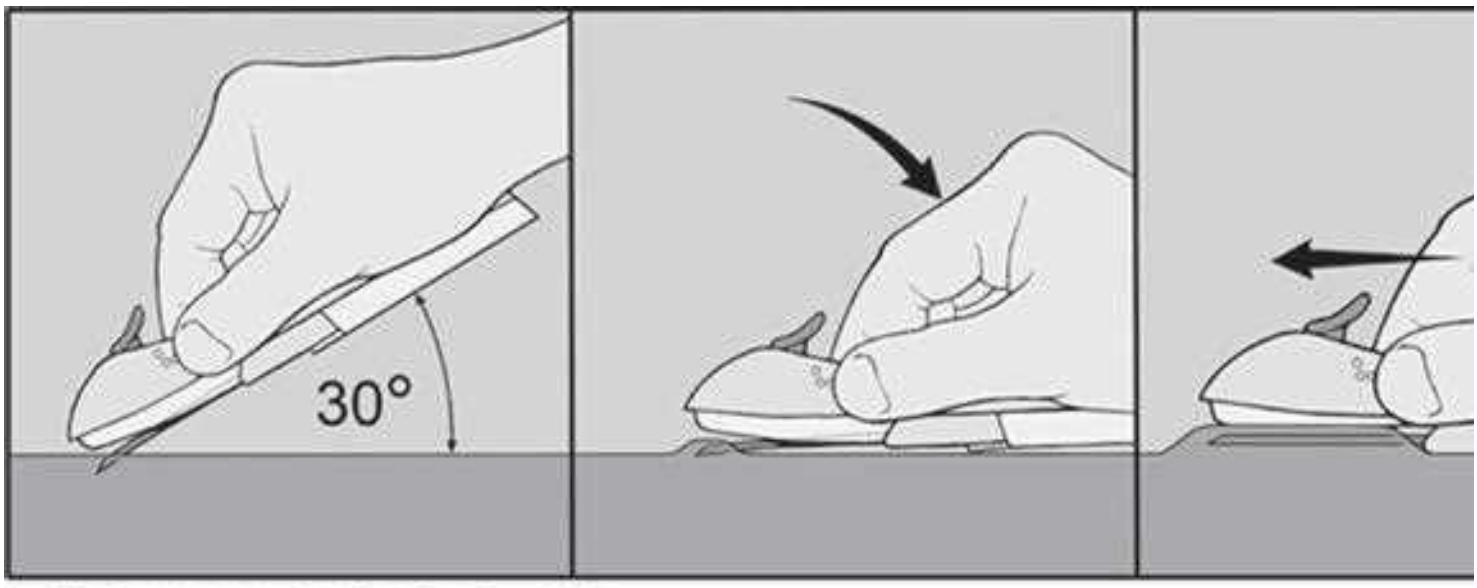
For those not currently using hormonal contraception, the etonogestrel implant is ideally inserted within 5 days of menses onset. With LNG-releasing implants, contraception is established within 24 hours if inserted within the first 7 days of the menstrual cycle (Sivin, 1997; Steiner, 2010). For transitioning methods, an implant is placed on the day of the first placebo combination oral contraceptive (COC) pill; on the day that the next depot-medroxyprogesterone injection would be due; or within 24 hours of taking the last POP (Merck, 2016a). In women certain that they are not pregnant, insertion at other times of the cycle is followed by alternative contraception for 7 days. Related to pregnancy, an implant may be inserted before discharge following delivery or abortion (Sothornwit, 2017).

Nexplanon Insertion Technique

With the patient lying down, her nondominant arm, forearm, and hand are outstretched on the bed with the inner aspects of each exposed upward, and the elbow is flexed. The insertion site is marked with a sterile pen 8 to 10 cm proximal to the medial condyle of the humerus. A second mark is placed 4 cm proximally and delineates the final path of the implant. The Nexplanon is inserted using sterile technique. The area is cleansed aseptically, and a 1-percent lidocaine anesthetic track is injected beneath the skin along the planned insertion path. The implant is then placed as shown in Figure 38-4. After placement, both patient and provider should palpate and identify both ends of the 4-cm implant. To minimize bruising at the site, a pressure bandage is created around the arm and is removed the following day.

FIGURE 38-4

Nexplanon insertion. A sterile pen marks the insertion site, which is 8 to 10 cm proximal to the medial humeral condyle. A second mark is placed 4 cm proximally along the arm's long axis. The area is cleaned aseptically, and a 1-percent lidocaine anesthetic track is injected along the planned insertion path. **A.** The insertion device is grasped at its gripper bubbles found on either side, and the needle cap is removed outward. The device can be seen within the needle bore. The needle bevel then pierces the skin at a 30-degree angle. **B.** Once the complete bevel is subcutaneous, the needle is quickly angled downward to lie horizontally. **C.** Importantly, the skin is tented upward by the needle as the needle is slowly advanced horizontally and subdermally. **D.** Once the needle is completely inserted, the lever on the top of the device is pulled backward toward the operator. This retracts the needle and thereby deposits the implant. The device is then lifted away from the skin. After placement, both patient and operator should palpate the 4-cm implant.



With implant extraction, the removal site is first cleansed with antiseptic. The proximal end of the implant is depressed with a finger to allow the distal end to bulge up toward the skin. After anesthetizing the skin over this bulge, the skin is incised 2 mm toward the elbow along the long axis of the arm. The proximal butt of the implant is then pushed toward this incision. Once visible, the distal end of the implant is grasped with a hemostat and removed. If present, superficial adhesions surrounding an implant may be dissected away with hemostat tips placed into the incision.

PROGESTIN-ONLY CONTRACEPTIVES

Actions and Side Effects

Progestin-only contraceptives include the implants just described, injectables, and pills. As their primary contraceptive action, these progestins suppress luteinizing hormone (LH) and in turn block ovulation. As other effects, cervical mucus is thickened to retard sperm passage, and atrophy renders the endometrium unfavorable for implantation. Fertility is restored rapidly following cessation of progestin-only contraception. An exception is DMPA, as described in Barrier Methods (Mansour, 2011).

For all progestin-only methods, irregular or heavy uterine bleeding is a distinct disadvantage. It is the most frequently reported adverse event leading to method discontinuation. Often, counseling and reassurance is sufficient. Troublesome bleeding may be improved by one to two cycles of combination oral contraceptives, by a 1- to 3-week course of estrogen alone, or by a short course of NSAIDs combined with the established method (Abdel-Aleem, 2013). Fortunately, with prolonged use, progestins induce endometrial atrophy, which leads to sustained amenorrhea. For the well-counseled patient, this is often an advantage.

Most progestin-only contraceptive methods do not significantly affect lipid metabolism, glucose levels, hemostatic factors, liver function, thyroid function, or blood pressure (Dorflinger, 2002). However, the increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels seen with DMPA may be less desirable for women with cardiac or vascular disease risks (Kongsayreepong, 1993).

Progestin-only methods do not impair milk production and are an excellent choice for lactating women. There are no increased risks of genital tract, liver, or breast neoplasia (Samson, 2016; Wilailak, 2012; World Health Organization, 1991a,b, 1992). Weight gain and bone fracture are not prominent side effects of this contraceptive group, except for depot progesterone, discussed in Barrier Methods (Lopez, 2012a, 2013a). Functional ovarian cysts develop with a greater frequency in women using progestin-only agents, although they do not usually necessitate intervention (European Society of Human Reproduction and Embryology, 2001; Hidalgo, 2006; Nahum, 2015). Last, an association between depression and DMPA or POPs is unclear (Civic, 2000; Pagano, 2016; Svendal, 2012; Westhoff, 1995). Women with depression may be prescribed these methods, but surveillance following initiation is reasonable.

Progestin Contraindications

These methods are ideal for most women, but contraindications and cautions are associated with a few conditions listed in Table 38-2. Current breast cancer and pregnancy are the only two absolute contraindications. In a few instances, manufacturer restrictions differ from the US MEC. First, manufacturer prescribing information lists thrombosis or thromboembolic disorders as contraindications (Merck, 2016a; Pfizer, 2015a,b). However, for individuals with these disorders, US MEC considers progestin-containing methods category 2. Moreover, evidence does not link progestin-only methods with thromboembolism, stroke, or cardiovascular disease (Mantha, 2012; Tepper, 2016b; World Health Organization, 1998). Second, for many progestin products, manufacturers note prior ectopic pregnancy as a contraindication. This is secondary to progesterone's effect of slowing fallopian tube motility and thereby delaying fertilized egg transport to the endometrial cavity. That said, effective contraception lowers pregnancy rates overall. Thus, for those with prior ectopic pregnancy, US MEC considers progestin injectables and implants category 1, and progestin-only pills are category 2.

HORMONAL CONTRACEPTIVES

These currently are available in forms that contain both estrogen and progestin or contain only progestin. Progestin-only injectables and pills are considered very effective, yet second-tier agents, due to the need for increased patient compliance. Similarly, products containing both estrogen and progestin, often termed combination hormonal contraception (CHC), are considered in this tier. These may be supplied as pills, transvaginal rings, or transdermal patches.

Combination Hormonal Contraceptives Mechanism of Action

Actions of combination hormonal contraceptives are multiple, but the most important effect is suppression of hypothalamic gonadotropin-releasing factors. This in turn blocks pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and thereby inhibits ovulation. The progestin component of CHCs provides ovulation prevention by suppressing LH; it thickens cervical mucus and thereby retards sperm passage; and it renders the endometrium unfavorable for implantation. Estrogen blocks ovulation by suppressing FSH release. To promote cycle control, estrogen stabilizes the endometrium, which prevents intermenstrual bleeding—also known as *breakthrough bleeding*. The net effect is an extremely effective yet highly reversible method (Mansour, 2011).

Combination Oral Contraceptive Pills

Composition

These pills are the most frequently used reversible birth control method in the United States. In a 2006 to 2010 survey, 16 percent of contracepting women in the United States were using these (Daniels, 2015). COCs are marketed in a wide variety of estrogen and progestin combinations. Most are available as generics, and the FDA (2016) confirms the bioequivalence of COC generics. The American College of Obstetricians and Gynecologists (2015a) supports the use of either branded or generic preparations.

Pharmacologically, ethinyl estradiol is the most common estrogen present in COC formulations in the United States. Less frequently, mestranol or estradiol valerate is used. Unwanted effects most often attributed to the estrogen component include breast tenderness, weight gain, nausea, and headache.

COCs also contain one of several progestins that are structurally related to progesterone, testosterone, or spironolactone. Thus, these progestins bind variably to progesterone, androgen, glucocorticoid, and mineralocorticoid receptors. These affinities explain many pill-related side effects and are often used to compare one progestin with another.

Most progestins used in COCs are related to testosterone and may impart androgenic side affects such as acne and adverse HDL and LDL levels. To avoid these effects, antiandrogenic progestins have been introduced and include *dienogest* and *nomegestrol acetate*. The latter is used in a COC approved outside the United

States. Despite these pharmacological differences, the true advantage of one progestin over another is less apparent clinically (Lawrie, 2011; Moreau, 2007).

Another progestin, *drospirenone*, is structurally similar to spironolactone. The doses in currently marketed COCs have effects similar to 25 mg of this diuretic (Seeger, 2007). Drospirenone displays antiandrogenic activity, provides an antialdosterone action to minimize water retention, and has antimineralocorticoid properties that may, in theory, cause potassium retention and hyperkalemia (Krattenmacher, 2000). Thus, it is avoided in women with renal or adrenal insufficiency or with hepatic dysfunction. Moreover, serum potassium level monitoring is recommended in the first month for patients chronically treated concomitantly with any drug associated with potassium retention. These include NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, heparin, aldosterone antagonists, and potassium-sparing diuretics (Bayer HealthCare Pharmaceuticals, 2015).

Since the development of COCs, their estrogen and progestin content has dropped remarkably to minimize adverse effects. Currently, the lowest acceptable dose is limited by the ability to prevent pregnancy and to avoid unacceptable breakthrough bleeding. Thus, the daily estrogen content varies from 10 to 50 µg of ethinyl estradiol, and most contain 35 µg or less.

In a few COCs, inert placebo pills have been replaced by tablets containing iron. These have the suffix Fe added to their name. In addition, *Beyaz* has a form of folate —levomefolate calcium—within both its active and placebo pills.

With COCs termed *monophasic pills*, the progestin dose remains constant throughout the cycle. In others, the dose frequently is varied, and term *biphasic, triphasic,* or *quadriphasic pill* is used depending on the number of dose changes within the cycle. In some formulations, the estrogen dose also varies. In general, phasic pills were developed to reduce the total progestin content per cycle without sacrificing contraceptive efficacy or cycle control. The theoretical advantage of a lower total progesterone dose per cycle, however, has not been borne out clinically (Moreau, 2007). Cycle control also appears to be comparable among mono- through triphasic pills (van Vliet, 2011a,b,c).

Administration

Hormones are taken daily for a specified time (21 to 81 days) and then replaced by placebo for a specified time (4 to 7 days), which is called the “pill-free interval.” During these pill-free days, withdrawal bleeding is expected.

With the trend toward lower estrogen doses to minimize side effects, follicular development and ovulation may occur. To counter this, the active-pill duration in some formulations is extended to 24 days. In comparison, these 24/4 regimens perform similarly to higher-estrogen-dose 21/7 regimens (Anttila, 2011; Marr, 2012).

Alternatively, longer durations of active hormone, designed to minimize the number of withdrawal episodes, have similar efficacy and safety profiles as more traditional administration (Edelman, 2014). These extended-cycle products produce a 13-week cycle, that is, 12 weeks of hormone use, followed by a week for withdrawal menses. The product *Amethyst* provides continuous active hormone pills for 365 days each year. Such extended or continuous regimens may be especially suited for women with significant menstrual symptoms (Mendoza, 2014).

For general initiation, women ideally begin COCs on the first day of a menstrual cycle. In such cases, a supplementary contraceptive method is unnecessary. With the more traditional “Sunday start,” women begin pills on the first Sunday that follows menses onset, and an additional method is needed for 1 week to prevent conception. If menses begin on a Sunday, then pills are begun that day and no supplemental method is required. Alternatively, with the “quick start” method, COCs are started on any day, commonly the day prescribed, regardless of cycle timing. An additional method is used during the first week (Westhoff, 2002, 2007b). If the woman is unknowingly already pregnant during quick start initiation, COCs are not teratogenic (Lammer, 1986; Rothman, 1978; Savolainen, 1981). However, a missed menses following COC initiation should prompt pregnancy testing. Similar same-day initiation can be implemented with the contraceptive vaginal ring or patch (Murthy, 2005; Schafer, 2006).

For maximum efficiency, pills are best taken at the same time each day. If one dose is missed, the missed pill is taken immediately; the scheduled dose for that day is taken on time; and then daily pills are continued. If two or more doses are missed, the most recent missed pill is taken immediately; the scheduled dose for that day is taken on time; and an effective barrier technique used for 7 days while daily pills are then continued (Curtis, 2016a). If withdrawal bleeding fails to occur during the pill-free interval, a woman should continue her pills but seek attention to exclude pregnancy.

With initiation of COCs, spotting or bleeding is common. It does not reflect contraceptive failure and typically resolves within one to three cycles. If unscheduled bleeding persists, those with bleeding during the first part of a pill pack may benefit from an increase in the estrogen dose, whereas those with bleeding during the second part may improve with a higher progestin dose (Nelson, 2011).

Method-Specific Effects

Altered Drug Efficacy

Some drugs decrease COC effectiveness, and choosing another contraceptive method is preferable. However, if a COC is selected for concurrent use in these instances, a preparation containing a minimum of 30 µg ethinyl estradiol is ideally chosen. Conversely, some COCs interfere with the actions of certain drugs (see Table 38-2).

In obese women, COCs are effective (Lopez, 2016). Some studies point to lowered hormone bioavailability, but overall efficacy remains high (Nakajima, 2016; Westhoff, 2010; Yamazaki, 2015). With the transdermal patch method, however, evidence is more robust that obesity may alter pharmacokinetics and lower efficacy, as discussed in Transdermal Patch.

Metabolic Changes

Combination oral contraceptives alter lipid synthesis and in general raise serum levels of triglycerides and of total cholesterol, HDL, and very-low density lipoprotein (VLDL) cholesterol. Estrogen lowers LDL cholesterol concentrations. Oral contraceptives are not atherogenic, and their effect on lipids is clinically inconsequential for most women (Wallach, 2000). In women with dyslipidemias, limited data suggest that COCs increase the risk for myocardial infarction and minimally so for venous thromboembolism or stroke (Dragoman, 2016). For those with multiple additional risk factors for vascular disease, alternative contraceptive methods are recommended.

With COCs, protein metabolism is affected, and estrogens boost hepatic production of various globulins. First, fibrinogen and many of the clotting factor levels rise in direct proportion to the estrogen dose and may lead to thrombosis. Angiotensinogen production is also augmented by COCs, and its conversion by renin to angiotensin I may be associated with "pill-induced hypertension," discussed subsequently. Last, COCs elevate sex hormone-binding globulin (SHBG) levels, which in turn lower concentrations of bioavailable testosterone and lessen androgenic side effects.

Regarding carbohydrate metabolism, current low-dose formulations have minimal effects in women who do not have diabetes (Lopez, 2014). And, the risk of developing diabetes is not increased (Kim, 2002). For diabetic women, COCs may be used in nonsmokers with disease duration <20 years and without associated vascular disease, nephropathy, retinopathy, or neuropathy (Curtis, 2016b).

Of other metabolic changes, thyroid-binding globulin and thyroid-stimulating hormone (TSH) levels are elevated, but free plasma thyroxine (FT_4) levels are unchanged (Raps, 2014). Studies have not supported a connection between COCs and weight gain (Gallo, 2014).

Cardiovascular Effects

Despite increased plasma angiotensinogen (renin substrate) levels, women using low-dose COC formulations rarely develop clinically significant hypertension (Chasan-Taber, 1996). However, it is common practice for patients to return 8 to 12 weeks after COC initiation for evaluation of blood pressure and other symptoms.

During initial contraception selection, a history of gestational hypertension does not preclude subsequent COC use. Among women with well-controlled hypertension, COC use is linked to greater risks than nonusers for stroke, acute myocardial infarction, and peripheral arterial disease, and in these women, COCs are considered US MEC category 3 (Curtis, 2016b). Severe forms of hypertension, especially those with end-organ involvement, preclude COC use.

For nonsmoking women younger than 35, the risk of stroke is extremely low (World Health Organization, 1996). COCs are associated with a small increased risk for ischemic stroke (Chan, 2004; Lidegaard, 2012). Rates increase significantly for women who have hypertension, who smoke, or who have migraine headaches with visual aura or other focal neurological changes *and* use COCs (MacClellan, 2007; Tepper, 2016c). The evidence for stroke risk in migraineurs without aura is less clear (Etminan, 2005; Schürks, 2009). COC initiation may be considered for women with preexisting migraines without aura if they are otherwise healthy, younger, normotensive nonsmokers. For women with prior stroke, COCs should not be considered due to risks for repeat events.

For women with prior myocardial infarction, COCs should not be considered. Also, in women with multiple cardiovascular risk factors, which include smoking, hypertension, older age, and diabetes, the risk for myocardial infarction outweighs the benefits of this method. However, for those without these risks, low-dose oral contraceptives are not associated with an increased risk of myocardial infarction (Margolis, 2007; World Health Organization, 1997).

The risks for deep-vein thrombosis and pulmonary embolism are increased in women who use COCs (Stadel, 1981). These clearly are estrogen-dose related, and rates have substantively declined with lower-dose formulations containing 10 to 35 µg of ethinyl estradiol. The general-population risk of venous thromboembolism (VTE) is 4 to 5 events per 100,000 woman-years. The incidence of VTE with COC use increases three- to fivefold compared with nonusers (Shaw, 2013; van Hylckama Vlieg, 2009). Obesity raises the VTE risk, which is compounded by COCs (Horton, 2016; Suchon, 2016). Accordingly, in an obese woman, COCs are considered a US MEC category 2. VTEs are significantly increased in women older than 35 years who smoke, and COCs are not recommended. Those most at risk for VTE include women with thrombophilias (ESHRE Capri Workshop Group, 2013). Moreover, COC use during the month before a major operative procedure appears to double the risk for postoperative VTE (Robinson, 1991). Thus, the American College of Obstetricians and Gynecologists (2016d) recommends balancing the risks of VTE and the degree of postoperative immobility with the risk of unintended pregnancy during the 4 to 6 weeks required to reverse the thrombogenic effects of COCs before surgery. In the early puerperium, VTE risks are also increased, and COCs are not recommended for women within the first 4 weeks after delivery.

Certain progestins within COC are linked with greater rates of thromboembolism. A slightly higher VTE risk with drospirenone-containing COCs has been shown in two studies. In response, an assessment of benefits and VTE risks in users of these pills has been emphasized (Food and Drug Administration, 2012; Jick, 2011; Parkin, 2011). Desogestrel and gestodene are also implicated and carry similarly elevated risks (Stegeman, 2013; Vinogradova, 2015).

Neoplasia

Most studies indicate that COCs overall are not associated with an increased risk of cancer (Cibula, 2010). In fact, a protective effect against ovarian and endometrial cancer has been shown (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Tsilidis, 2011). As an exception, the relative risk of cervical dysplasia and cervical cancer is higher in current COC users, but this declines after use is discontinued. Following 10 or more years, risk returns to that of never users (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). It is unclear whether COCs contribute to breast cancer development. Major studies show no risk or a small risk among current users, which drops with time following cessation (Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Hannaford, 2007; Marchbanks, 2002).

Although COC use in the past was linked to development of hepatic *focal nodular hyperplasia* and *benign hepatic adenoma*, large studies do not support this (Heinemann, 1998). Moreover, no evidence supports concern for greater risk of hepatocellular cancer (Maheshwari, 2007). For women with known tumors, COCs may be used in those with focal nodular hyperplasia, but avoided in those with benign hepatic adenoma and hepatocellular carcinoma (Kapp, 2009b). Rates of colorectal cancer appear to be reduced in ever users (Bosetti, 2009; Luan, 2015).

Other Effects

Cholestasis and cholestatic jaundice are uncommon, but they resolve when COCs are discontinued. In women who have active hepatitis, COCs should not be initiated, but these may be continued in women who experience a flare of their liver disease while already taking COCs. Use of progestin-only contraception in these women is not restricted. Moreover, there is no reason to withhold COCs from women who have recovered. Mild compensated cirrhosis does not limit the use of COCs or progestin-only methods. But in those with severe decompensated disease, all hormonal methods are avoided (Kapp, 2009a).

Chloasma, which is hyperpigmentation of the face and forehead, is more likely in women who demonstrated such a change during pregnancy (Chap. 4, Breasts). This is less common with low-dose estrogen formulations. Although previously used for treating functional ovarian cysts, low-dose COC formulations have been shown to have no effects related to cyst resolution or prevention (European Society of Human Reproduction and Embryology, 2001; Grimes, 2014).

Many noncontraceptive benefits are associated with COC use (American College of Obstetricians and Gynecologists, 2016c). And indeed, COCs may be used for these effects, even in those without contraceptive needs. Dysmenorrhea and heavy menstrual bleeding lessen with COC use. Another action is to improve androgenic conditions such as acne and hirsutism. For women with premenstrual dysphoric disorder (PMDD), several studies have shown symptom improvement in those who use the drospirenone-containing COC *Yaz* (Lopez, 2012b; Pearlstein, 2005; Yonkers, 2005).

Transdermal Patch

The *Ortho Evra* patch contains ethinyl estradiol and the progestin norelgestromin. It has an inner layer containing an adhesive and hormone matrix, and a water-resistant outer layer. Thus, women can wear the patch in bathtubs, showers, swimming pools, saunas, and whirlpools without decreased efficacy. The patch may be applied to buttocks, upper outer arm, lower abdomen, or upper torso, but the breasts are avoided. Because the hormones are combined with the adhesive, improper skin adherence will lower hormone absorption and efficacy. Therefore, if a patch is so poorly adhered that it requires reinforcement with tape, it should be replaced.

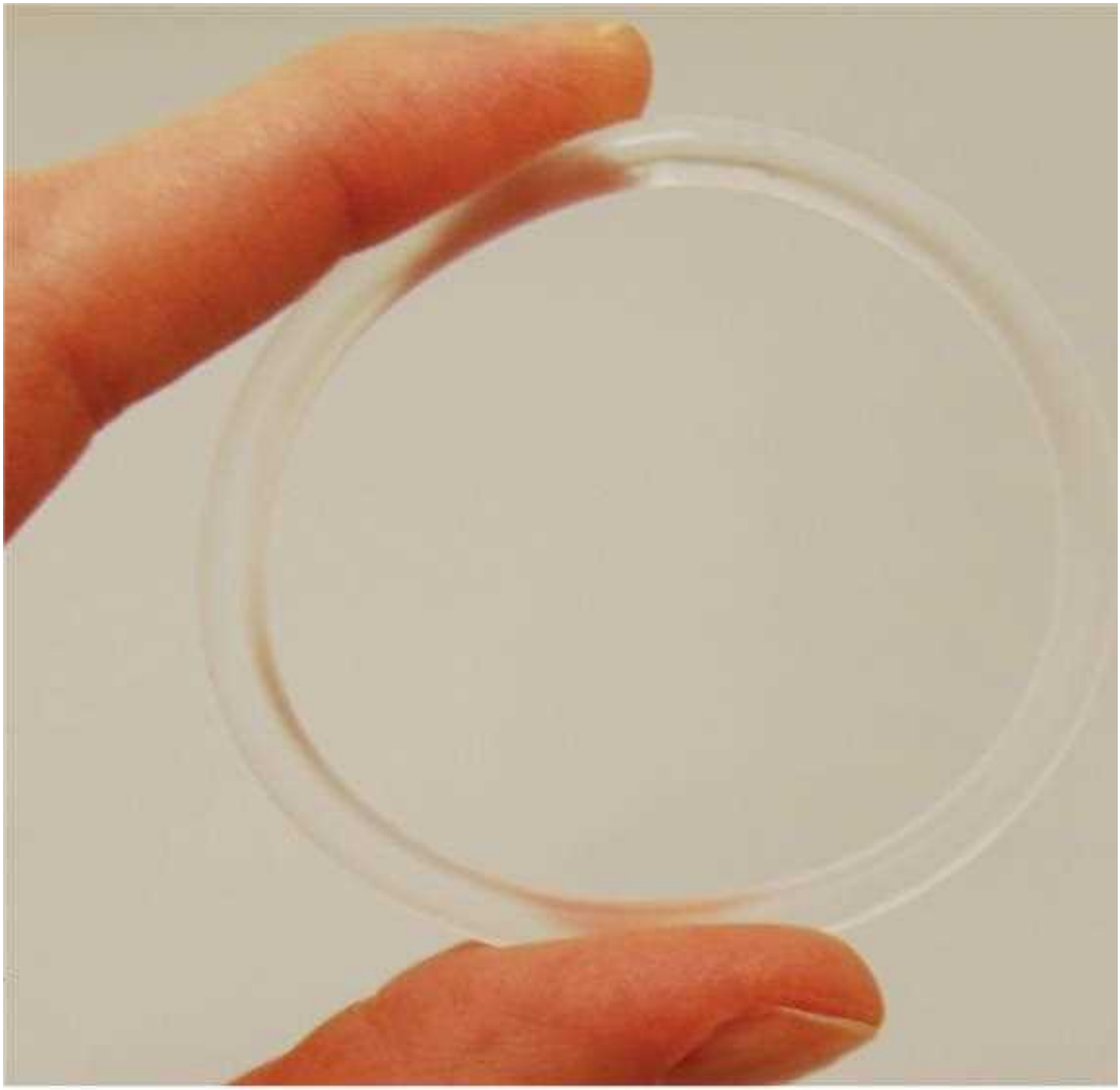
Initiation of the patch is the same as for COCs, and a new patch is applied weekly for 3 weeks, followed by a patch-free week to allow withdrawal bleeding. Although a patch is ideally worn no longer than 7 days, hormone levels remain in an effective range for up to 9 days. This affords a 2-day window for patch-change delays (Abrams, 2001).

In general, the transdermal patch and vaginal ring produce metabolic changes, side effects, and efficacy rates comparable to those with COC pills. However, the patch has been associated with a higher thromboembolism risk in some but not all studies (Cole, 2007; Jick, 2010; Lidegaard, 2011). In response, the Food and Drug Administration (2015b) approved labeling for the patch to state that the risk for VTE may be increased compared with other COCs, and relative risk estimates range from 1.2 to 2.2. Obesity—90 kg or greater—may be associated with a higher risk for patch contraceptive failure (Janssen Pharmaceuticals, 2015; Zieman, 2002). Finally, application-site reaction and breast tenderness are more frequent during initial cycles in patch wearers (Urdl, 2005).

Transvaginal Ring

The *NuvaRing* is yet another form of combination hormonal contraception and is a flexible intravaginal ring. The ring is constructed of ethinyl vinyl acetate, and it measures 54 mm in diameter and 4 mm in cross section (Fig. 38-5). During insertion, the ring is compressed and threaded into the vagina, but no specific final orientation within the vagina is required. Its core releases ethinyl estradiol and the progestin etonogestrel, which are absorbed across the vaginal epithelium. Before being dispensed, the rings are refrigerated, and once dispensed, their shelf life is 4 months. The ring is placed within 5 days of menses onset and, after 3 weeks of use, is removed for 1 week to allow withdrawal bleeding. Contraception will still be afforded if a ring is left in place for a fourth week (Merck, 2016b).

FIGURE 38-5
NuvaRing: estrogen-progestin–releasing vaginal contraceptive ring.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Ellen M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Patient satisfaction is high with this method, although vaginitis, ring-related events, and leukorrhea are more common (Lopez, 2013b; Oddsson, 2005). Despite this, no deleterious affect on lower reproductive tract or endometrial epithelia has been found (Lete, 2013; Veres, 2004). A ring may be used concurrently with vaginal medications or with a tampon (Haring, 2003; Verhoeven, 2004a,b). Approximately 70 percent of partners feel the ring during intercourse (Dieben, 2002). If this is bothersome, the ring may be removed for intercourse but should be replaced within 3 hours to maintain efficacy.

Injectable Progestin Contraceptives

Both intramuscular depot medroxyprogesterone acetate—Depo-Provera (DMPA)—150 mg every 3 months, and norethisterone enanthate, 200 mg every 2 months, are injectable progestin contraceptives used worldwide. Of the two, DMPA is available in the United States. DMPA is injected into the deltoid or gluteus muscle, but massage is avoided to ensure that the drug is released slowly. Alternatively, a subcutaneous version, *depo-subQ provera 104*, is also available and is injected into the subcutaneous tissue of the anterior thigh or abdomen every 3 months.

DMPA is effective, and as with other progestin-only methods, contraception is provided by ovulation inhibition, greater cervical mucus viscosity, and creation of an endometrium unfavorable for ovum implantation. Initial injection is given within the first 5 days following menses onset. Serum levels sufficient for contraception are observed by 24 hours. Thus, no additional contraceptive method is required for initiation within this window. Alternatively, limited data support a “quick wtart,”

or initiation of DMPA regardless of cycle day. If so implemented, investigators recommend an initial negative pregnancy test result before injection, a supplemental contraceptive method during the 7 days following injection, and a second pregnancy test after 3 to 6 weeks to identify an early pregnancy (Rickert, 2007; Sneed, 2005). Pregnancies conceived during DMPA use are not associated with a higher risk of fetal malformation (Katz, 1985). For women who present for intramuscular DMPA reinjection more than 13 weeks or for subcutaneous DMPA reinjection more than 14 weeks after the prior dose, the manufacturer recommends exclusion of pregnancy before reinjection (Pfizer, 2015a,b).

Actions and Side Effects

Injected progestins offer the convenience of a 3-month dosing schedule, contraceptive efficacy comparable with or better than COCs, and minimal to no lactation impairment. Iron-deficiency anemia is less likely in long-term users because of amenorrhea, which develops in up to 50 percent after 1 year and in 80 percent after 5 years.

Similar to other progestin-only contraceptive, irregular menstrual bleeding is common, and a fourth of women discontinued DMPA in the first year because of this (Cromer, 1994). Unique to DMPA, prolonged anovulation can follow discontinuation, which results in delayed fertility resumption. After injections are stopped, a fourth of patients do not resume regular menses for up to 1 year (Gardner, 1970). Accordingly, DMPA may not be ideal for women who plan to use birth control only briefly before attempting conception.

As with other progestins, DMPA has not been associated with cardiovascular events or stroke in otherwise healthy women. However, in those with severe hypertension, a higher risk of stroke has been found in DMPA users (World Health Organization, 1998). Moreover, the US MEC authors express concerns regarding hypoestrogenic effects and reduced HDL levels from DMPA in women with vascular disease or multiple risks for cardiovascular disease.

Weight gain is generally attributed to DMPA, and these increases are comparable between the two depot forms (Bahamondes, 2001; Vickery, 2013; Westhoff, 2007c). In long-term users, loss of bone mineral density is also a potential problem (Petitti, 2000; Scholes, 1999). In 2004, the FDA added a black box warning to DMPA labeling, which notes that this concern is probably most relevant for adolescents, who are building bone mass, and perimenopausal women, who will soon have increased bone loss during menopause. That said, World Health Organization (1998) and American College of Obstetricians and Gynecologists (2016b) believe that DMPA should not be restricted in those high-risk groups. And, it seems prudent to reevaluate overall risks and benefits during extended use. It is somewhat reassuring that bone loss appears to be reversible after discontinuation of therapy, although reversal is still not complete after 18 to 24 months (Clark, 2006; Scholes, 2002).

Progestin-Only Pills

So-called *mini-pills* are progestin-only contraceptives that are taken daily. These contraceptives have not achieved widespread popularity and are used by only 0.4 percent of reproductive-aged American women (Hall, 2012). Unlike COCs, they do not reliably inhibit ovulation. Rather, their effectiveness depends more on cervical mucus thickening and endometrial atrophy. Because mucus changes are not sustained longer than 24 hours, mini-pills should be taken at the same time every day to be maximally effective. If a progestin-only pill is taken even 4 hours late, a supplemental form of contraception must be used for the next 48 hours. Progestin-only pills are contraindicated in women with known breast cancer or pregnancy. Other cautions are listed in Table 38-2.

BARRIER METHODS

Male Condom

For many years, male and female condoms, vaginal diaphragms, and periodic abstinence have been used for contraception with variable success (see Table 38-2). When used properly, condoms provide considerable but not absolute protection against a broad range of sexually transmitted diseases, including HIV (Eaton, 2014). Contraceptive efficacy of the male condom is enhanced appreciably by a reservoir tip and probably by the addition of a spermicide. Such agents, as well as those used for lubrication, should be water-based because oil-based products degrade latex condoms and diaphragms.

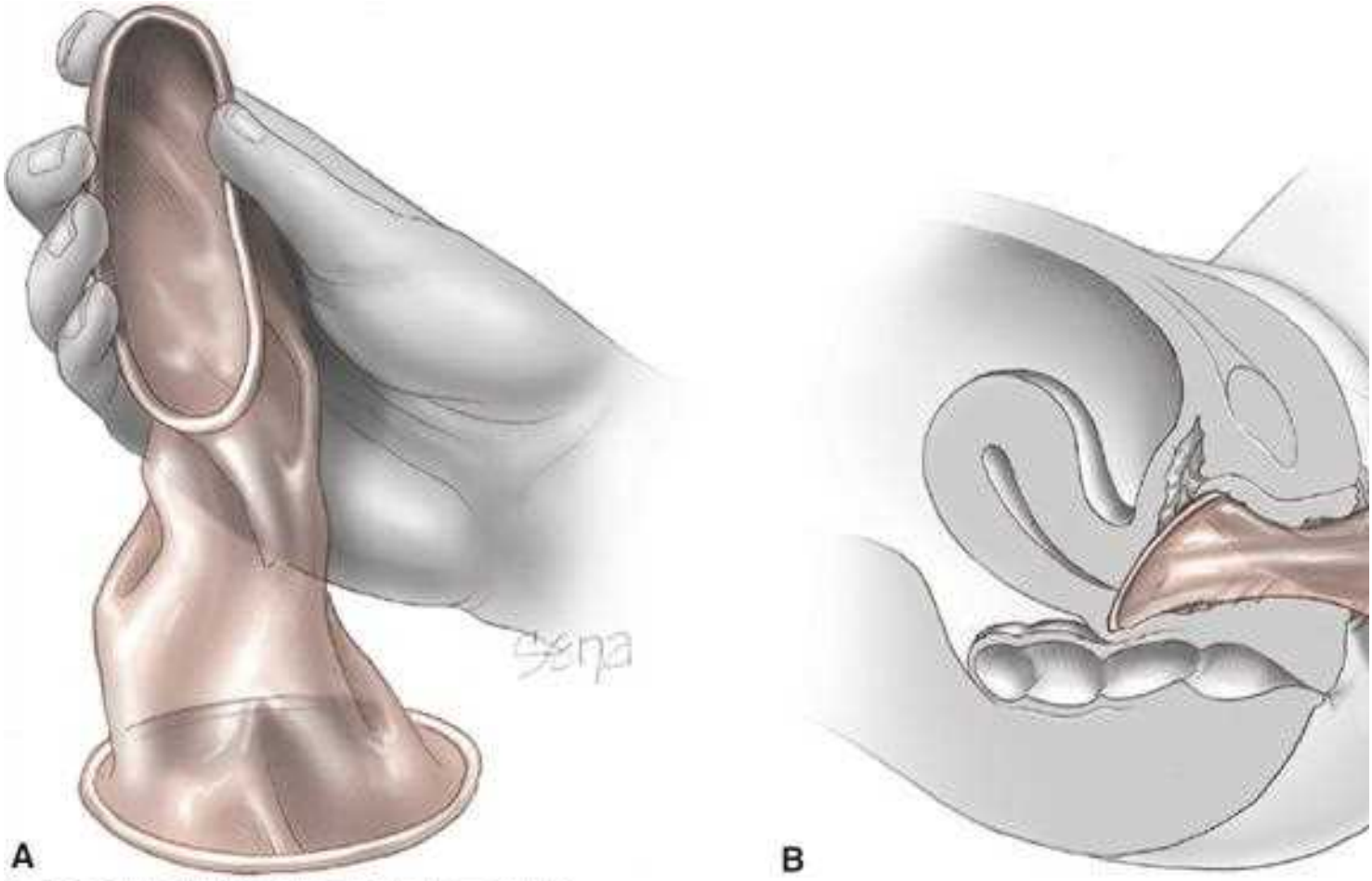
For individuals sensitive to latex, condoms made from lamb intestines are effective, but they do not provide infection protection. Fortunately, nonallergenic condoms have been developed that are made of polyurethane or of synthetic elastomers. Polyurethane condoms are effective against STDs but have a higher breakage and slippage rate compared with latex condoms (Gallo, 2012a).

Female Condom

The only female condom available in the United States is marketed as the *FC2 Female Condom*. It is a synthetic nitrile sheath with one flexible polyurethane ring at each end. Its open ring remains outside the vagina, whereas its closed internal ring is fitted under the symphysis like a diaphragm (Fig. 38-6). The female condom can be used with both water-based and oil-based lubricants. Male condoms should not be used concurrently because simultaneous use may cause friction that leads to condom slipping, tearing, and displacement. Following use, the female condom outer ring should be twisted to seal the condom so that no semen spills. As an added value, the female condom may offer some protection against STDs (Minnis, 2005).

FIGURE 38-6

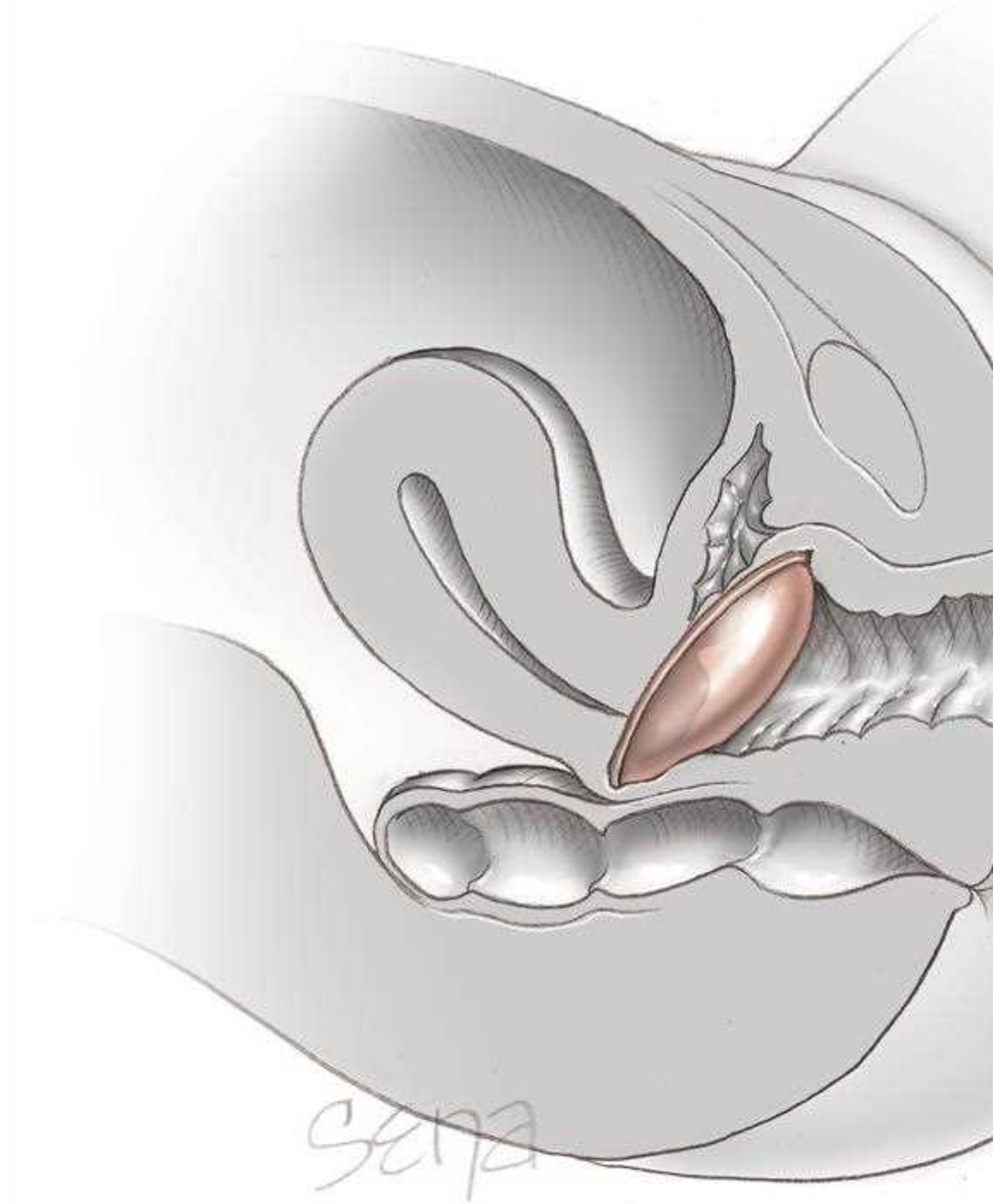
FC2 Female Condom insertion and positioning. **A.** The inner ring is squeezed for insertion. The sheath is inserted similarly to a diaphragm. **B.** The inner ring is pushed inward with an index finger.



Diaphragm Plus Spermicide

The diaphragm consists of a circular latex dome of variable diameter supported by a circumferential latex-covered metal spring. It is effective when used in combination with spermicidal jelly or cream. The spermicide is applied into the dome cup and along the device rim. The diaphragm is then positioned so that the cup faces the cervix and that the cervix, vaginal fornices, and anterior vaginal wall are partitioned effectively from the remainder of the vagina and the penis. In this fashion, the centrally placed spermicide is held against the cervix. When appropriately positioned, one rim is lodged deep in the posterior vaginal fornix, and the opposite rim fits behind the inner surface of the symphysis and immediately below the urethra (Fig. 38-7). If a diaphragm is too small, it will not remain in place. If it is too large, it is uncomfortable when forced into position. A coexistent cystocele or uterine prolapse typically leads to instability and expulsion. Because size and spring flexibility must be individualized, the diaphragm is fitted by providers and available only by prescription.

FIGURE 38-7
A diaphragm in place creates a physical barrier between the vagina and cervix.



For use, the diaphragm and spermicide can be inserted hours before intercourse. If more than 6 hours elapse, the diaphragm can remain but additional spermicide is placed in the upper vagina for maximum protection. Spermicide is reapplied before each subsequent coital episode. The diaphragm is not removed for at least 6 hours after intercourse. Because toxic shock syndrome has been described following its use, it may be worthwhile to remove the diaphragm at 6 hours, or at least the

next morning, to minimize this rare event. Diaphragm use is associated with a slightly greater rate of urinary infections, presumably from urethral irritation by the ring under the symphysis.

Cervical Cap

FemCap is currently the only available cervical cap in the United States. Made of silicone rubber, it has a sailor-cap shape with a dome that covers the cervix and a flared brim, which allows the cap to be held in place by the muscular walls of the upper vagina. Available in 22-, 26-, and 30-mm sizes, it is used with a spermicide applied once at insertion to both sides of the dome cup. For contraception, it should remain in place for 6 hours following coitus and may remain for up to 48 hours. Even with proper fitting and correct use, pregnancy rates with this method are higher that with the diaphragm (Gallo, 2012b; Mauck, 1999).

FERTILITY AWARENESS-BASED METHODS

These family planning methods attempt to identify the fertile days each cycle and advise sexual abstinence during these days. Their major drawback is their limited efficacy, which is shown in Table 38-1. Common forms of these fertility awareness-based (FAB) methods include Standard Days, Temperature Rhythm, Cervical Mucus, and Symptothermal Methods. Some smartphone applications aim to assist these practices (Fehring, 2013).

The *Standard Days Method* counsels women to avoid unprotected intercourse during cycle days 8 through 19. For successful use, women must have regular monthly cycles of 26 to 32 days. Those who use this method can mark a calendar or can use *Cycle-Beads*, which is a ring of counting beads, to keep track of their days.

The *Temperature Rhythm Method* relies on a sustained 0.4°F rise in the basal body temperature, which usually precedes ovulation. For maximum efficacy, the woman must abstain from intercourse from the first day of menses through the third day after the temperature increase.

The *Cervical Mucus Method*, also called the Two-Day Method or Billings Method, relies on awareness of vaginal “dryness” and “wetness.” These reflect changes in the amount and quality of cervical mucus at different times in the menstrual cycle. With the Billings Method, abstinence is required from the beginning of menses until 4 days after slippery mucus is identified. With the Two-Day Method, intercourse is considered safe if a woman did not note mucus on the day of planned intercourse or the day prior.

The *Symptothermal Method* combines changes in cervical mucus—onset of fertile period; changes in basal body temperature—end of fertile period; and calculations to estimate the time of ovulation. This method is more complex to learn and apply, but it does not appreciably improve efficacy.

SPERMICIDES

These contraceptives are marketed variously as creams, jellies, suppositories, films, and aerosol foam. Most can be purchased without a prescription. They are considered a less effective method (see Table 38-1). If pregnancy does occur, they are not teratogenic (Briggs, 2015).

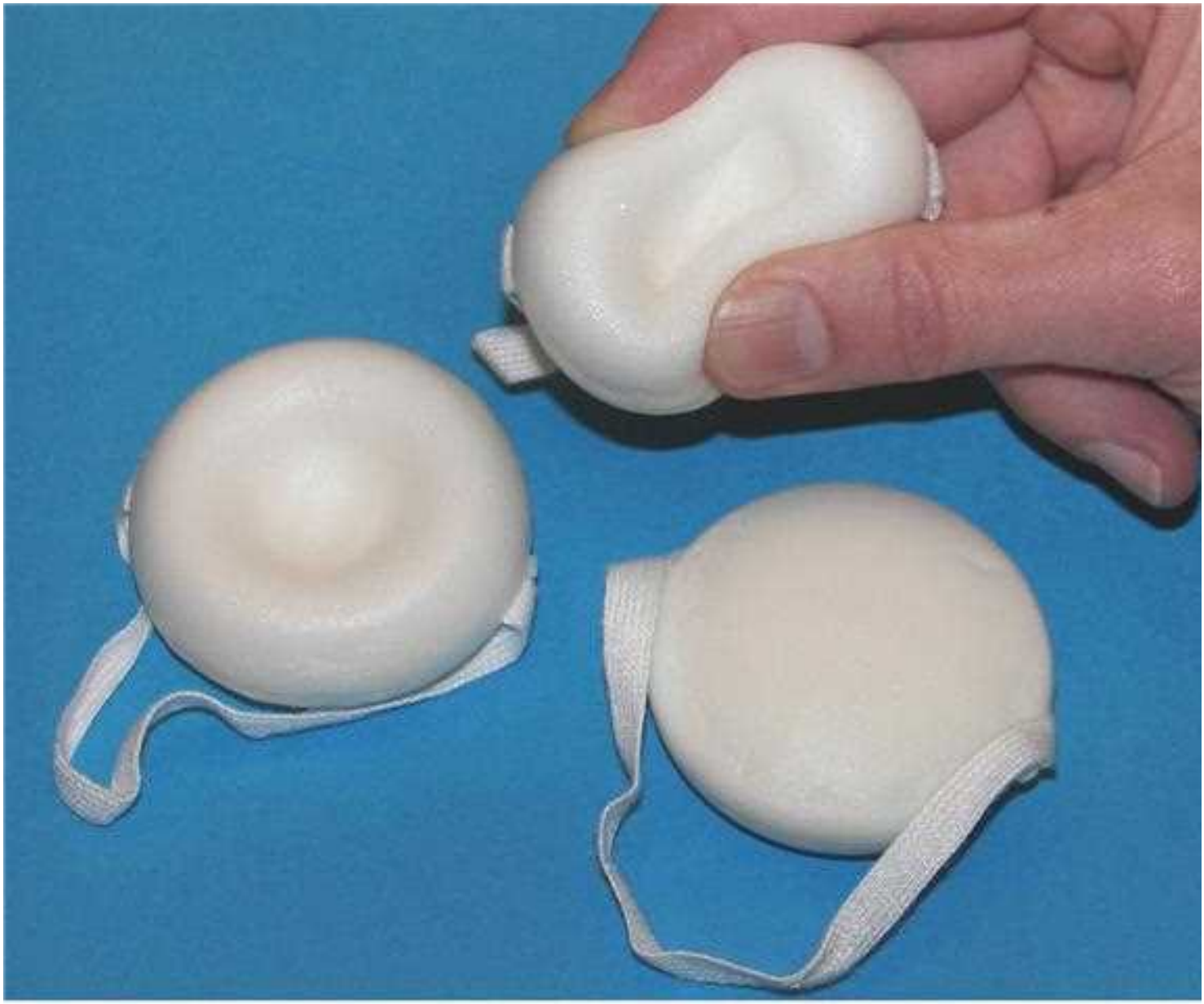
Typically, spermicides function by providing a physical barrier to sperm penetration and a chemical spermicidal action. The active ingredient is nonoxynol-9 or octoxynol-9. Although these are spermicidal, they do not provide STD protection. Ideally, spermicides must be deposited high in the vagina in contact with the cervix shortly before intercourse. Their duration of maximal effectiveness is usually no more than 1 hour, and thereafter, they must be reinserted before repeat intercourse. Douching is avoided for at least 6 hours after coitus.

Contraceptive Sponge

The *Today* contraceptive sponge is an over-the-counter, one-size-fits-all device. The nonoxynol-9–impregnated polyurethane disc is 2.5 cm thick and 5.5 cm wide and has a dimple on one side and satin loop on the other (Fig. 38-8). The sponge can be inserted up to 24 hours prior to intercourse, and while in place, it provides contraception regardless of coital frequency. It should remain in place for 6 hours after intercourse. Pregnancy is prevented primarily by the spermicide nonoxynol-9 and to a lesser extent by covering the cervix and absorbing semen.

FIGURE 38-8

Today sponges. The sponge is moistened with tap water and gently squeezed to create light suds. It is then positioned with the dimple directly against the cervix. The fabric loop trails within the vagina and can be hooked with a finger to later extract the sponge.



Although the sponge is possibly more convenient than the diaphragm or condom, it is less effective than either (Kuyoh, 2013). Most common causes for method discontinuance are pregnancy, irritation, discomfort, or vaginitis (Beckman, 1989). Although toxic shock syndrome has been reported with the contraceptive sponge, it is rare, and evidence suggests that the sponge may actually limit production of the responsible staphylococcal exotoxin (Remington, 1987). Still, it is recommended that the sponge not be used during menses or the puerperium.

EMERGENCY CONTRACEPTION

Following unprotected sexual intercourse, many women present for contraceptive care. Several emergency contraception (EC) regimens substantially lower the likelihood of an unwanted pregnancy when used correctly. Current methods include COCs, progestins, progesterone antagonists, and copper-containing IUDs (Table 38-3). Overall, the IUD is most effective, and ulipristal acetate is the most efficient oral regimen (American College of Obstetricians and Gynecologists, 2017a). Patients can obtain information regarding emergency contraception by calling 1–888-NOT-2-LATE or accessing The Emergency Contraception Website: http://not-2-late.com.

TABLE 38-3

Methods Available for Use as Emergency Contraception

Method	Formulation	Pills per Dose	Number of Doses[a]
Progestin-Only Pill			
Plan B One-Step Next Choice One Dose	150 mg LNG	1	1
PRM Pill			
Ella	30 mg ulipristal acetate	1	1
COC Pills[b,c]			
Ogestrel	0.05 mg EE + 0.5 mg norgestrel	2	2
Cryselle, Low-Ogestrel	0.03 mg EE + 0.3 mg norgestrel	4	2
Enpresse (orange), Trivora (pink)	0.03 mg EE + 0.125 mg LNG	4	2
Levora, Seasonale	0.03 mg EE + 0.15 mg LNG	4	2
Aviane, LoSeasonique (orange)	0.02 mg EE + 0.1 mg LNG	5	2
Copper-Containing IUD	Paragard T 380A		

[a]Doses taken 12 hours apart if multiple.

[b]Other COC brands with formulations identical to those above may also be used.

[c]Use of an antiemetic agent before taking the medication will lessen the risk of nausea, which is a common side effect.

COC = combination oral contraceptive; EE = ethinyl estradiol; IUD = intrauterine device; LNG = levonorgestrel; PRM = progesterone-receptor modulator.

Hormonal Emergency Contraception

Except for allergy to a particular component, no conditions in the US MEC contraindicate hormonal EC methods. With progestin-only regimens, levonorgestrel is taken as a single, one-time 1.5-mg dose (Arowojolu, 2002). This is now recommended instead of two 0.75-mg doses separated by 12 or 24 hours (Ngai, 2005). Dosing begins ideally within 72 hours of unprotected coitus but may be given up to 120 hours. Notably, the single-dose regimen is available over-the-counter without a prescription to all reproductive-aged women (Food and Drug Administration, 2013, 2015a).

One progesterone-receptor modulator currently available for EC is ulipristal acetate and is marketed as *Ella.* It is taken as a single 30-mg tablet up to 120 hours after unprotected intercourse (Brache, 2010; Watson, 2010).

Also known as the *Yuzpe method*, this older EC method provides a minimum of 100 µg of ethinyl estradiol and 0.5 mg of levonorgestrel in each of two doses. As shown in Table 38-3, a sufficient dose may be achieved by two or more pills. The first dose is taken ideally within 72 hours of intercourse but may be given up to 120 hours. The initial dose is followed 12 hours later by a second equivalent dose.

The major mechanism with all hormonal regimens is inhibition or delay of ovulation. Of oral methods, failure rates are lowest with ulipristal (1 to 2 percent) and greatest with the Yuzpe method (2 to 3.5 percent) (Cleland, 2014). If EC fails to prevent pregnancy or is mistimed, no associations with major congenital malformation or pregnancy complications have been noted with these hormonal methods (Jatlaoui, 2016; Levy, 2014).

With EC administration, nausea and vomiting can be an important side effect (American College of Obstetricians and Gynecologists, 2015b; Gemzell-Danielsson, 2013). Accordingly, an oral antiemetic may be prescribed at least 1 hour before each dose (Rodriguez, 2013). If a woman vomits within 2 hours of a dose, the dose is repeated.

Copper-Containing Intrauterine Devices

For women who are candidates, Cu-IUD insertion is the most effective emergency contraceptive method and provides an effective 10-year method of contraception (Cheng, 2012). If an IUD is placed up to 5 days after unprotected coitus, the failure rate approximates only 0.1 percent (Cleland, 2012; Wu, 2010).

PUERPERAL CONTRACEPTION

For mothers who are nursing exclusively, ovulation during the first 10 weeks after delivery is unlikely. Nursing, however, is not a reliable method of family planning for women whose infants are on a daytime-only feeding schedule. Moreover, waiting for first menses involves a risk of pregnancy, because ovulation usually antedates menstruation. Certainly, after the first menses, contraception is essential unless the woman desires pregnancy.

As shown in Table 38-2, all methods may be suitable for nursing mothers after the initial weeks, during which thromboembolism risks are still great. With all hormonal methods, very small quantities are excreted in breast milk, but no adverse effects on infants have been reported (Phillips, 2015; World Health Organization, 1988). Although not robust, some older studies link decreased infant weight gain or milk volume with early initiation of combination oral contraceptives before 6 weeks postpartum (Lopez, 2015c; Tepper, 2016a).

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CHAPTER 39: Sterilization

In order, therefore, to render a woman permanently sterile by an operation upon the tubes, they must be excised by wedge-shaped incisions at the cornua of the uterus and the wounds closed by sutures.

—J. Whitridge Williams (1903)

INTRODUCTION

Sterilization is a popular choice of contraception for millions of men and women. Among women using contraception, one third rely on either male or female sterilization (Daniels, 2015). This procedure is indicated in those requesting sterilization and who clearly understand its permanence and its difficult and often unsuccessful reversal. All persons considering sterilization should also be counseled regarding alternative contraceptive choices (American College of Obstetricians and Gynecologists, 2017a,c).

Female sterilization is usually accomplished by occlusion, excision, or division of the fallopian tubes. *Puerperal sterilization* procedures follow cesarean or vaginal delivery and approximately 7 percent of all live births in the United States (Moniz, 2017). *Nonpuerperal tubal sterilization* is done at a time unrelated to recent pregnancy and is also termed interval sterilization.

PUERPERAL TUBAL STERILIZATION

Timing

For several days postpartum, the uterine fundus lies at the level of the umbilicus, and fallopian tubes are accessible directly beneath the abdominal wall. Moreover, abdominal laxity allows easy repositioning of the incision over each uterine cornu.

On our service, puerperal tubal ligation is performed by a surgical team dedicated to this role the morning after delivery. This timing minimizes hospital stay but lowers the likelihood that postpartum hemorrhage would complicate recovery following surgery. In addition, the status of the newborn can be better ascertained before surgery. In contrast, some prefer to perform sterilization immediately following delivery and use neuraxial analgesia already placed for labor. In this model, barriers to sterilization can be lessened by designating these postpartum surgeries as urgent, especially in high-volume labor and delivery units, which usually prioritize limited operating-room availability for intrapartum procedures (American College of Obstetricians and Gynecologists, 2016; Potter, 2013).

Technique

Various techniques are now used to disrupt tubal patency. In general, a midtubal segment of fallopian tube is excised, and the severed ends seal by fibrosis and peritoneal regrowth. Commonly used methods of puerperal sterilization include the Parkland, Pomeroy, and modified Pomeroy techniques (American College of Obstetricians and Gynecologists, 2017a). Less often, Filshie clips are used (Madari, 2011). Irving and Uchida techniques or Kroener fimbriectomy are rarely used because of their increased required dissection or unfavorably high failure rates. Also, in the absence of uterine or other pelvic disease, hysterectomy solely for sterilization at the time of cesarean delivery, early in the puerperium, or even remote from pregnancy is difficult to justify. It carries significantly increased surgical morbidity compared with tubal sterilization.

Evidence suggests that the fallopian tube may be the origin of pelvic serous carcinomas, especially those of the ovary. With this knowledge, the Society of Gynecologic Oncologists (2013) and American College of Obstetricians and Gynecologists (2017b) recommend consideration of salpingectomy to lower cancer risks. Specifically, for women at average risk of ovarian cancer, risk-reducing salpingectomy should be discussed and considered with patients at the time of abdominal or pelvic surgery, at hysterectomy, or in lieu of tubal ligation.

Spinal analgesia is typically selected for cases scheduled for the first postpartum day. If done more proximate to delivery, the same epidural catheter used for labor analgesia can be used for sterilization analgesia. Notably, for those with preeclampsia, HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome, or gestational thrombocytopenia, platelet levels should be >100,000 for spinal blockade (Chap. 25, Contraindications). General anesthesia may be less desirable due to residual pregnancy-related airway vulnerabilities (Bucklin, 2003). The bladder is emptied before surgery to avoid its laceration. A full bladder can also push the fundus above the umbilicus.

A small infraumbilical incision is ideal for several reasons. As noted, the fundus in most cases lies near the umbilicus. Second, the umbilicus usually remains the thinnest portion of the anterior abdominal wall and requires less subcutaneous dissection to reach the linea alba fascia. Third, an infraumbilical incision offers fascia with sufficient integrity to provide a closure that has minimal risk for later incisional hernia. Last, incisions that follow the natural curve of the lower umbilical skin fold yield suitable cosmesis. A 2- to 4-cm transverse or vertical skin incision is usually sufficient for normal-weight women. For obese women, a 4- to 6-cm incision may be needed for adequate abdominal access.

Beneath this incision, the subcutaneous tissue is bluntly separated to reach the linea alba fascia. For this, an Allis clamp can be opened and closed as downward pressure is exerted. Similarly, the blades of two army-navy retractors both pulling in downward yet opposite directions can part the subcutaneous layer. Clearing this

fatty tissue away from the fascia isolates the fascia for incision and for later closure without intervening fat, which may impede wound healing.

The fascial incision may be transverse or vertical and follows the same orientation of the skin incision. For this, once the linea alba is reached, it is grasped with two Allis clamps—one placed on either side of the planned fascial incision. The purchase of tissue with each clamp should be substantial and creates a small roll of fascia to be incised. Often, the peritoneum is incorporated simultaneously and entered. If not, the peritoneum is grasped with two hemostats and sharply cut. Others may prefer to bluntly enter with a single index finger. Notably, if the initial fascial incision is too small, it can be extended with curved Mayo scissors.

Adequate exposure is critical, and army-navy or appendiceal retractors are suitable. For obese women, a slightly larger incision and narrow deeper retractors may be required. If bowel or omentum is obstructing, Trendelenburg position can help displace these cephalad. Digitally packing with a single, moist, fanned-out piece of surgical gauze can also be used, but a hemostat should always be attached to the distal end to avert its retention. At times, tilting the entire table to the opposite side of the tube being exposed assists tube isolation.

The fallopian tube is identified and grasped at its midportion with a Babcock clamp, and the distal fimbria confirmed. This prevents confusing the round ligament with the midportion of the tube. A common reason for sterilization failure is ligation of the wrong structure, typically the round ligament. Therefore, identification and isolation of the distal tube prior to ligation is necessary. Whenever the tube is inadvertently dropped, it is mandatory to repeat this identification process. Surgical steps for ligation are outlined in Figures 39-1 and 39-2.

FIGURE 39-1

Parkland method. **A.** An avascular site in the mesosalpinx adjacent to the fallopian tube is perforated with a small hemostat. The jaws are opened to separate the fallopian tube from the adjacent mesosalpinx for approximately 2.5 cm. **B.** The freed fallopian tube is ligated proximally and distally with 0-chromic suture. The intervening segment of approximately 2 cm is excised, and the excision site is inspected for hemostasis. This method was designed to avoid the initial intimate proximity of the cut ends of the fallopian tube inherent with the Pomeroy procedure. (Reproduced with permission from Hoffman BL, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Bradshaw KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)

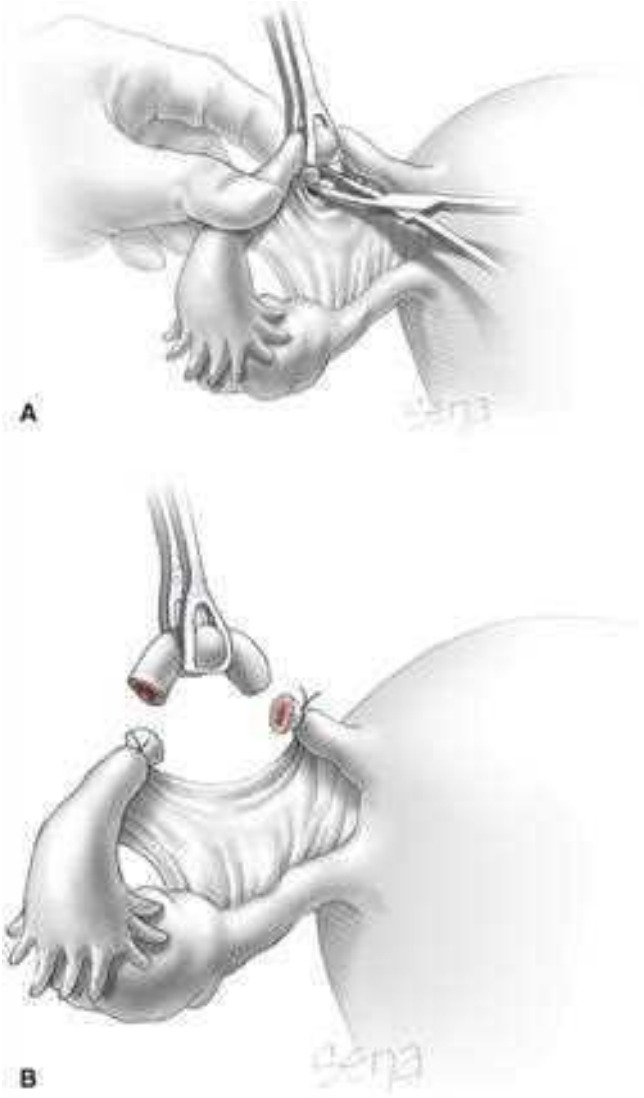
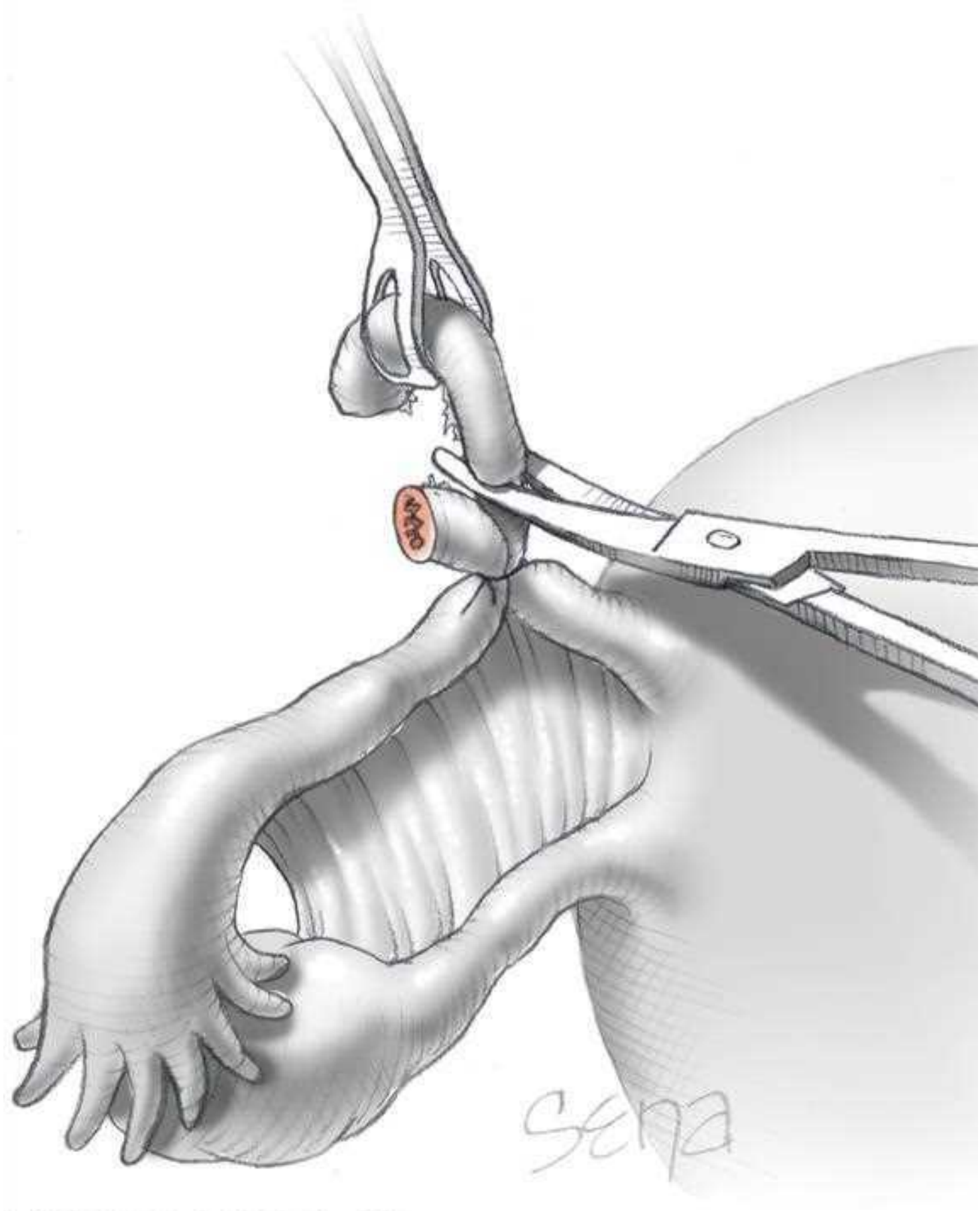


FIGURE 39-2

Pomeroy method. During ligation of a midsegment tubal loop, plain catgut is used to ensure prompt absorption of the ligature and subsequent separation of the severed tubal ends. (Reproduced with permission from Hoffman BL, Corton MM: Surgeries for benign gynecologic conditions. In Hoffman BL, Schorge JO, Bradshaw

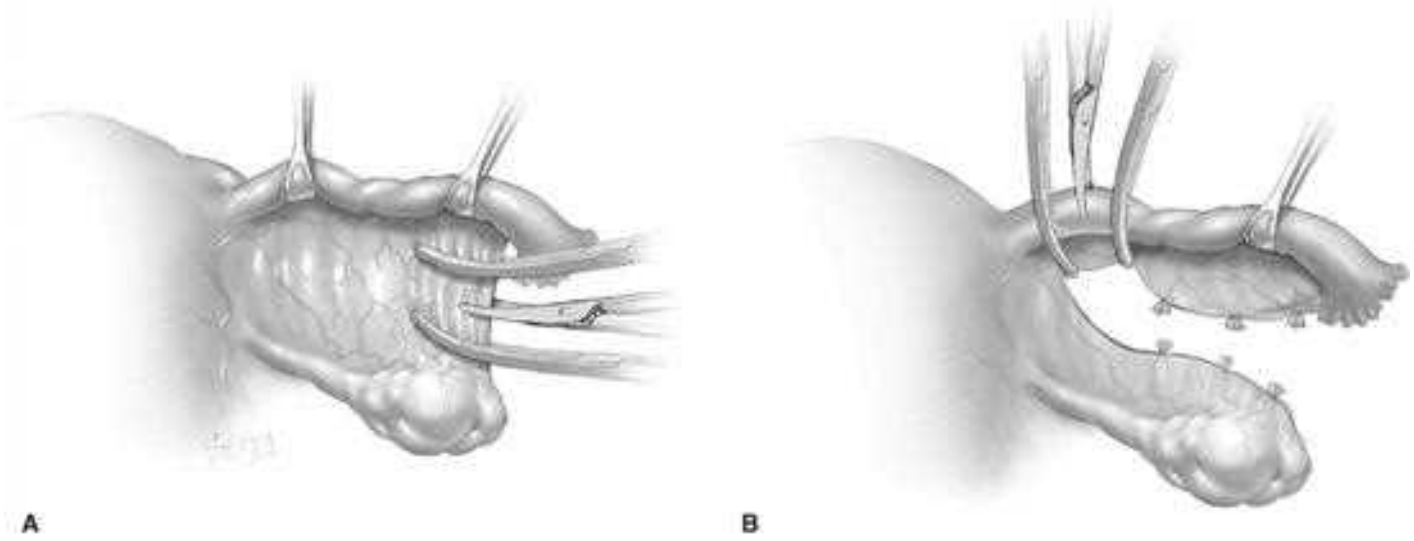
KD, et al: Williams Gynecology, 3rd ed. New York, McGraw-Hill Education, 2016.)



Steps of salpingectomy are shown in Figure 39-3. The umbilical incision generally will need to be larger to allow an adequate view of the tube and mesosalpinx and to place clamps. With total salpingectomy, the entire mesosalpinx must be divided to free the fallopian tube.In two small cohorts undergoing salpingectomy after vaginal birth, surgical times were longer than for tubal occlusion, and in one report, blood loss was increased (Danis, 2016; Powell, 2017). With salpingectomy and cesarean delivery, total blood loss rates were not statistically higher (Powell, 2017; Shinar, 2017).

FIGURE 39-3

A. With salpingectomy, the mesosalpinx is sequentially clamped, cut, and ligated. **B.** At the cornu, clamps are placed across the fallopian tube and its adjacent mesosalpinx prior to tubal transection. (Reproduced with permission from Stuart GS: Puerperal sterilization. In Yeomans ER, Hoffman BL, Gilstrap, III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill, 2017.)



After surgery, diet is given as tolerated. Ileus is infrequent and should prompt concern for bowel injury, albeit rare. Most women have an uncomplicated course and are discharged on the first postoperative day.

NONPUERPERAL TUBAL STERILIZATION

These techniques and other modifications basically consist of (1) ligation and resection at laparotomy as described earlier for puerperal sterilization; (2) application of permanent rings, clips, or inserts to the fallopian tubes by laparoscopy or hysteroscopy; or (3) electrocoagulation of a tubal segment, usually through a laparoscope. A detailed description and illustration of these can be found in *Williams Gynecology, 3rd edition* (Thompson, 2016).

In the United States, a laparoscopic approach to interval tubal sterilization is the most common. The procedure is frequently performed in an ambulatory surgical setting under general anesthesia. In almost all cases, the woman can be discharged within several hours. Minilaparotomy using a 3-cm suprapubic incision is also popular, especially in resource-poor countries. Major morbidity is rare with either minilaparotomy or laparoscopy. Although not often used, the peritoneal cavity can be entered through the posterior vaginal fornix via colpotomy to perform tubal interruption.

LONG-TERM COMPLICATIONS

Contraceptive Failure

Pregnancy following sterilization is infrequent. The Collaborative Review of Sterilization (CREST) study followed 10,863 women who had undergone tubal sterilization from 1978 through 1986 (Peterson, 1996). The cumulative failure rate for the various tubal procedures was 18.5 per 1000 or approximately 0.5 percent. The study found puerperal sterilization to be highly effective. The 5-year failure rate was 5 per 1000, and for 12 years, it was 7 per 1000.

Puerperal sterilization fails for two major reasons. First, surgical errors occur and include transection of the round ligament or only partial transection of the tube. For this reason, both tubal segments are submitted for pathological confirmation. Second, a fistulous tract or spontaneous reanastomosis may form between the severed tubal stumps.

Approximately 30 percent of pregnancies that follow a failed tubal sterilization procedure are ectopic. This rate is 20 percent for those following a postpartum procedure (Peterson, 1996, 1997). Thus, any symptoms of pregnancy in a woman after tubal sterilization must be investigated, and an ectopic pregnancy excluded.

Other Effects

Overall, risks for ovarian cancer decline and for breast cancer are unaffected following sterilization (Gaudet, 2013; Pearce, 2015). Women who have undergone tubal sterilization are highly unlikely to subsequently have salpingitis (Levgur, 2000). For menorrhagia and intermenstrual bleeding following tubal sterilization, most studies of the risk have found no association (DeStefano, 1985; Peterson, 2000; Shy, 1992).

Less objective but important psychological sequelae of sterilization have also been evaluated. In the CREST study, Costello (2002) found that tubal ligation did not change sexual interest or pleasure in 80 percent of women. In most of the 20 percent of women who did report a change, positive effects were 10 to 15 times more likely.

Invariably, a number of women express regrets regarding sterilization, and this is especially true if it is performed at a younger age (Curtis, 2006; Kelekçi, 2005). In the CREST study, Jamieson (2002) reported that 7 percent of women who had undergone tubal ligation had regrets by 5 years. This is not limited to their own sterilization, because 6.1 percent of women whose husbands had undergone vasectomy had similar regrets.

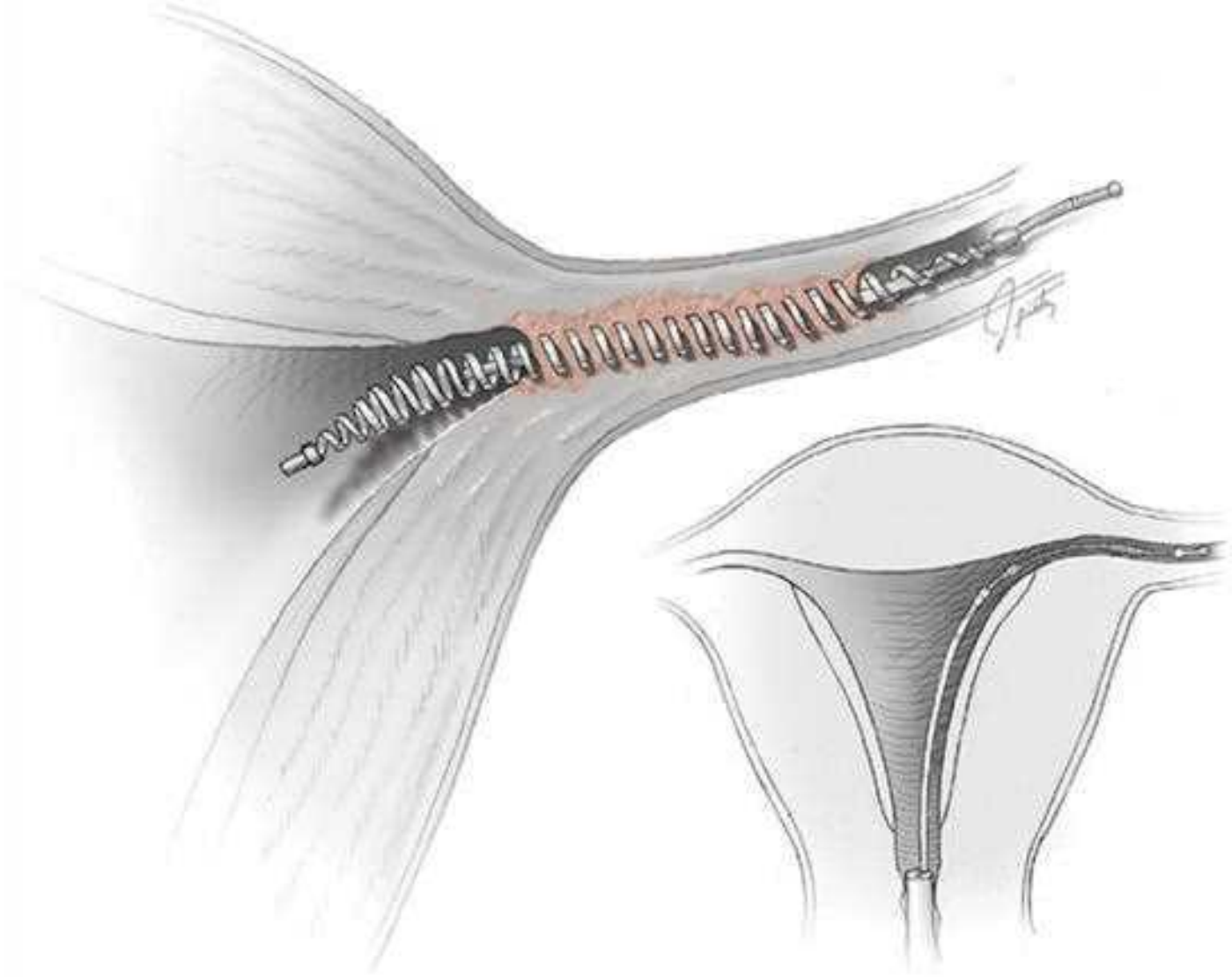
Tubal Sterilization Reversal

No woman should undergo tubal sterilization believing that subsequent fertility is guaranteed either by surgery or by assisted reproductive techniques. Both approaches are technically difficult, expensive, and not always successful. In general, pregnancy rates after tubal reversal favor women with age younger than 35 years, with 7 cm of remaining tube, with a short time from antecedent sterilization, and with isthmic–isthmic repairs. With reanastomosis via laparotomy, rates of live births range from 44 to 82 percent (Deffieux, 2011; Malacova, 2015). The rate of ectopic pregnancy is 2 to 10 percent after reanastomosis (American Society for Reproductive Medicine, 2015). With reanastomosis to reverse *Essure* sterilization, only 27 percent of women had subsequent live births (Monteith, 2014).

TRANSCERVICAL STERILIZATION

Devices can be inserted via hysteroscopy to occlude the proximal fallopian tubes. The *Essure* microinsert has a fine stainless-steel inner coil enclosed in polyester fibers and an expandable outer coil of Nitinol—a nickel and titanium alloy (Fig. 39-4). The outer coil expands after placement, allowing the inner fibers to expand. These synthetic fibers incite a chronic inflammatory response to prompt local tissue ingrowth that leads to complete tubal lumen occlusion. For hysteroscopic placement, sedation, paracervical block, or both may be used, and in-office insertion is often elected. Devices cannot be placed in all women, and some do not tolerate the procedure while awake (Duffy, 2005). Bilateral placement is achieved in 81 to 98 percent of cases on a first attempt (la Chapelle, 2015).

FIGURE 39-4
Essure microinsert placement hysteroscopically and ingrowth of tissue. (Reproduced with permission from Thompson M, Kho K: Minimally invasive surgery. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw-Hill, 2016.)



Since the introduction of *Essure*, cited adverse events include abnormal bleeding, perforation of the uterus or fallopian tubes from device migration, and allergy or hypersensitivity reactions, especially to the nickel component (Al-Safi, 2013; Mao, 2015). Some events resulted in device removal that requires abdominal surgery (Casey, 2016; Lazorwitz, 2017). To provide more information of the risks and benefits, the Food and Drug Administration (2016) has drafted a black box warning and patient-decision checklist to aid counseling.

Because complete tubal blockage is not 100 percent, it must be confirmed by hysterosalpingography (HSG) 3 months following surgery (Bayer Healthcare, 2002). With such confirmation, efficacy rates for these devices reach 98 to 99 percent (Chudnoff, 2015; Munro, 2014). In real-world settings, pregnancies following transcervical sterilization are most frequently attributed to conception before insertion or HSG and to noncompliance with HSG or its misinterpretation. Although data are limited to small case series, pregnancies conceived with *Essure* in place do not appear to be at increased risk from the device (Arora, 2014; Veersema, 2014).

Another insert, *Adiana,* also stimulates tissue ingrowth for tubal occlusion using a cylindrical, nonabsorbent silicone elastomer matrix. However, for financial reasons, production of this device has now been discontinued by the manufacturer (Hologic, 2012). That said, patients with these inserts may be encountered and can consider their device effective.

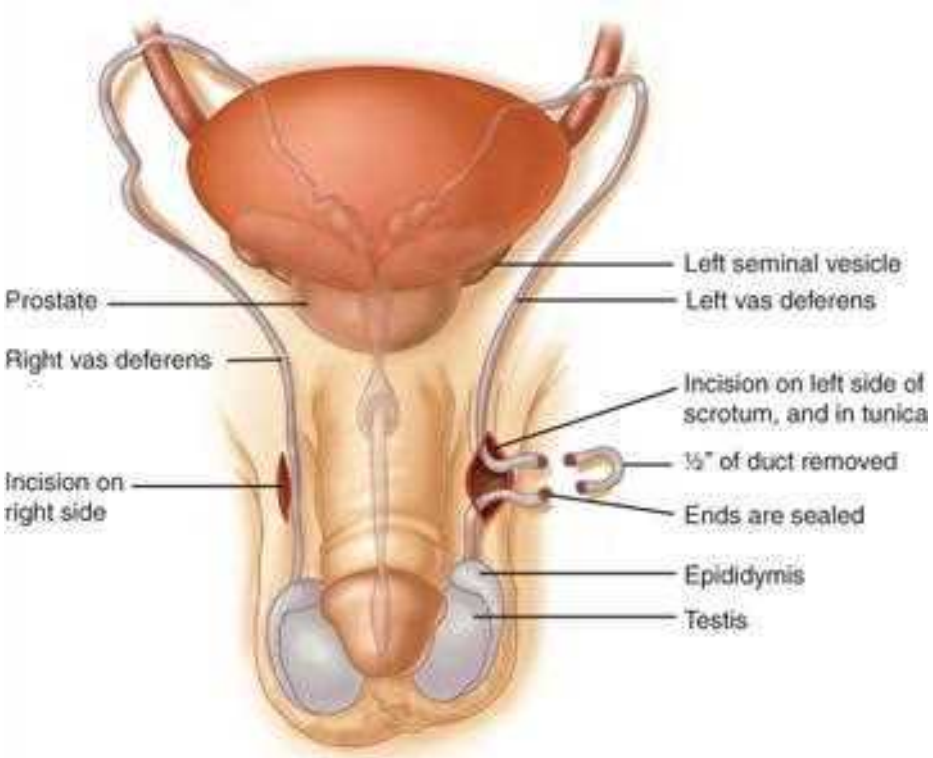
Although not currently available in the United States, *quinacrine pellets* cause sclerosis at the tubal ostia. Placement at the uterine fundus with an IUD-type inserter method allows pellet migration into the tubal ostia. Of drawbacks, prior cancer associations have been disproved (Sokal, 2010a,b). Efficacy appears enhanced by technique modification. In one early cohort of 1335 treated women, pregnancy rates at 10 years were 12 percent (Sokal, 2008). Following insertion technique improvement, a 2-year failure rate of 1.2 percent was calculated by Lippes (2015).

VASECTOMY

Currently, up to a half million men in the United States undergo vasectomy each year (Barone, 2006; Eisenberg, 2010). And 5 percent of women rely on this method for contraception (Daniels, 2015). For sterilization, the vas deferens lumen is disrupted to block the passage of sperm from the testes. Most commonly, a *no-scalpel vasectomy (NSV)* accomplishes this with one specialized instrument that grasps the vas deferens and surrounding skin together. A second dissector tool punctures the skin and then isolates the vas (Rogers, 2013). As clarified by the American Urological Association, *minimally invasive vasectomy* includes any vas isolation

procedure, including the no-scalpel technique, which uses a skin incision measuring ≤1 cm and requires minimal vas dissection (Fig. 39-5) (Sharlip, 2012). Compared with *conventional vasectomy* that employs incisions >1 cm and greater dissection, the no-scalpel technique is associated with fewer minor surgical complications, but each is equally effective (Cook, 2014).

FIGURE 39-5
Anatomy of male reproductive system showing procedure for vasectomy.



Vasectomy is safer than tubal sterilization because it is less invasive and is performed with local analgesia (American College of Obstetricians and Gynecologists, 2017a). In a review to compare the two, Hendrix and associates (1999) found that, compared with vasectomy, female tubal sterilization has a 20-fold increased complication rate, a 10- to 37-fold failure rate, and costs three times as much.

One disadvantage is that sterilization following vasectomy is not immediate. Complete release of sperm stored in the reproductive tract beyond the interrupted vas deferens takes approximately 3 months or 20 ejaculations. The American Urological Association recommends a postprocedural semen analysis at 8 to 16 weeks to document sterility (Sharlip, 2012). During the period before azoospermia is documented, another form of contraception should be used.

The failure rate for vasectomy during the first year is 9.4 per 1000 procedures and 11.4 per 1000 at 2, 3, and 5 years (Jamieson, 2004). Failures result from unprotected intercourse too soon after ligation, incomplete occlusion of the vas deferens, or recanalization (Awsare, 2005; Deneux-Tharaux, 2004).

Other than regrets, long-term consequences are rare. One is troublesome chronic scrotal pain, which develops in up to 15 percent of men (Leslie, 2007; Manikandan, 2004). Previous concerns for atherogenesis, immune-complex mediated disease, testicular cancer, and prostate cancer have been allayed by a number of investigators (Bernal-Delgado, 1998; Giovannucci, 1992; Goldacre, 1983; Møller, 1994).

Reanastomosis of the vas deferens can be completed most effectively using microsurgical techniques. In general, conception rates following reversal are adversely affected by longer duration from vasectomy, poor sperm quality found at reversal, and type of reversal procedure required (American Society for Reproductive Medicine, 2008).

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CHAPTER 40: Hypertensive Disorders

An eclamptic convulsion sometimes occurs without warning, "like a bolt from a clear sky", in women who are apparently in perfect health. In the majority of cases, however, the outbreak is preceded for a longer or shorter period by premonitory symptoms indicative of toxemia of pregnancy, among the more common being oedema, headache, epigastric pain, and possibly disturbances of vision.

—J. Whitridge Williams (1903)

INTRODUCTION

At the time of this textbook's first edition, it was accepted that "toxemia" preceded most cases of eclampsia. The central role of hypertension had not yet been discovered, and after many years, it became apparent that preeclampsia was a syndrome of which hypertension was only one important facet. Still, the mechanisms by which pregnancy incites or aggravates hypertension remain unsolved. Indeed, hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. These disorders complicate 5 to 10 percent of all pregnancies, and together they are one of the deadly triad—along with hemorrhage and infection—that contributes greatly to maternal morbidity and mortality rates. Of hypertensive disorders, the *preeclampsia syndrome*, either alone or superimposed on chronic hypertension, is the most dangerous. As subsequently discussed, new-onset hypertension during pregnancy—termed *gestational hypertension*—is followed by signs and symptoms of preeclampsia almost half the time, and preeclampsia is identified in 4 to 5 percent of all pregnancies (Martin, 2012).

The World Health Organization (WHO) systematically reviews maternal mortality worldwide, and in developed countries, 16 percent of maternal deaths were attributed to hypertensive disorders (Khan, 2006). In the United States from 2011 to 2013, 7.4 percent of 2009 pregnancy-related maternal deaths were caused by preeclampsia or eclampsia (Creanga, 2017). A similar rate was 10 percent in France from 2003 through 2007 (Saucedo, 2013). Importantly, more than half of these hypertension-related deaths were deemed preventable (Berg, 2005).

TERMINOLOGY AND DIAGNOSIS

To update and codify the terminology and classification of hypertensive disorders of pregnancy, a Task Force of the American College of Obstetricians and Gynecologists (2013) has provided evidence-based recommendations for clinical practice. The previous basic classification was retained and describes four types of hypertensive disease:

1. Preeclampsia and eclampsia syndrome
2. Chronic hypertension of any etiology
3. Preeclampsia superimposed on chronic hypertension
4. Gestational hypertension—definitive evidence for the preeclampsia syndrome does not develop and hypertension resolves by 12 weeks postpartum.

Importantly, this classification differentiates the preeclampsia syndrome from other hypertensive disorders because it is potentially more ominous.

Diagnosis of Hypertensive Disorders

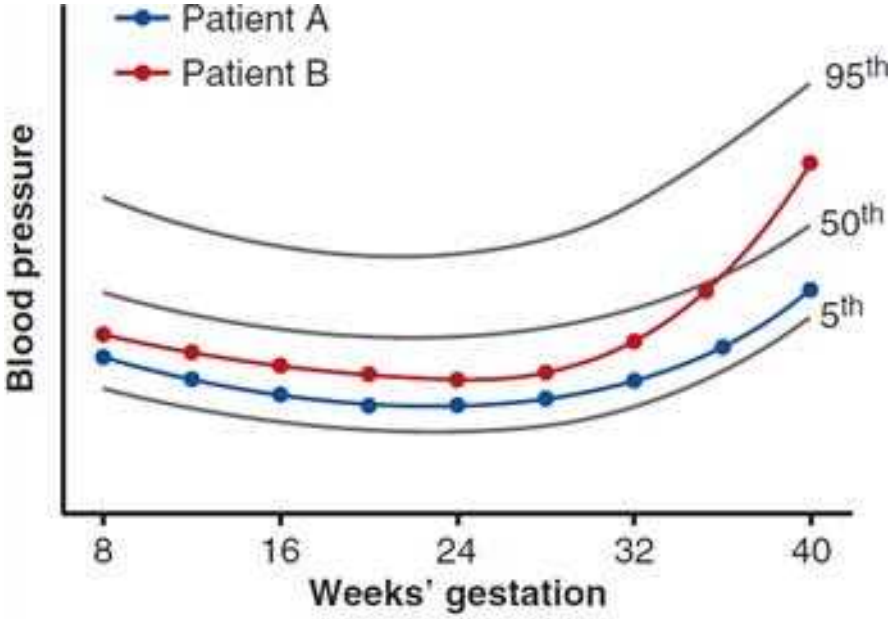
Hypertension is diagnosed empirically when appropriately taken blood pressure exceeds 140 mm Hg systolic or 90 mm Hg diastolic. Korotkoff phase V is used to define diastolic pressure. Previously, incremental increases of 30 mm Hg systolic or 15 mm Hg diastolic above blood pressure values taken at midpregnancy had also been used as diagnostic criteria, even when absolute values were <140/90 mm Hg. These incremental changes are no longer used to define hypertension, but it is recommended that such women be observed more closely because eclamptic seizures develop in some whose blood pressures have stayed below 140/90 mm Hg (Alexander, 2006). Also, a sudden rise in mean arterial pressure but still in a normal range—"delta hypertension"—may signify preeclampsia (Macdonald-Wallis, 2012; Zeeman, 2007).

Concept of "Delta Hypertension"

The systolic and diastolic blood pressure levels of 140/90 mm Hg have been arbitrarily used since the 1950s to define "hypertension" in nonpregnant individuals. However, these levels were selected by insurance companies to characterize a group of middle-aged men. It seems more realistic to define normal-range blood pressures that fall between an upper and lower limit for a particular population—such as young, healthy, pregnant women. A schematic example using arbitrary mean arterial blood pressure readings is shown in Figure 40-1. Data curves for both women show blood pressure measurements near the 25th percentile until 32 weeks. These begin to rise in patient B, who by term has substantively higher blood pressures. However, her pressures are still <140/90 mm Hg, and thus she is considered to be "normotensive." We use the term *delta hypertension* to describe this rather acute rise in blood pressure. Some of these women will go on to have obvious preeclampsia, and some even develop eclamptic seizures or HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome while still normotensive.

FIGURE 40-1

Schematic shows normal reference ranges for mean arterial blood pressure changes across pregnancy. Patient A (*blue*) has mean blood pressures near the 20th percentile throughout pregnancy. Patient B (*red*) has a similar pattern with mean pressures at the 25th percentile until approximately 36 weeks when her blood pressure begins to rise. By term, it is substantively higher and in the 75th percentile, but she is still considered "normotensive."



Gestational Hypertension

This diagnosis is made in women whose blood pressures reach 140/90 mm Hg or greater for the first time after midpregnancy, but in whom *proteinuria is not identified.* Almost half of these women subsequently develop preeclampsia syndrome. Even so, when blood pressure increases appreciably, it is dangerous to both mother and fetus to ignore this rise only because proteinuria has not yet developed. As Chesley (1985) emphasized, 10 percent of eclamptic seizures develop before overt proteinuria can be detected. Finally, gestational hypertension is reclassified by some as *transient hypertension* if evidence for preeclampsia does not develop and the blood pressure returns to normal by 12 weeks postpartum.

Preeclampsia Syndrome

Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually every organ system. In addition, it heralds a higher incidence of cardiovascular disease later in life (Long-Term Consequences). Although preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important diagnostic criterion. Thus, proteinuria is an *objective* marker and reflects the system-wide endothelial leak that characterizes the preeclampsia syndrome.

In some women with the preeclampsia syndrome, neither overt proteinuria nor fetal-growth restriction are features (Sibai, 2009). Because of this, the Task Force (2013) suggests other diagnostic criteria, which are shown in Table 40-1. Evidence of multiorgan involvement may include thrombocytopenia, renal dysfunction, hepatocellular necrosis, central nervous system perturbations, or pulmonary edema.

TABLE 40-1

Classification and Diagnosis of Pregnancy-Associated Hypertension

Condition	Criteria Required
Gestational hypertension	BP >140/90 mm Hg after 20 weeks in previously normotensive women
Preeclampsia: Hypertension plus	
Proteinuria	• ≥300 mg/24 h, or • Urine protein: creatinine ratio ≥0.3, or • Dipstick 1+ persistent[a]
or	
Thrombocytopenia	• Platelet count <100,000/**μL**
Renal insufficiency	• Creatinine level >1.1 mg/dL or doubling of baseline[b]
Liver involvement Cerebral symptoms	• Serum transaminase levels[c] twice normal • Headache, visual disturbances, convulsions
Pulmonary edema	—

[a]Recommended only if sole available test.

[b]No prior renal disease.

[c]AST (aspartate transaminase) or ALT (alanine transaminase).

BP = blood pressure.

Modified with permission from American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy: Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy, Obstet Gynecol. 2013 Nov;122(5):1122–31

Indicators of Preeclampsia Severity

The markers listed in Table 40-1 are also used to classify preeclampsia syndrome severity. Although many use a dichotomous "mild" and "severe" classification, the Task Force (2013) discourages the use of "mild preeclampsia." It is problematic that there are criteria for the diagnosis of "severe" preeclampsia, but the default classification is either implied or specifically termed as "mild," "less severe," or "nonsevere" (Alexander, 2003; Lindheimer, 2008b). There are no generally agreed-on criteria for "moderate" preeclampsia—an elusive third category. We use the criteria listed in Table 40-2, which are categorized as "severe" versus "nonsevere."

TABLE 40-2

Indicators of Severity of Gestational Hypertensive Disorders[a]

Abnormality	Nonsevere[b]	Severe
Diastolic BP	<110 mm Hg	≥110 mm Hg
Systolic BP	<160 mm Hg	≥160 mm Hg
Proteinuria[c]	None to positive	None to positive
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia (<100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked
Fetal-growth restriction	Absent	Present
Pulmonary edema	Absent	Present
Gestational age	Late	Early

[a]Compare with criteria in Table 40-1.

[b]Includes "mild" and "moderate" hypertension not specifically defined.

[c]Most disregard degrees of proteinuria to classify nonsevere or severe.

BP = blood pressure.

Some symptoms are considered ominous. *Headaches* or *visual disturbances* such as scotomata can precede *eclampsia*, which is a convulsion not attributable to another cause. The seizures are generalized and may appear before, during, or after labor. The proportion that develops seizures later, after 48 hours postpartum, approximates 10 percent (Sibai, 2005; Zwart, 2008). Another symptom, *epigastric or right upper quadrant pain*, frequently accompanies hepatocellular necrosis, ischemia, and edema that ostensibly stretches Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels. Finally, *thrombocytopenia* also signifies worsening preeclampsia. It represents platelet activation and aggregation as well as microangiopathic hemolysis. Other factors indicative of severe preeclampsia include renal or cardiac involvement, obvious fetal-growth restriction, and early-onset disease.

The more profound these signs and symptoms, the less likely it is that they can be temporized, and the more likely that delivery will be required. *A caveat is that differentiation between nonsevere and severe gestational hypertension or preeclampsia can be misleading because what might be apparently mild disease may progress rapidly to severe disease.*

Preeclampsia Superimposed on Chronic Hypertension

Regardless of its cause, any chronic hypertensive disorder predisposes a woman to develop superimposed preeclampsia syndrome. Chronic underlying hypertension is diagnosed in women with documented blood pressures >140/90 mm Hg before pregnancy or before 20 weeks' gestation, or both. Hypertensive disorders can create difficult problems with diagnosis and management in women who are not first seen until after midpregnancy. This is because blood pressure normally drops during the second and early third trimesters in both normotensive and chronically hypertensive women (see Fig. 40-1). Thus, a woman with previously undiagnosed chronic vascular disease who is seen before 20 weeks frequently has blood pressures within normal range. During the third trimester, however, as blood pressures return to their originally hypertensive levels, it may be difficult to determine whether hypertension is chronic or induced by pregnancy. Even a careful search for evidence of preexisting end-organ damage may be futile, as many of these women have mild disease and no evidence of ventricular hypertrophy, retinal vascular changes, or renal dysfunction.

In some with chronic hypertension, blood pressure rises to obviously abnormal levels, typically after 24 weeks' gestation. If new-onset or worsening baseline hypertension is accompanied by new-onset proteinuria or other findings listed in Table 40-1, then superimposed preeclampsia is diagnosed. Compared with "pure" preeclampsia, superimposed preeclampsia commonly develops earlier in pregnancy. It also tends to be more severe and more often is accompanied by fetal-growth restriction. The same criteria shown in Table 40-2 are also used to further characterize severity of superimposed preeclampsia.

INCIDENCE AND RISK FACTORS

Young and nulliparous women are particularly vulnerable to developing preeclampsia, whereas older women are at greater risk for chronic hypertension with superimposed preeclampsia. The incidence is markedly influenced by race and ethnicity—and thus by genetic predisposition. In one study by the Maternal-Fetal Medicine Units (MFMU) Network, the incidence of preeclampsia was 5 percent in white, 9 percent in Hispanic, and 11 percent in African-American women (Myatt, 2012a,b). In addition, black women have greater morbidity (Shahul, 2015). In several worldwide studies reviewed by Staff and coworkers (2015), the incidence of preeclampsia in nulliparous populations ranged from 3 to 10 percent. The incidence of preeclampsia in multiparas also varies and ranges from 1.4 to 4 percent (Fisher, 2015).

Bartsch and associates (2016) extracted data from more than 25 million pregnancies and calculated relative risks for several clinical factors shown in Table 40-3. Others include the metabolic syndrome and hyperhomocysteinemia (Karumanchi, 2016a; Masoudian, 2016; Scholten, 2013). Pregnancies with a male fetus are also at slightly higher risk (Jaskolka, 2017). Although smoking during pregnancy causes various adverse pregnancy outcomes, ironically, it carries a *reduced risk* for hypertension during pregnancy (Bainbridge, 2005; Kraus, 2014). Other factors are human immunodeficiency virus (HIV) seropositivity and sleep-disordered breathing (Facco, 2017; Sansone, 2016).

TABLE 40-3

Selected Clinical Risk Factors for Preeclampsia

Risk Factor	Pregnancies (millions)	Pooled Unadjusted Relative Risk (95% CI)
SLE	2.43	2.5 (1.0–6.3)
Nulliparity	2.98	2.1 (1.9–2.4)
Age >35	5.24	1.2 (1.1–1.3)
Prior stillbirth	0.063	2.4 (1.7–3.4)
CKD	0.97	1.8 (1.5–2.1)
ART	1.46	1.8 (1.6–2.1)
BMI >30	5.92	2.8 (2.6–3.1)
Multifetal	7.31	2.9 (2.6–3.1)
Prior abruption	0.29	2.0 (1.4–2.7)
Diabetes	2.55	3.7 (3.1–4.3)
Prior preeclampsia	3.72	8.4 (7.1–9.9)
CHTN	6.59	5.1 (4.0–6.5)
APA	0.22	2.8 (1.8–4.3)

APA = antiphospholipid antibody; ART = assisted reproductive technology; BMI = body mass index; CHTN = chronic hypertension; CKD = chronic kidney disease; SLE = systemic lupus erythematosus.

Data from Bartsch, 2016.

For eclampsia, the incidence has declined in areas where health care is more readily available. In the United States in 1998, it affected 1 in 3250 births (Ventura, 2000). Except for Iceland, which has an extremely low rate, in countries with adequate resources the incidence averages 1 in 2000 to 3000 deliveries (Andersgaard, 2006; Jaatinen, 2016; O'Connor, 2013; Royal College of Obstetricians and Gynaecologists, 2006; Zwart, 2008).

ETIOPATHOGENESIS

Any satisfactory theory concerning the origins of preeclampsia must account for the observation that gestational hypertensive disorders are more likely to develop in women with the following characteristics:

Are exposed to chorionic villi for the first time

Are exposed to a superabundance of chorionic villi, as with twins or hydatidiform mole

Have preexisting conditions associated with endothelial cell activation or inflammation, such as diabetes, obesity, cardiovascular or renal disease, immunological disorders, or hereditary influences

Are genetically predisposed to hypertension developing during pregnancy.

A fetus is not a requisite for preeclampsia to develop. And, although chorionic villi are essential, they need not be intrauterine. For example, preeclampsia can develop with an abdominal pregnancy (Worley, 2008). *Regardless of precipitating etiology, the cascade of events leading to the preeclampsia syndrome is characterized by abnormalities that result in systemic vascular endothelial damage with resultant vasospasm, transudation of plasma, and ischemic and thrombotic sequelae.*

Phenotypic Expression of Preeclampsia Syndrome

The preeclampsia syndrome varies widely in its clinical phenotypic expression. But, at least two major subtypes are differentiated by whether or not remodeling of uterine spiral arterioles by endovascular trophoblasts is defective. This concept has given rise to the “two-stage disorder” theory of preeclampsia pathogenesis. According to Redman and coworkers (2015a), stage 1 is caused by faulty endovascular trophoblastic remodeling that downstream causes the stage 2 clinical syndrome. Importantly, stage 2 can be modified by preexisting maternal conditions that are also manifest by endothelial cell activation or inflammation and are listed in the third prior bullet.

Such staging is artificial, and it seems logical that preeclampsia syndrome presents clinically as a spectrum of worsening disease. Moreover, evidence is accruing that many “isoforms” exist as discussed subsequently. Examples include differences in maternal and fetal characteristics, placental findings, and early- versus late-onset disease (Phillips, 2010; Valensise, 2008; van der Merwe, 2010).

Etiology

An imposing number of mechanisms have been proposed to explain the cause of preeclampsia. Those currently considered important include:

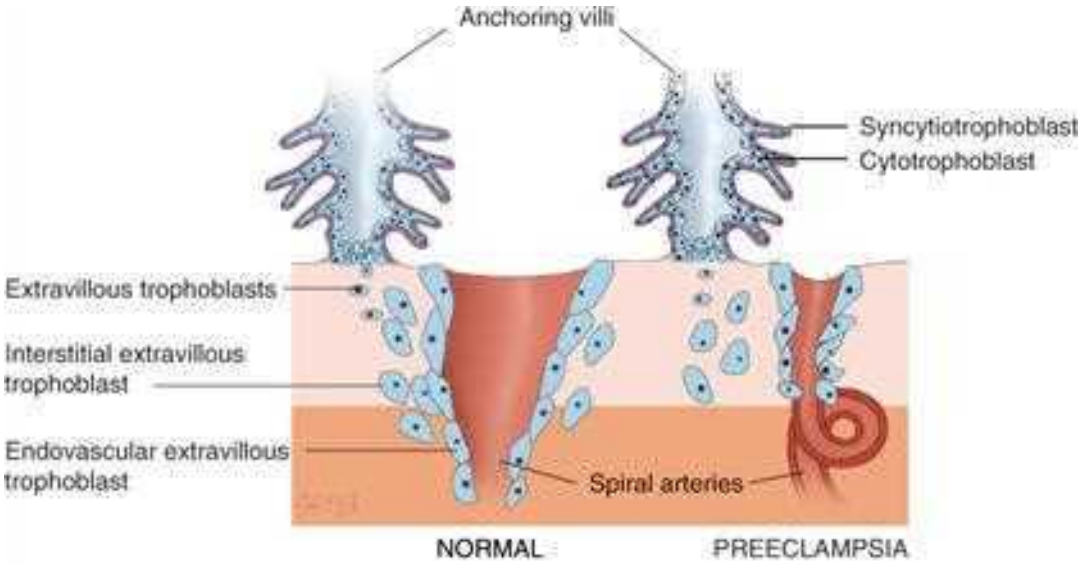
1. Placental implantation with abnormal trophoblastic invasion of uterine vessels
2. Immunological maladaptive tolerance between maternal, paternal (placental), and fetal tissues
3. Maternal maladaptation to cardiovascular or inflammatory changes of normal pregnancy
4. Genetic factors including inherited predisposing genes and epigenetic influences.

Abnormal Trophoblastic Invasion

Discussed in Chapter 5 (Blastocyst), normal implantation is characterized by extensive remodeling of the spiral arterioles within the decidua basalis (Fig. 40-2). Endovascular trophoblasts replace the vascular endothelial and muscular linings to enlarge the vessel diameter (Zhou, 1997). The veins are invaded only superficially.

FIGURE 40-2

Schematic representation of normal placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall to create a dilated low-resistance vessel. With preeclampsia, defective implantation is characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts. This results in a small-caliber vessel with high resistance to flow.



In some cases of preeclampsia, however, trophoblastic invasion may be incomplete. With this, decidual vessels, but not myometrial vessels, become lined with endovascular trophoblasts. The deeper myometrial arterioles thus do not lose their endothelial lining and musculoelastic tissue, and their mean external diameter is only half that of corresponding vessels in normal placentas (Fisher, 2015). In general, the magnitude of defective trophoblastic invasion correlates with the severity of the hypertensive disorder (Madazli, 2000). And importantly, it is more prevalent in women with early-onset preeclampsia (Khodzhaeva, 2016). McMahon and associates (2014) found that lower levels of soluble antiangiogenic growth factors may be involved in this faulty endovascular remodeling.

From placental electron microscopy studies, early preeclamptic changes include endothelial damage, insudation of plasma constituents into vessel walls, proliferation of myointimal cells, and medial necrosis (De Wolf, 1980). Hertig (1945) referred to lipid accumulation in myointimal cells and macrophages as *atherosis*. These findings are more common in placentas from women diagnosed with preeclampsia before 34 weeks (Nelson, 2014b). Acute placental vascular atherosis may also identify a group of women at greater risk for later atherosclerosis and cardiovascular disease (Staff, 2015). In pregnancy, the abnormally narrow lumen of spiral arterioles likely impairs placental blood flow. Diminished perfusion and a hypoxic environment eventually lead to release of *placental debris* or *microparticles.*

At this point, these changes incite a systemic inflammatory response, which is stage 2 of the preeclampsia syndrome (Lee, 2012; Redman, 2012). Defective placentation is posited to further cause the susceptible woman to develop gestational hypertension, the preeclampsia syndrome, preterm delivery, a growth-restricted fetus, and/or placental abruption (Brosens, 2011; Labarrere, 2017; Nelson, 2014b).

Immunological Factors

Maternal immune tolerance to paternally derived placental and fetal antigens is discussed in Chapter 5 (Fetal–Maternal Interface). Loss of this tolerance is another cited theory for preeclampsia (Erlebacher, 2013). Certainly, the histological changes at the maternal-placental interface are suggestive of acute graft rejection.

Inferential data also suggest that preeclampsia is an immune-mediated disorder. For example, the risk of preeclampsia is appreciably enhanced in circumstances in which formation of blocking antibodies to placental antigenic sites *might* be impaired. In this scenario, the first pregnancy would carry a higher risk. Tolerance dysregulation might also explain an elevated risk when the paternal antigenic load is increased, that is, with two sets of paternal chromosomes—a "double dose." Namely, women with molar pregnancies have a high incidence of early-onset preeclampsia. Women with a trisomy 13 fetus also have a 30- to 40-percent incidence of preeclampsia. These women have elevated serum levels of antiangiogenic factors. The gene for one of these factors, *soluble fms-like tyrosine kinase 1*, is on chromosome 13 (Bdolah, 2006). Conversely, women previously exposed to paternal antigens, such as a prior pregnancy with the *same* partner, are "immunized" against preeclampsia. This phenomenon is not as apparent in women with a prior abortion (Strickland, 1986). Multiparas impregnated by a new consort have a greater risk of preeclampsia (Mostello, 2002).

Redman and colleagues (2015a) reviewed the possible role of *immune maladaptation* in preeclampsia pathophysiology. In women destined to be preeclamptic, extravillous trophoblasts early in pregnancy express reduced amounts of immunosuppressive nonclassic human leukocyte antigen G (HLA G). Black women more commonly have the 1597ΔC gene allele that further predisposes to preeclampsia (Loisel, 2013). These changes may contribute to the defective placental vascularization in stage 1 of the preeclampsia syndrome. As discussed in Chapter 4 (Leukocytes and Lymphocytes), T-helper (Th) lymphocytes during normal pregnancy are produced so that type 2 activity is increased in relation to type 1—so-called *type 2 bias* (Redman, 2012, 2015a). Th2 cells promote humoral immunity, whereas Th1 cells stimulate inflammatory cytokine secretion. Beginning in the early second trimester in women who develop preeclampsia, Th1 action is increased.

Endothelial Cell Activation

Inflammatory changes are believed to be a continuation of stage 1 alterations. In response to ischemia or other inciting causes, placental factors are released and begin a cascade of events (Davidge, 2015). Thus, antiangiogenic and metabolic factors and other inflammatory leukocyte mediators are thought to provoke systemic endothelial cell injury, which is used synonymously here with *endothelial cell activation* or *dysfunction*.

Endothelial cell dysfunction may result from an extreme activated state of leukocytes in the maternal circulation (Faas, 2000; Gervasi, 2001). Briefly, cytokines such as tumor necrosis factor-α (TNF-α) and the interleukins may contribute to the systemic oxidative stress associated with preeclampsia. This is characterized by reactive oxygen species and free radicals that lead to formation of self-propagating lipid peroxides (Manten, 2005). These peroxides in turn generate highly toxic

radicals that injure systemic vascular endothelial cells, modify nitric oxide production by these cells, and interfere with prostaglandin balance. Other consequences of oxidative stress include production of the lipid-laden macrophage foam cells seen in placental atherosis, activation of systemic microvascular coagulation manifested by thrombocytopenia, and greater systemic capillary permeability reflected by edema and proteinuria.

Genetic Factors

Preeclampsia appears to be a multifactorial, polygenic disorder. In one study of almost 1.2 million Swedish births, a genetic association for gestational hypertension and for preeclampsia was found (Nilsson, 2004). Ward and Taylor (2015) cite an incident risk for preeclampsia of 20 to 40 percent for daughters of preeclamptic mothers; 11 to 37 percent for sisters of preeclamptic women; and 22 to 47 percent for twins. Ethnoracial factors are important, as evidenced by the high incidence of preeclampsia in African-American women. It may be that Latina women have a lower incidence because of interactions of American Indian and white race genes (Shahabi, 2013).

The hereditary predisposition for preeclampsia likely stems from interactions of literally hundreds of inherited genes—both maternal and paternal—that control myriad enzymatic and metabolic functions throughout every organ system (Triche, 2014). Plasma-derived factors may induce some of these genes in preeclampsia (Mackenzie, 2012). Thus, the clinical manifestation in any given woman with the preeclampsia syndrome will occupy a spectrum. In this regard, phenotypic expression will differ among similar genotypes depending on interactions with environmental components (Yang, 2013).

Hundreds of genes have been studied for their possible association with preeclampsia (Buurma, 2013; Sakowicz, 2016; Ward, 2015). Several that may have a significant association with the syndrome are listed in Table 40-4. However, because of the complex phenotypic expression of preeclampsia, it is doubtful that any *one* candidate gene will be found responsible. Indeed, Majander and associates (2013) have linked preeclampsia predisposition to even *fetal* genes on chromosome 18.

TABLE 40-4

Genes with Possible Associations with Preeclampsia Syndrome

Gene (Polymorphism)	Function Affected
MTHFR (C677T)	Methylene tetrahydrofolate reductase
F5 (Leiden)	Factor V_{Leiden}
AGT (M235T)	Angiotensinogen
HLA (Various)	Human leukocyte antigens
NOS3 (Glu 298 Asp)	Endothelial nitric oxide
F2 (G20210A)	Prothrombin (factor II)
ACE (I/D^{at}Intron 16)	Angiotensin-converting enzyme
CTLA4	Cytotoxic T-lymphocyte-associated protein
LPL	Lipoprotein lipase
SERPINE1	Serine peptidase inhibitor
GNA promoter	Decreased methylation

Data from Buurma, 2013; Staines-Urias, 2012; Triche, 2014; Ward, 2014; Ye, 2016.

Pathogenesis

Vasospasm

The concept of vasospasm with preeclampsia has been advanced for a century (Volhard, 1918). Systemic endothelial activation causes vasospasm that elevates resistance to produce subsequent hypertension. Concurrently, systemic endothelial cell injury promotes interstitial leakage, and blood constituents, including platelets and fibrinogen, are deposited subendothelially. Endothelial junctional proteins are also disrupted, and the subendothelial region of resistance arteries undergoes ultrastructural change (Suzuki, 2003; Wang, 2002). The much larger venous circuit is similarly involved.

With diminished blood flow because of maldistribution from vasospasm and interstitial leakage, ischemia of the surrounding tissues can lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. One important clinical correlate to this is the markedly attenuated blood volume seen in women with severe preeclampsia (Zeeman, 2009).

Endothelial Cell Injury

Injury to systemic endothelial cells is now a centerpiece of preeclampsia pathogenesis (Davidge, 2015). In this scheme, protein factor(s)—likely placental—are secreted into the maternal circulation and provoke activation and dysfunction of the systemic vascular endothelium. Many facets of the clinical syndrome of preeclampsia are thought to result from these widespread endothelial cell changes.

Intact endothelium has anticoagulant properties. Also, systemic endothelial cells, by releasing nitric oxide, blunt the response of vascular smooth muscle to agonists. Injured or activated endothelial cells may produce less nitric oxide and may secrete substances that promote coagulation and greater sensitivity to vasopressors. Further evidence of endothelial activation includes the characteristic changes in glomerular capillary endothelial morphology, greater capillary permeability, and elevated blood concentrations of substances associated with endothelial activation. Likely, multiple factors in the plasma of preeclamptic women combine to exert these vasoactive effects (Myers, 2007; Walsh, 2009).

Increased Pressor Responses

As discussed in Chapter 4 (Renin, Angiotensin II, and Plasma Volume), pregnant women normally develop refractoriness to infused vasopressors (Abdul-Karim, 1961). Women with early preeclampsia, however, have enhanced vascular reactivity to infused norepinephrine and angiotensin II (Raab, 1956; Talledo, 1968). Moreover, increased sensitivity to angiotensin II clearly precedes the onset of gestational hypertension (Gant, 1974). Paradoxically, women who develop preterm preeclampsia have lower circulating levels of angiotensin II (Chase, 2017).

Several prostaglandins are thought to be central to preeclampsia syndrome pathophysiology. Specifically, the blunted pressor response seen in normal pregnancy is at least partially due to diminished vascular responsiveness mediated by endothelial prostaglandin synthesis. For example, compared with normal pregnancy, endothelial prostacyclin (PGI_2) production is lower in preeclampsia. This action appears to be mediated by phospholipase A_2 (Davidge, 2015). At the same time, thromboxane A_2 secretion by platelets is increased, and the prostacyclin:thromboxane A_2 ratio declines. The net result favors greater sensitivity to infused angiotensin II and, ultimately, vasoconstriction (Spitz, 1988). These changes are apparent as early as 22 weeks' gestation in gravidas who later develop preeclampsia (Chavarria, 2003).

Nitric oxide is a potent vasodilator synthesized from L-arginine by endothelial cells. Inhibition of nitric oxide synthesis raises mean arterial pressure, lowers heart rate, and reverses the pregnancy-induced refractoriness to vasopressors. In humans, nitric oxide likely is the compound that maintains the normal low-pressure vasodilated state characteristic of fetoplacental perfusion (Myatt, 1992; Weiner, 1992). The effects of nitric oxide production in preeclampsia are unclear. It appears that the syndrome is associated with decreased endothelial nitric oxide synthase expression, thus resulting in lower nitric oxide activity (Davidge, 2015).

Endothelins are 21-amino-acid peptides and potent vasoconstrictors. Endothelin-1 (ET-1) is the primary isoform produced by human endothelium (Karumanchi, 2016b). Plasma ET-1 levels are elevated in normotensive pregnant women, but women with preeclampsia have even higher levels (Ajne, 2003). According to Taylor and Roberts (1999), the placenta is not the source of increased ET-1 concentrations, and they likely arise from systemic endothelial activation. Interestingly, treatment of preeclamptic women with magnesium sulfate lowers ET-1 concentrations (Sagsoz, 2003). And, in animal studies, sildenafil reduces ET-1 concentrations (Gillis, 2016).

Angiogenic and Antiangiogenic Proteins

Placental vasculogenesis is evident by 21 days after conception. The list of pro- and antiangiogenic substances involved in placental vascular development is extensive, and the families of vascular endothelial growth factor (VEGF) and angiopoietin are the most studied. *Angiogenic imbalance* describes excessive amounts of antiangiogenic factors, which are thought to be stimulated by worsening hypoxia at the uteroplacental interface. Trophoblast of women destined to develop preeclampsia overproduces at least two antiangiogenic peptides that enter the maternal circulation (Karumanchi, 2016a).

First, *soluble fms-like tyrosine kinase 1 (sFlt-1)* is a receptor for VEGF. As depicted in Figure 40-3, elevated maternal sFlt-1 levels inactivate and reduce circulating free placental growth factor (PlGF) and VEGF concentrations, leading to endothelial dysfunction (Maynard, 2003). Importantly, sFlt-1 levels begin to rise in maternal serum months before preeclampsia is evident (Fig. 40-4). These high levels in the second trimester are associated with a doubling of the risk for preeclampsia (Haggerty, 2012). This divergence from normal levels appears to develop even sooner with early-onset preeclampsia (Vatten, 2012). These factors are also operative in pregnancies complicated by fetal-growth restriction (Herraiz, 2012).

FIGURE 40-3

Schematic of the receptor blocking action of sFlt-1 (soluble fms-like tyrosine kinase 1) and soluble endoglin (sEng).

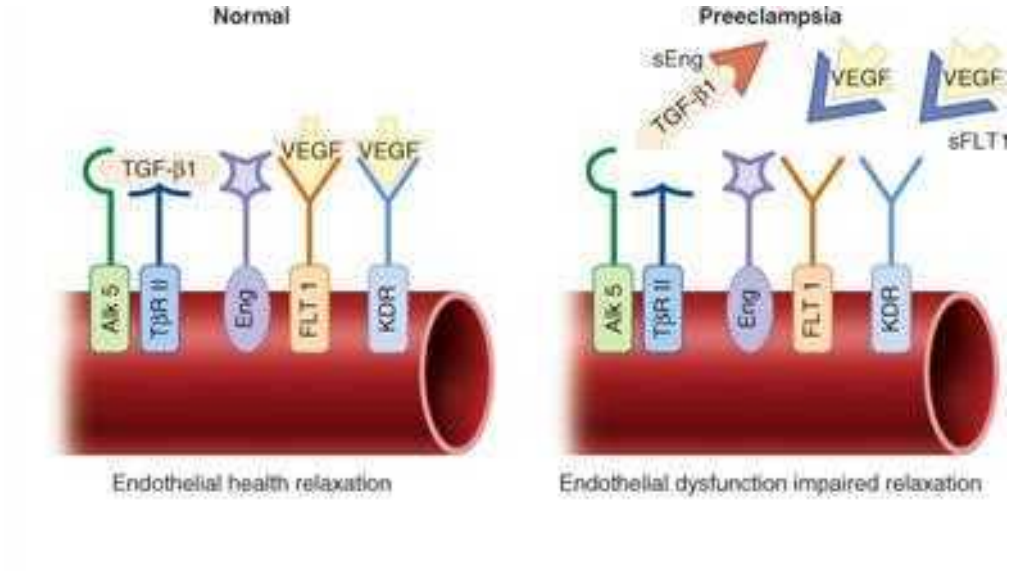
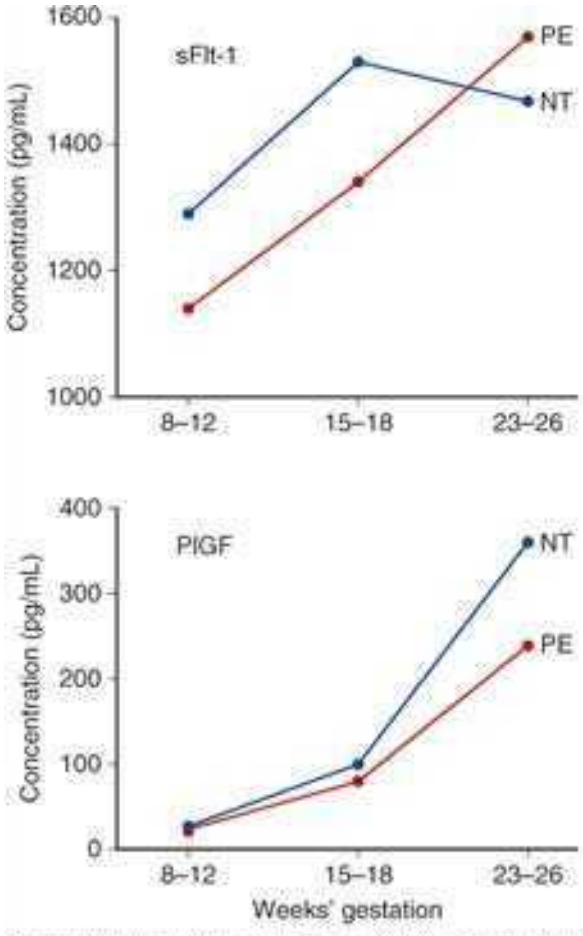


FIGURE 40-4

Angiogenic and antiangiogenic factors in normotensive (NT) and preeclamptic (PE) women across pregnancy. Both pairs of factors are significantly divergent by 23 to 26 weeks' gestation. sFlt = soluble fms-like tyrosine kinase 1; PlGF = placental growth factor. (Data from Myatt, 2013.)



A second antiangiogenic peptide, soluble endoglin (sEng), inhibits various transforming growth factor beta (TGF-β) isoforms from binding to endothelial receptors (see Fig. 40-3). Endoglin is one of these receptors. Decreased binding to endoglin diminishes endothelial nitric oxide-dependent vasodilatation. Serum levels of sEng also begin to rise months before clinical preeclampsia develops (Haggerty, 2012). Interestingly, metformin reduces antiangiogenic secretion from human tissues (Brownfoot, 2016).

In one systematic review, third-trimester elevation of sFlt-1 levels and lower PlGF concentrations correlate with preeclampsia development after 25 weeks' gestation (Widmer, 2007). Subsequently, Haggerty and coworkers (2012) reported that doubling of expressions of sFlt-1 and sEng increased the preeclampsia risk by 39 and 74

percent, respectively. The cause of placental overproduction of antiangiogenic proteins remains an enigma. There is a racial-ethnic difference in their secretion (Yang, 2016). Concentrations of the soluble forms are not higher in fetal circulation or amnionic fluid of preeclamptic women, and their levels in maternal blood dissipate after delivery (Staff, 2007).

Clinical research aims to employ antiangiogenic proteins in the prediction and diagnosis of preeclampsia. One preliminary report described therapeutic apheresis to reduce sFlt-1 levels (Thadhani, 2016).

PATHOPHYSIOLOGY

Evidence for preeclampsia manifestation begins early in pregnancy with covert pathophysiological changes that gain momentum across gestation and eventually become clinically apparent. Unless delivery supervenes, these changes ultimately lead to multiorgan involvement with a clinical spectrum ranging from meager findings to one of cataclysmic deterioration. As discussed, these are thought to be a consequence of endothelial dysfunction, vasospasm, and ischemia. Although the many maternal consequences of the preeclampsia syndrome are usually described in terms of individual organ systems, they frequently are multiple and overlap.

Cardiovascular System

Cardiovascular disturbances are common with preeclampsia syndrome. These are related to: (1) greater cardiac afterload caused by hypertension; (2) cardiac preload, which is reduced by a pathologically diminished volume expansion during pregnancy and which is increased by intravenous crystalloid or oncotic solutions; and (3) endothelial activation leading to interendothelial extravasation of intravascular fluid into the extracellular space and, importantly, into the lungs.

Hemodynamic Changes and Cardiac Function

The cardiovascular aberrations of pregnancy-related hypertensive disorders vary depending on several modifiers. These factors include preeclampsia severity, hypertension severity, presence of underlying chronic disease, and the part of the clinical spectrum in which these are studied. In some women, these cardiovascular changes may precede hypertension (De Paco, 2008; Easterling, 1990; Khalil, 2012; Melchiorre, 2013). Nevertheless, with the clinical onset of preeclampsia, cardiac output declines, due at least in part to greater peripheral resistance. When assessing cardiac function in preeclampsia, consideration is given to echocardiographic measures of *myocardial function* and to clinically relevant *ventricular function*.

Myocardial Function

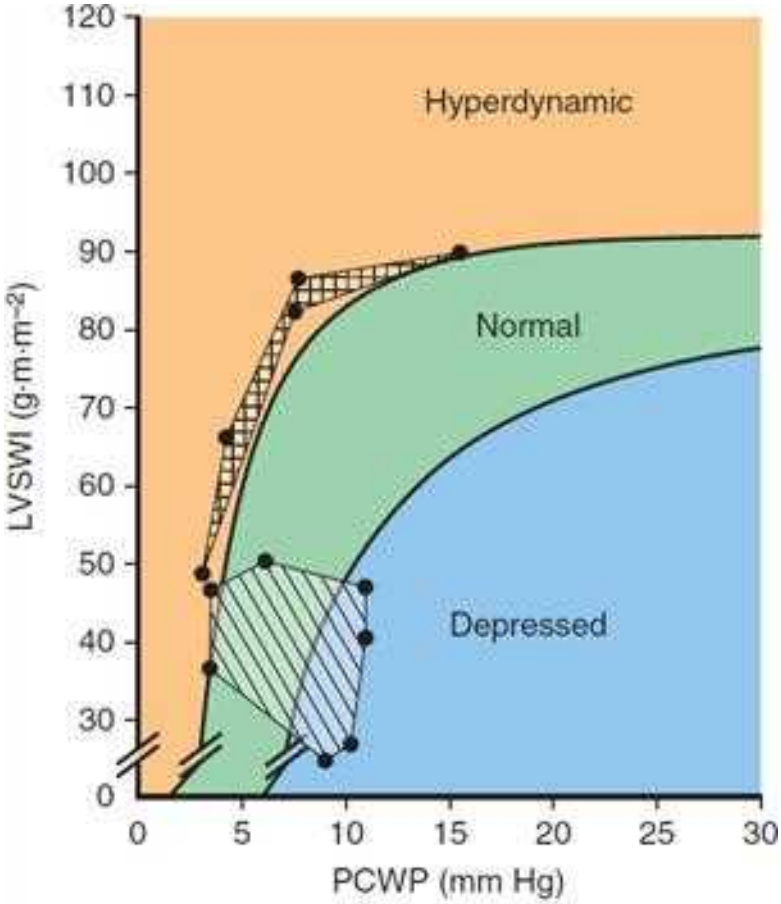
Of women with preeclampsia, serial echocardiographic studies document diastolic dysfunction in 40 to 45 percent (Guirguis, 2015; Melchiorre, 2012). With this dysfunction, ventricles do not properly relax and cannot fill properly. In some of these women, functional differences persist up to 4 years after delivery (Evans, 2011; Orabona, 2017). Diastolic dysfunction stems from ventricular remodeling, which is judged to be an adaptive response to maintain normal contractility despite the increased afterload of preeclampsia. High levels of antiangiogenic proteins may be contributory (Shahul, 2016). In the otherwise healthy pregnant woman, these changes are usually clinically inconsequential. But when combined with underlying ventricular dysfunction—for example, concentric ventricular hypertrophy from chronic hypertension—further diastolic dysfunction may cause cardiogenic pulmonary edema (Wardhana, 2017). This is discussed further in Chapters 47 (Acute Respiratory Distress Syndrome) and 49 (Heart Failure).

Ventricular Function

Despite the relatively high frequency of diastolic dysfunction with preeclampsia, clinical cardiac function in most affected women is appropriate (Hibbard, 2015). In some preeclamptic women, cardiac troponin levels are slightly elevated, and amino-terminal pro-brain natriuretic peptide (Nt pro-BNP) levels are elevated with severe preeclampsia (Pergialiotis, 2016; Zachary, 2017). Importantly, both normally pregnant women and those with preeclampsia syndrome can have normal or slightly hyperdynamic ventricular function (Fig. 40-5). Thus, both have a cardiac output that is appropriate for left-sided filling pressures. Filling pressures are dependent on the volume of intravenous fluids. Thus, aggressive hydration results in overtly *hyperdynamic* ventricular function. This is accompanied by elevated pulmonary capillary wedge pressures, and pulmonary edema may develop despite normal ventricular function. This is because of an alveolar endothelial-epithelial leak, and it is compounded by decreased oncotic pressure from a low serum albumin concentration. In sum, aggressive fluid administration to otherwise normal women with severe preeclampsia substantially elevates normal left-sided filling pressures and raises a physiologically normal cardiac output to hyperdynamic levels.

FIGURE 40-5

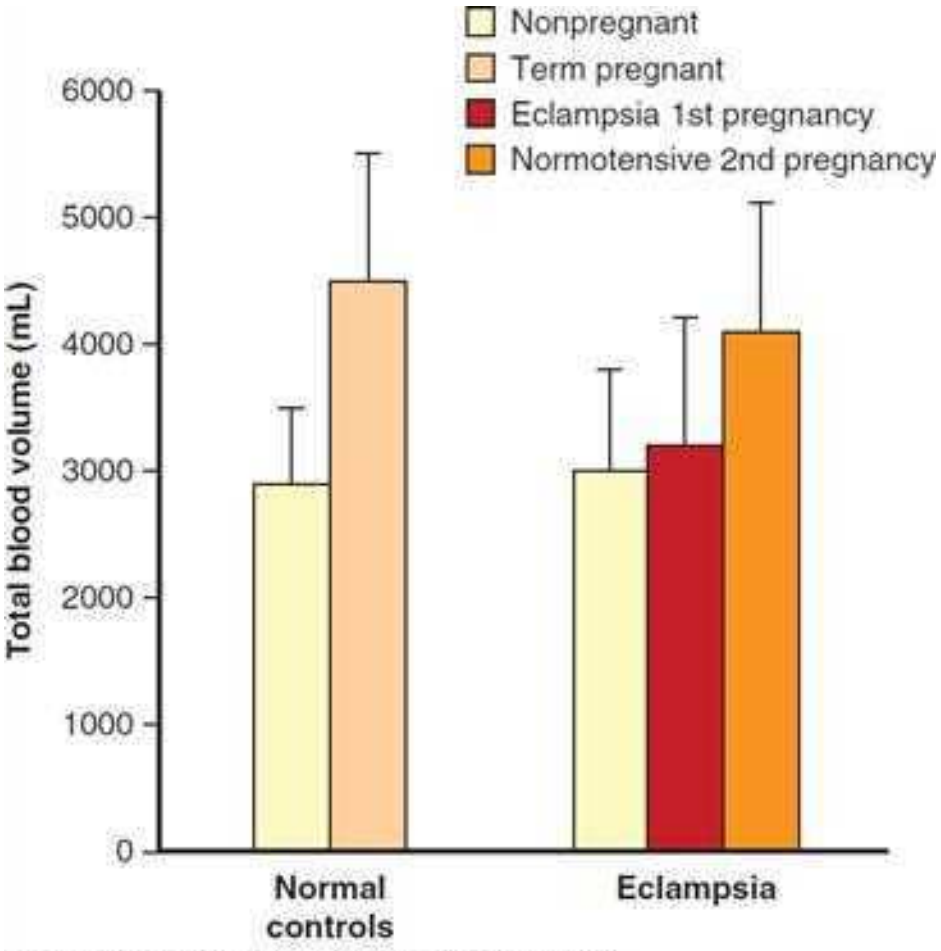
Ventricular function in normally pregnant women (*striped area*) and in women with eclampsia (*boxed area*) is plotted on a Braunwald ventricular function curve. Normal values are from Clark (1989), and those for eclampsia are from Hankins (1984). PCWP = pulmonary capillary wedge pressure; LVSWI = left ventricular stroke work index.



Blood Volume

Hemoconcentration is a hallmark of eclampsia. This concept was precisely quantified by Zeeman and colleagues (2009), who expanded the prior observations of Pritchard and associates (1984). They showed in *eclamptic* women that the normally expected pregnancy blood volume expansion is severely curtailed (Fig. 40-6). Women of average size have a blood volume of 3000 mL, and during the last several weeks of a normal pregnancy, this averages 4500 mL. With *eclampsia*, however, much or all of the anticipated 1500 mL excess is lost. Such hemoconcentration results from generalized vasospasm that follows endothelial activation and leakage of plasma into the interstitial space. In women with *preeclampsia*, and depending on its severity, hemoconcentration is usually not as marked.

FIGURE 40-6
Total blood volumes in normotensive women compared with those with eclampsia. The vertical extensions are one standard deviation from the mean. In eclamptic women, blood volume is minimally increased compared with a subsequent normotensive pregnancy. (Data from Zeeman, 2009.)



These changes have substantial clinical consequences. Importantly, women with severe hemoconcentration are unduly sensitive to blood loss at delivery that otherwise may be considered normal. Vasospasm and endothelial leakage of plasma persist for a variable time after delivery as the endothelium is restored to normalcy. As this takes place, vasoconstriction reverses, and as the blood volume reexpands, the hematocrit usually falls. *Importantly, a substantive cause of this fall in hematocrit, however, is usually the blood loss incurred at delivery.* Anemia may also partially result from greater erythrocyte destruction as subsequently described.

Maternal Thrombocytopenia

The platelet count is routinely measured in women with any form of gestational hypertension. Decreased platelet concentrations with eclampsia were described more than 100 years ago. The frequency and intensity of thrombocytopenia vary and are dependent on the severity and duration of the preeclampsia syndrome (Heilmann, 2007; Hupuczi, 2007). Overt thrombocytopenia—defined by a platelet count <100,000/μL—indicates severe disease (see Table 40-2). In general, the lower the platelet count, the higher the rates of maternal and fetal morbidity and mortality (Leduc, 1992). In most cases, delivery is advisable because worsening thrombocytopenia usually ensues. After delivery, the platelet count may continue to decline for the first day or so. It then usually rises progressively to reach a normal level within 3 to 5 days. As discussed later (Brain), in some instances with HELLP syndrome, the platelet count continues to fall after delivery. If these do not reach a nadir until 48 to 72 hours, then preeclampsia syndrome may be incorrectly attributed to one of the thrombotic microangiopathies discussed in Chapter 56 (Thrombotic Microangiopathies).

Myriad other platelet alterations are attributed to the preeclampsia syndrome. These were reviewed by Kenny and coworkers (2015) and include platelet activation with increased α-degranulation producing β-thromboglobulin, factor 4, and enhanced clearance. Paradoxically, in most studies, in vitro platelet aggregation is reduced compared with the normal increase that is characteristic of pregnancy. This likely is due to platelet "exhaustion" following in vivo activation. Although the cause is unknown, immunological processes or simply platelet deposition at sites of endothelial damage may be implicated. Levels of platelet-bound and circulating platelet-bindable immunoglobulins are elevated, which suggests platelet surface alterations.

Abnormally low platelets do not develop in the fetuses or neonates born to preeclamptic women despite severe maternal thrombocytopenia (Kenny, 2015; Pritchard, 1987). *Thus, maternal thrombocytopenia in a hypertensive woman is not a fetal indication for cesarean delivery.*

Hemolysis

Severe preeclampsia is frequently accompanied by hemolysis, which manifests as elevated serum lactate dehydrogenase levels and reduced haptoglobin levels. Other evidence comes from schizocytosis, spherocytosis, and reticulocytosis in peripheral blood (Cunningham, 1985; Pritchard, 1954, 1976). These derangements result in part from *microangiopathic hemolysis* caused by endothelial disruption with platelet adherence and fibrin deposition. Cunningham and coworkers (1995)

postulated that erythrocyte morphology was partially caused by serum lipid alterations. Related, substantively decreased long-chain fatty acid content is found in erythrocytes of preeclamptic women (Mackay, 2012).

After early reports of hemolysis and thrombocytopenia with severe preeclampsia, descriptions were added of abnormally elevated serum liver transaminase levels that indicated hepatocellular necrosis (Chesley, 1978). Weinstein (1982) referred to this combination of events as the *HELLP syndrome*—and this term now is used worldwide. Also, facets of the HELLP syndrome are included in criteria that differentiate severe from nonsevere preeclampsia (see Table 40-2). The HELLP syndrome is discussed further in that section (Brain).

Coagulation Changes

Subtle changes consistent with intravascular coagulation, and less often erythrocyte destruction, commonly are found with preeclampsia and especially eclampsia (Cunningham, 2015; Kenny, 2015). Some of these changes include elevated factor VIII consumption, increased levels of fibrinopeptides A and B and of d-dimers, and reduced levels of regulatory proteins—antithrombin III and proteins C and S. Coagulation aberrations generally are mild and are seldom clinically significant (Kenny, 2015; Pritchard, 1984). Unless placental abruption is comorbid, plasma fibrinogen levels do not differ remarkably from levels found in normal pregnancy. Fibrin degradation products such as d-dimers are minimally elevated. As preeclampsia worsens, so do abnormal findings with *thromboelastography* (Pisani-Conway, 2013). Despite these changes, routine laboratory assessments of coagulation, such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and plasma fibrinogen level, are not required in the management of pregnancy-associated hypertensive disorders.

Endocrine and Hormonal Alterations

Plasma levels of *renin, angiotensin II, angiotensin 1–7, aldosterone, deoxycorticosterone,* and *atrial natriuretic peptide (ANP)* are substantively augmented during normal pregnancy. ANP is released during atrial wall stretching from blood volume expansion, and it responds to cardiac contractility (Chap. 4, Renin, Angiotensin II, and Plasma Volume). Levels of serum ANP rise in pregnancy, and its secretion is further enhanced in women with preeclampsia (Luft, 2009). Levels of its precursor—*proatrial natriuretic peptide*—are also increased in preeclampsia (Sugulle, 2012). *Vasopressin* levels are similar in nonpregnant, normally pregnant, and preeclamptic women even though the metabolic clearance is elevated in the latter two (Dürr, 1999).

Fluid and Electrolyte Alterations

In women with severe preeclampsia, the volume of *extracellular fluid,* manifest as edema, is usually much greater than that in normal pregnant women. As discussed, the mechanism responsible for pathological fluid retention is endothelial injury (Davidge, 2015). In addition to generalized edema and proteinuria, these women have reduced plasma oncotic pressure. This reduction creates a filtration imbalance and further displaces intravascular fluid into the surrounding interstitium. Electrolyte concentrations do not differ appreciably in women with preeclampsia compared with those of normal pregnant women.

Following an eclamptic convulsion, the *serum pH* and *bicarbonate* concentration are lowered due to lactic acidosis and compensatory respiratory loss of carbon dioxide. The intensity of acidosis relates to the amount of lactic acid produced—metabolic acidosis—and the rate at which carbon dioxide is exhaled—respiratory acidosis.

Kidney

During normal pregnancy, renal blood flow and glomerular filtration rate rise appreciably (Chap. 4, Urinary System). With preeclampsia, several reversible anatomical and pathophysiological changes ensue. Of clinical importance, renal perfusion and glomerular filtration are reduced. Levels that are much less than normal nonpregnant values are infrequent and are the consequence of severe disease. Most of the decrement in glomerular filtration is from higher renal afferent arteriolar resistance that may be elevated up to fivefold (Conrad, 2015; Cornelis, 2011). Morphological changes are characterized by *glomerular endotheliosis*, which blocks the barrier that allows filtration. Diminished filtration causes serum creatinine levels to rise to values seen in nonpregnant individuals, that is, 1 mg/mL, and sometimes higher (Lindheimer, 2008a). Abnormal values usually begin to normalize 10 days or later after delivery (Cornelis, 2011; Spaan, 2012a).

In most preeclamptic women, the urine sodium concentration is elevated. Urine osmolality rises, urine:plasma creatinine ratio is elevated, and fractional excretion of sodium is low, which all indicated that a prerenal mechanism is involved. Sodium-containing crystalloid infusion raises left ventricular filling pressure, and although oliguria temporarily improves, rapid infusions may cause clinically apparent pulmonary edema. Intensive intravenous fluid therapy is not indicated as “treatment” for preeclamptic women with oliguria unless urine output is diminished from hemorrhage or fluid loss from vomiting or fever.

Plasma uric acid concentration is typically elevated in preeclampsia. The elevation exceeds that attributable to the reduction in glomerular filtration rate and likely is also due to enhanced tubular reabsorption (Chesley, 1945). At the same time, preeclampsia is associated with diminished urinary excretion of calcium, perhaps because of greater tubular reabsorption (Taufield, 1987).

Proteinuria

As shown in Table 40-1, detection of proteinuria helps to establish the diagnosis of preeclampsia. Abnormal protein excretion is empirically defined by 24-hour urinary excretion exceeding 300 mg; a urine protein:creatinine ratio ≥0.3; or persistent protein values of 30 mg/dL (1+ dipstick) in random urine samples. Although worsening or nephrotic-range proteinuria has been considered by most to be a sign of severe disease, this does not appear to be the case (Airoldi, 2007). Certainly, this concept was not accepted by the 2013 Task Force.

Problematically, the optimal method of establishing abnormal levels of either urine protein or albumin remains to be defined. For a 24-hour quantitative specimen, the “consensus” threshold value used is ≥300 mg/24 h (American College of Obstetricians and Gynecologists, 2013). Using a urinary protein excretion threshold of 165 mg in a 12-hour sample shows equivalent efficacy (Stout, 2015; Tun, 2012).

Determination of urinary protein:creatinine ratio may supplant the cumbersome 24-hour quantification (Kyle, 2008; Morris, 2012). Chen and associates (2008) found that clean-catch and catheterized urine specimens correlate well. In one systematic review, random urine protein:creatinine ratios below 130 to 150 mg/g, that is, 0.13 to 0.15, indicate a low likelihood of proteinuria exceeding 300 mg/d (Papanna, 2008). Ratios <0.08 or >1.19 have negative- or positive-predictive values of 86 and 96 percent, respectively (Stout, 2013). However, midrange ratios, that is, 300 mg/g or 0.3, have poor sensitivity and specificity. Thus, many recommend that with midrange ratio values, 24-hour protein excretion should be quantified.

With urine dipstick assessment, determinations depend on urine concentration and are notorious for false-positive and -negative results. Thus, assessment may show a dipstick value of 1+ to 2+ from concentrated urine specimens from women who excrete <300 mg/d.

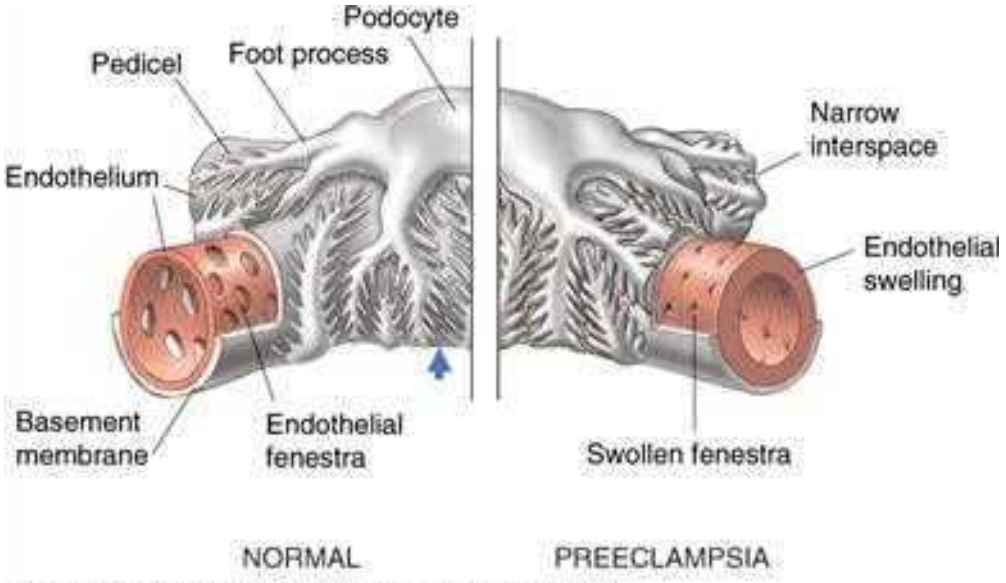
Importantly, proteinuria may develop late, and some women may already be delivered or have had an eclamptic convulsion before it appears. For example, 10 to 15 percent of women with HELLP syndrome do not have proteinuria at presentation (Sibai, 2004). In one report, 17 percent of eclamptic women did not have proteinuria by the time of seizures (Zwart, 2008).

Anatomical Changes

Sheehan and Lynch (1973) frequently found changes identifiable at autopsy by light and electron microscopy in the kidneys of eclamptic women. Glomeruli are enlarged by approximately 20 percent, they are "bloodless," and capillary loops variably are dilated and contracted. Endothelial cells are swollen—termed *glomerular capillary endotheliosis* (Spargo, 1959). Endothelial cells are often so swollen that they block or partially block the capillary lumens (Fig. 40-7) (Hecht, 2017). Homogeneous subendothelial deposits of proteins and fibrin-like material are seen.

FIGURE 40-7

Schematic showing glomerular capillary endotheliosis. The capillary of the normal glomerulus shown on the left has wide endothelial fenestrations, and the pedicels emanating from the podocytes are widely spaced (*arrow*). The illustration on the right is of a glomerulus with changes induced by the preeclampsia syndrome. The endothelial cells are swollen and their fenestrae narrowed, as are the pedicels that now abut each other.



Endothelial swelling may result from angiogenic protein "withdrawal" caused by the complexing of free angiogenic proteins with a compatible circulating antiangiogenic protein receptor (see Fig. 40-3). The angiogenic proteins are crucial for podocyte health, and their inactivation leads to podocyte dysfunction and endothelial swelling (Conrad, 2015; Karumanchi, 2009). Also, eclampsia is characterized by greater excretion of these epithelial podocytes (Wagner, 2012; White, 2014).

Acute Kidney Injury

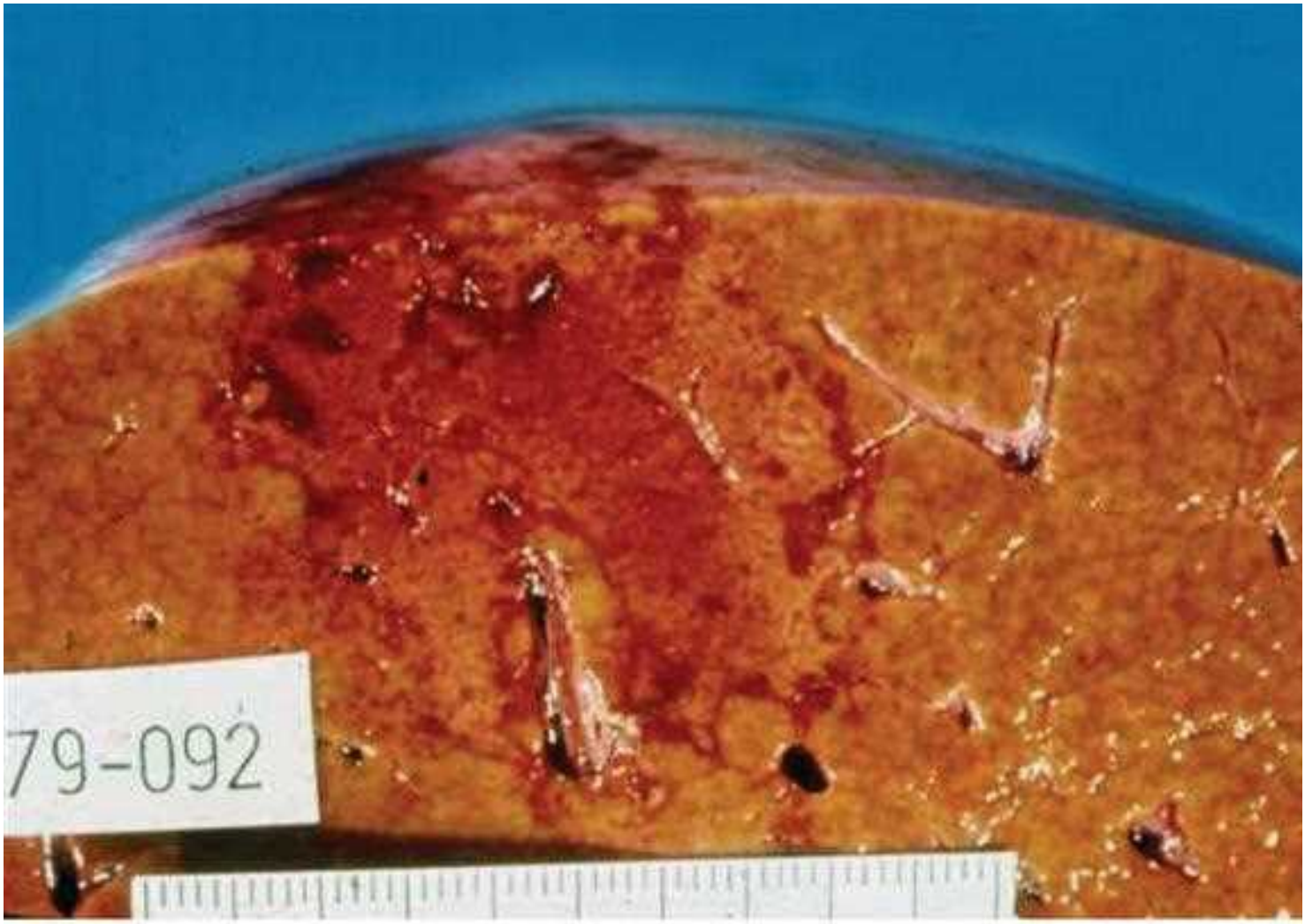
Although mild degrees of acute kidney injury are encountered, clinically apparent *acute tubular necrosis* is almost invariably induced by comorbid hemorrhage with hypovolemia and hypotension (Chap. 41, General Considerations). This is usually caused by severe obstetrical bleeding—especially placental abruption—coupled with inadequate blood replacement. Drakeley and coworkers (2002) described 72 women with preeclampsia and renal failure. Half had HELLP syndrome, and a third had placental abruption. In one review of 183 women with HELLP syndrome, 5 percent had kidney injury (Haddad, 2000). Of those with renal injury, half had placental abruption, and most had postpartum hemorrhage. Last, irreversible *renal cortical necrosis* develops rarely (Chap. 53, Lower Genital Tract Lesions).

Liver

The characteristic hepatic lesions with eclampsia are regions of periportal hemorrhage in the liver periphery (Hecht, 2017). However, lesions as extensive as those shown in Figure 40-8 are unusual. Sheehan and Lynch (1973) described that some degree of hepatic infarction accompanied hemorrhage in almost half of women who died with eclampsia. These findings corresponded with reports during the 1960s that described elevated serum hepatic transaminase levels. Along with the earlier observations by Pritchard and associates (1954), who described hemolysis and thrombocytopenia with eclampsia, this constellation of hemolysis, hepatocellular necrosis, and thrombocytopenia was later termed *HELLP syndrome*.

FIGURE 40-8

Gross liver specimen from a woman with preeclampsia who died from aspiration pneumonitis. Periportal hemorrhagic necrosis was seen microscopically. (Reproduced with permission from Cunningham FG: Liver disease complicating pregnancy. Williams Obstetrics, 19th ed. (Suppl 1), Norwalk, Appleton & Lange, 1993.)



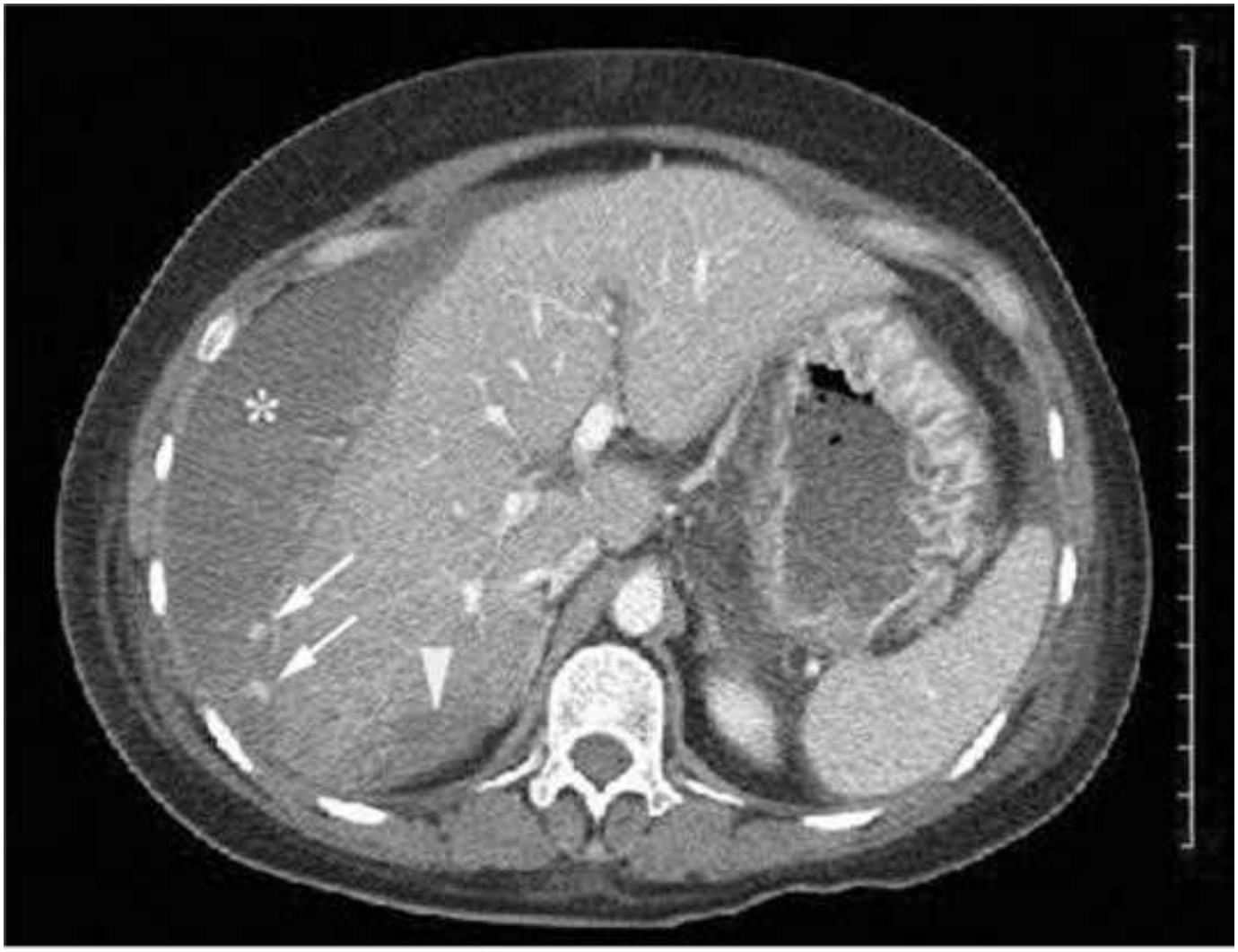
Liver involvement with preeclampsia may clinically display at least three manifestations. First, pain is considered a sign of severe disease. It typically manifests by moderate-to-severe right upper quadrant or midepigastric pain and tenderness. Such women usually have elevated serum aspartate transaminase (AST) or alanine transaminase (ALT) levels. In some cases, however, the amount of hepatic tissue involved with infarction may be surprisingly extensive yet still clinically insignificant (Nelson, 2017). In our experiences, infarction may be worsened by hypotension from obstetrical hemorrhage, and it occasionally causes hepatic failure—also called shock liver (Alexander, 2009; Yoshihara, 2016).

Second, elevations of serum AST and ALT levels are markers for severe preeclampsia. Values seldom exceed 500 U/L, but levels reaching more than 2000 U/L have been reported (Chap. 55, Hepatic Disorders). In general, serum concentrations inversely follow platelet levels, and they both usually normalize within 3 days following delivery.

As a third presentation, hemorrhagic infarction may extend to form a hepatic hematoma. This in turn can extend to form a subcapsular hematoma that may rupture. Computed tomography (CT) scanning or magnetic resonance (MR) imaging greatly aids diagnosis (Fig. 40-9). Unruptured hematomas are probably more common than clinically suspected and are more likely to be found with HELLP syndrome. Although once considered a surgical condition, current management of a hepatic hematoma usually consists of observation unless bleeding is ongoing. In some cases, however, prompt surgical intervention or angiographic embolization may be lifesaving. In one review of 180 cases of hepatic hematoma or rupture, 94 percent of affected gravidas had HELLP syndrome, and in 90 percent of the total, the capsule had ruptured (Vigil-De Gracia, 2012). The maternal mortality rate was 22 percent, and the perinatal mortality rate was 31 percent. In rare cases, liver transplantation is necessary (Hunter, 1995; Wicke, 2004).

FIGURE 40-9

Abdominal CT imaging performed postpartum in a woman with severe HELLP syndrome and right-upper quadrant pain. A large subcapsular hematoma (*asterisk*) is seen confluent with intrahepatic infarction and hematoma (*arrowhead*). Numerous flame-shaped hemorrhages are seen at the hematoma interface (*arrows*).



Acute fatty liver of pregnancy is sometimes confused with preeclampsia (Nelson, 2013; Sibai, 2007a). It too has an onset in late pregnancy, and often there is accompanying hypertension, elevated serum transaminase and creatinine levels, and thrombocytopenia. However, the hallmark of acute fatty liver is significant liver dysfunction, and Table 55-1 highlights these clinical differences.

Last, no convincing data link pancreatic involvement with preeclampsia syndrome (Sheehan, 1973). Thus, the occasional case of concurrent hemorrhagic pancreatitis is likely unrelated (Lynch, 2015; Swank, 2012). In our experiences from Parkland Hospital, amylase levels were seldom elevated in preeclamptic women (Nelson, 2014a).

HELLP Syndrome

There is no universally accepted strict definition of HELLP syndrome, and thus its incidence varies by investigator. In the previously noted study of 183 women with HELLP syndrome, 40 percent had adverse outcomes, and two mothers died (Haddad, 2000). Complications included eclampsia in 6 percent, placental abruption—10 percent, acute kidney injury—5 percent, and pulmonary edema—10 percent. Stroke, hepatic hematoma, coagulopathy, acute respiratory distress syndrome, and sepsis were other serious complications.

Women with preeclampsia and HELLP syndrome typically have worse outcomes than preeclamptic women without the HELLP constellation (Kozic, 2011; Martin, 2012, 2013). In one review of 693 women with HELLP syndrome, 10 percent had concurrent eclampsia (Keiser, 2011). Sep and associates (2009) described a significantly higher risk for complications in women with HELLP syndrome compared with those with "isolated preeclampsia." These included eclampsia—15 versus 4 percent; preterm birth—93 versus 78 percent; and perinatal mortality rate—9 versus 4 percent, respectively. Because of these marked clinical differences, it has been postulated that HELLP syndrome has a distinct pathogenesis (Reimer, 2013; Vaught, 2016).

Brain

Headaches and visual symptoms are common with severe preeclampsia, and associated convulsions define eclampsia. The earliest anatomical descriptions of brain involvement came from autopsy specimens, but CT and MR imaging and Doppler studies have added many important insights.

Neuroanatomical Lesions

From early anatomical descriptions, brain pathology accounted for only about a third of fatal cases such as the one shown in Figure 40-10. In fact, most deaths were from pulmonary edema, and brain lesions were coincidental. Thus, although gross intracerebral hemorrhage was seen in up to 60 percent of eclamptic women, it

was fatal in only half of these (Melrose, 1984; Richards, 1988; Sheehan, 1973). As shown in Figure 40-11, other principal lesions found at autopsy of eclamptic women were cortical and subcortical petechial hemorrhages. The classic microscopic vascular lesions consist of fibrinoid necrosis of the arterial wall and perivascular microinfarcts and hemorrhages. Other frequently described major lesions include subcortical edema, multiple nonhemorrhagic areas of "softening" throughout the brain, and hemorrhagic areas in the white matter (Hecht, 2017). There also may be hemorrhage in the basal ganglia or pons, sometimes with rupture into the ventricles.

FIGURE 40-10
This autopsy brain slice shows a fatal hypertensive hemorrhage in a primigravida with eclampsia.

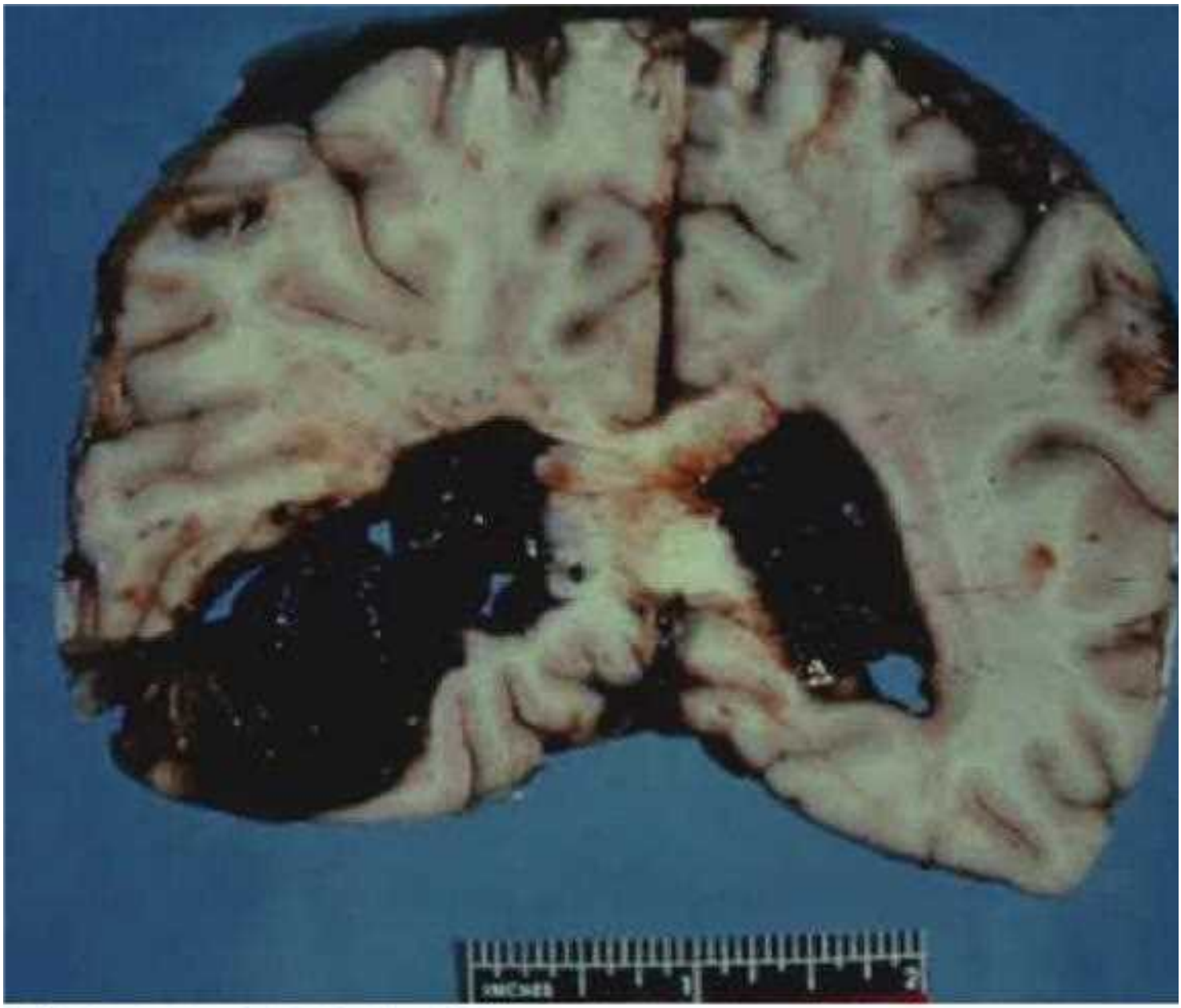
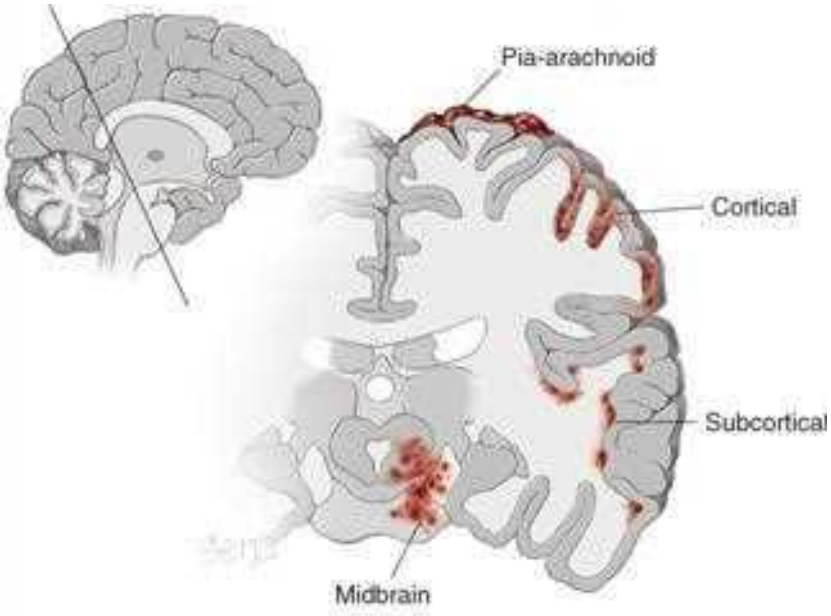


FIGURE 40-11
Composite illustration showing location of cerebral hemorrhages and petechiae in women with eclampsia. Insert shows the level of the brain from which the main image was constructed. (Data from Sheehan, 1973.)



Cerebrovascular Pathophysiology

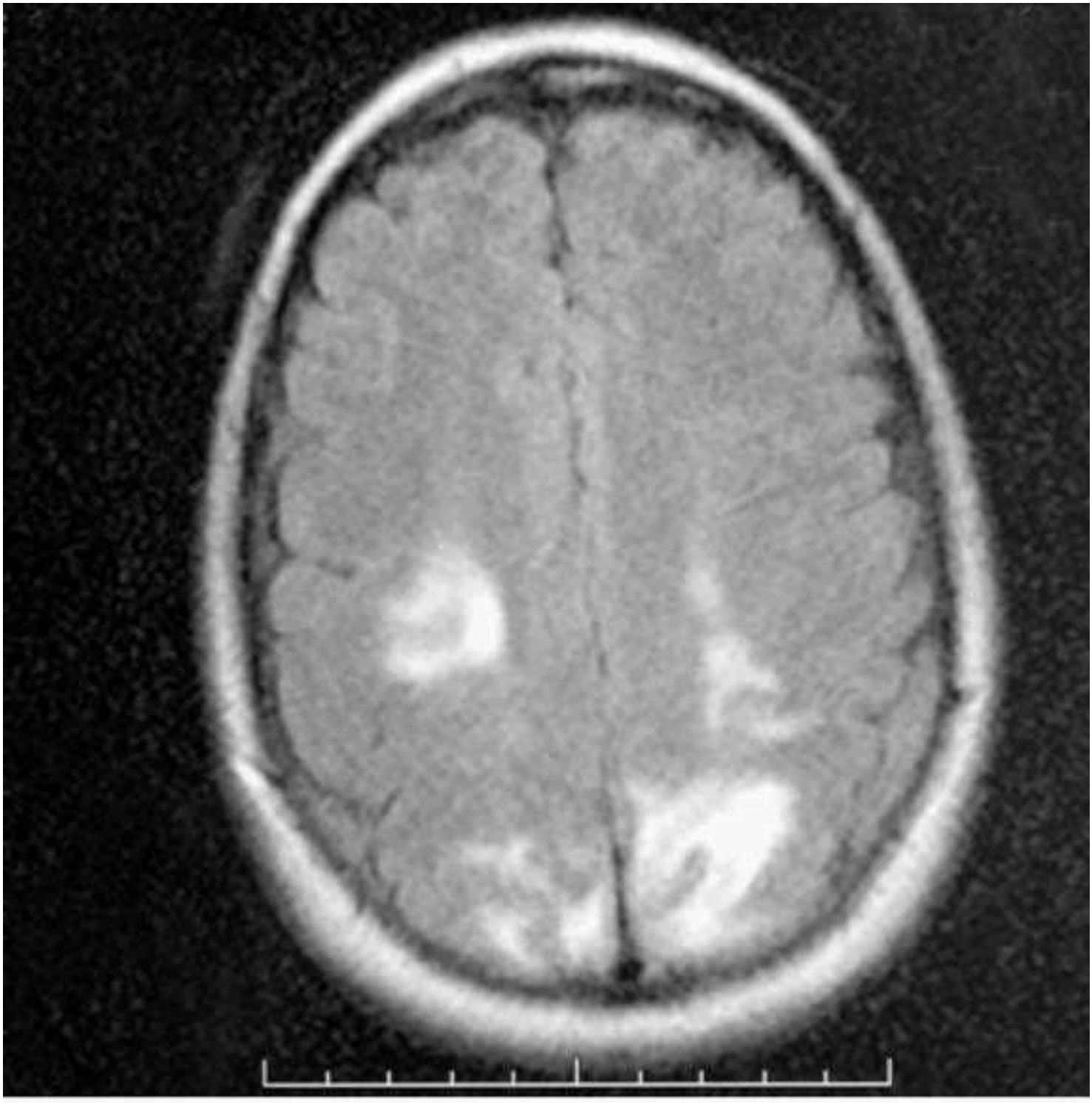
Clinical, pathological, and neuroimaging findings have led to two general theories to explain cerebral abnormalities with eclampsia. Importantly, endothelial cell dysfunction that characterizes the preeclampsia syndrome likely is a key in both. The first theory suggests that in response to acute and severe hypertension, cerebrovascular overregulation leads to vasospasm (Trommer, 1988). In this scheme, diminished cerebral blood flow is hypothesized to result in ischemia, cytotoxic edema, and eventually tissue infarction. Little objective evidence supports this mechanism.

The second theory is that sudden elevations in systemic blood pressure exceed the normal cerebrovascular autoregulatory capacity (Hauser, 1988; Schwartz, 2000). Regions of forced vasodilation and vasoconstriction develop, especially in arterial boundary zones. At the capillary level, disruption of end-capillary pressure causes increased hydrostatic pressure, hyperperfusion, and extravasation of plasma and red cells through endothelial tight-junction openings. This leads to *vasogenic edema*. The recent description of a central nervous system lymphatic vasculature lends credibility to this theory (Louveau, 2015).

The most likely mechanism is a combination of the two. Thus, a preeclampsia-associated interendothelial cell leak develops at blood pressure (hydraulic) levels much lower than those that usually cause vasogenic edema and is coupled with a loss of upper-limit autoregulation (Fugate, 2015; Zeeman, 2009). With imaging studies, these manifest as the *posterior reversible encephalopathy syndrome* (Fig. 40-12) (Fugate, 2015; Hinchey, 1996). The lesions of this syndrome principally involve the posterior brain—the occipital and parietal cortices. But, in at least a third of cases, other areas are involved (Edlow, 2013; Zeeman, 2004a).

FIGURE 40-12

Cranial magnetic-resonance imaging in a nullipara with eclampsia. Multilobe T2-FLAIR high-signal lesions are apparent. FLAIR = fluid-attenuated inversion recovery. (Used with permission from Dr. Gerda Zeeman.)



Cerebral Blood Flow

Autoregulation is the mechanism by which cerebral blood flow remains relatively constant despite alterations in cerebral perfusion pressure. Remember that cerebral perfusion pressure is the difference between mean arterial pressure and intracranial pressure. In nonpregnant individuals, this autoregulation protects the brain from hyperperfusion when mean arterial pressures rise to as high as 160 mm Hg. These are pressures far greater than those seen in all but a very few women with eclampsia. Thus, to explain eclamptic seizures, it was theorized that autoregulation must be altered by pregnancy. Studies by Cipolla and colleagues (2007, 2009, 2015) have convincingly shown that autoregulation is unchanged across pregnancy in rodents. But, some investigators have provided evidence of impaired autoregulation in women with preeclampsia (Janzarik, 2014; van Veen, 2013).

Zeeman and associates (2003) showed that cerebral blood flow during the first two trimesters of normal pregnancy is similar to nonpregnant values. But during the last trimester, flow significantly drops by 20 percent. This group also found greater cerebral blood flow in this trimester in women with severe preeclampsia compared with that in normotensive pregnant women (Zeeman, 2004b). Taken together, these findings suggest that eclampsia occurs when cerebral hyperperfusion forces capillary fluid interstitially because of endothelial damage. This leak leads to perivascular edema characteristic of the preeclampsia syndrome.

Neurological Manifestations

Several neurological manifestations typify the preeclampsia syndrome. Each signifies severe involvement and requires immediate attention.

First, *headache and scotomata* are thought to arise from cerebrovascular hyperperfusion that has a predilection for the occipital lobes. Up to 75 percent of women have headaches, and 20 to 30 percent have visual changes preceding eclamptic convulsions (Sibai, 2005; Zwart, 2008). The headaches may be mild to severe and intermittent to constant. In our experiences, they are unique in that they do not usually respond to traditional analgesia, but they frequently improve after magnesium sulfate infusion.

Convulsions are diagnostic for eclampsia. These are caused by excessive release of excitatory neurotransmitters—especially glutamate; massive depolarization of network neurons; and bursts of action potentials (Meldrum, 2002). Clinical and experimental evidence suggests that extended seizures can cause significant brain injury and later brain dysfunction.

Blindness is rare with preeclampsia alone, but it complicates eclamptic convulsions in up to 15 percent of women (Cunningham, 1995). Blindness may develop up to a week or more following delivery (Chambers, 2004). There are at least two types of blindness, as discussed subsequently.

Generalized cerebral edema may develop and is usually manifest by mental status changes that vary from confusion to coma. This situation is particularly dangerous because fatal transtentorial herniation can result.

Last, women with eclampsia have been shown to have some cognitive decline when studied 5 to 10 years following an eclamptic pregnancy. This is discussed further in the final section (Renal Sequelae).

Neuroimaging Studies

With CT imaging, localized hypodense lesions at the gray- and white-matter junction, primarily in the parietooccipital lobes, are typically found in eclampsia. Such lesions may also be seen in the frontal and inferior temporal lobes, the basal ganglia, and thalamus (Brown, 1988). These hypodense areas correspond to petechial hemorrhages and local edema. Edema of the occipital lobes or diffuse cerebral edema may cause symptoms such as blindness, lethargy, and confusion (Cunningham, 2000). Widespread edema can appear as marked compression or even obliteration of the cerebral ventricles. Such women may develop signs of impending life-threatening transtentorial herniation.

Several MR imaging acquisitions are used to study eclamptic women. Common findings are hyperintense T2 lesions—namely, posterior reversible encephalopathy syndrome (PRES)—in the subcortical and cortical regions of the parietal and occipital lobes (see Fig. 40-12). Also, the basal ganglia, brainstem, and cerebellum are relatively commonly involved (Brewer, 2013; Zeeman, 2004a). Again, these lesions represent focal cerebral edema. Although these PRES lesions are almost universal in women with eclampsia, their incidence in women with preeclampsia approximates 20 percent (Mayama, 2016). Lesions are more likely in women who have severe disease and who have neurological symptoms. And although usually reversible, a fourth of these hyperintense lesions represent cerebral infarctions that have persistent findings (Loureiro, 2003; Zeeman, 2004a).

Visual Changes and Blindness

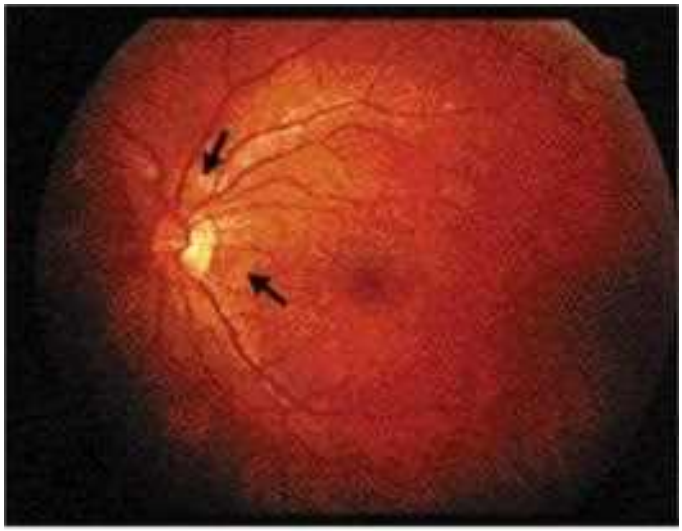
Scotomata, blurred vision, or diplopia are common with severe preeclampsia and eclampsia. These usually improve with magnesium sulfate therapy and/or lowered blood pressure. Blindness is less common, is usually reversible, and may arise from three potential areas. These are the visual cortex of the occipital lobe, the lateral geniculate nuclei, and the retina. In the retina, pathological lesions may be ischemia, infarction, or detachment (Handor, 2014; Roos, 2012).

Occipital blindness is also called *amaurosis*—from the Greek *dimming*. With imaging, affected women usually have evidence of extensive occipital lobe vasogenic edema. Of 15 women cared for at Parkland Hospital, occipital blindness lasted from 4 hours to 8 days, but it resolved completely in all cases (Cunningham, 1995). Rarely, extensive cerebral infarctions may result in total or partial visual defects.

Blindness from retinal lesions is caused either by serous retinal detachment or rarely by retinal infarction, which is termed *Purtscher retinopathy* (Fig. 40-13). *Serous retinal detachment* is usually unilateral and seldom causes total visual loss. In fact, asymptomatic serous retinal detachment is relatively common with preeclampsia (Saito, 1998). In most cases of eclampsia-associated blindness, visual acuity subsequently improves. However, if blindness is caused by retinal artery occlusion, vision may be permanently impaired (Lara-Torre, 2002; Moseman, 2002; Roos, 2012).

FIGURE 40-13

Purtscher retinopathy caused by choroidal ischemia and infarction in preeclampsia syndrome. Ophthalmoscopy shows scattered yellowish, opaque lesions of the retina (*arrows*). (Reproduced with permission from Lam DS, Chan W: Images in clinical medicine. Choroidal ischemia in preeclampsia. N Engl J Med 344(10):739, 2001.)



Cerebral Edema

Clinical manifestations suggesting widespread cerebral edema are worrisome. During 13 years at Parkland Hospital, 10 of 175 women (6 percent) with eclampsia were diagnosed with symptomatic cerebral edema (Cunningham, 2000). Symptoms ranged from lethargy, confusion, and blurred vision to obtundation and coma. In most cases, symptoms waxed and waned. Mental status changes generally correlated with the degree of involvement seen with CT and MR imaging studies. *These women are very susceptible to sudden and severe blood pressure elevations, which can acutely worsen the already widespread vasogenic edema.* Thus, careful blood pressure control is essential. In the 10 women with generalized edema, three became comatose and had imaging findings of transtentorial herniation, from which one died. Consideration is given for treatment with mannitol or dexamethasone.

Uteroplacental Perfusion

Compromised uteroplacental perfusion is almost certainly a major culprit in the greater perinatal morbidity and mortality rates seen with preeclampsia (Harmon, 2015). Defects in endovascular trophoblastic invasion with the preeclampsia syndrome were discussed earlier (Etiology). Thus, measurement of uterine, intervillous, and placental blood flow would likely be informative. Attempts to assess these in humans have been hampered by several obstacles that include inaccessibility of the placenta, the complexity of its venous effluent, and the need for radioisotopes or invasive techniques.

Measurement of uterine artery blood flow velocity has been used to estimate resistance to uteroplacental blood flow (Chap. 17, Amnionic Fluid Volume). Vascular resistance is estimated by comparing arterial systolic and diastolic velocity waveforms. By the completion of placentation, impedance of uterine artery blood flow is markedly decreased, but with abnormal placentation, abnormally high resistance persists (Everett, 2012; Ghidini, 2008; Napolitano, 2012). Earlier studies were done to assess this by measuring peak systolic:diastolic velocity ratios from uterine and umbilical arteries in preeclamptic pregnancies. In some cases, but certainly not all, there was higher resistance (Fleischer, 1986; Trudinger, 1990).

Another Doppler waveform—uterine artery "notching"—has been associated with elevated risks for preeclampsia or fetal-growth restriction (Groom, 2009). In the MFMU Network study reported by Myatt and colleagues (2012a), however, notching had a low predictive value except for early-onset severe disease.

Resistance in *uterine spiral arteries* has also been measured. Impedance was higher in peripheral than in central vessels—a "ring-like" distribution (Matijevic, 1999). Mean resistance values were greater in all women with preeclampsia compared with those in normotensive controls. One study used MR imaging and other techniques to assess placental perfusion ex vivo in myometrial arteries removed from women with preeclampsia or fetal-growth restriction (Ong, 2003). In both conditions, myometrial arteries exhibited endothelium-dependent vasodilatory response. Moreover, other pregnancy conditions are also associated with increased resistance (Urban, 2007). One major adverse effect, fetal-growth restriction, is discussed in Chapter 44 (Fetal-Growth Restriction).

de Almeida Pimenta and colleagues (2014) assessed placental vascularity using a three-dimensional power Doppler histogram and described a *placental vascularity index.* This index value was reduced in women with any pregnancy-associated hypertensive disorders—11.1 percent compared with 15.2 percent in normal controls.

Despite these findings, evidence for compromised uteroplacental circulation is found in only a few women who go on to develop preeclampsia. Indeed, when preeclampsia develops during the third trimester, only a third of women with severe disease have abnormal uterine artery velocimetry (Li, 2005). In a study of 50 women with HELLP syndrome, only a third had abnormal uterine artery waveforms (Bush, 2001). In general, the extent of abnormal waveforms correlates with severity of fetal involvement (Ghidini, 2008; Groom, 2009).

PREDICTION

Various biological markers implicated in the preeclampsia syndrome have been measured to help predict its development. Although most have been evaluated in the first half of pregnancy, some have been tested as predictors of severity in the third trimester (Chaiworapongsa, 2013; Lai, 2013; Mosimann, 2013). Others have been used to forecast recurrent preeclampsia (Demers, 2014; Eichelberger, 2015). Some of these tests are listed in Table 40-5, which is by no means all inclusive.

TABLE 40-5

Predictive Tests for Development of the Preeclampsia Syndrome

Testing Related To:	Examples
Placental perfusion/vascular resistance	Roll-over test, isometric handgrip or cold pressor test, pressor response to aerobic exercise, angiotensin-II infusion, midtrimester mean arterial pressure, platelet angiotensin-II binding, renin, 24-hour ambulatory blood pressure monitoring, uterine artery or fetal transcranial Doppler velocimetry
Fetal-placental unit endocrine dysfunction	Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), estriol, pregnancy-associated protein A (PAPP A), inhibin A, activin A, placental protein 13, procalcitonin, corticotropin-releasing hormone, A disintegrin, ADAM-12, kisspeptin
Renal dysfunction	Serum uric acid, microalbuminuria, urinary calcium or kallikrein, microtransferrinuria, *N*-acetyl-β-glucosaminidase, cystatin C, podocyturia, podocalyxin
Endothelial dysfunction/oxidant stress	Platelet count and activation, fibronectin, endothelial adhesion molecules, prostaglandins, prostacyclin, MMP-9, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteine, lipids, insulin resistance, resistin, antiphospholipid antibodies, plasminogen activator-inhibitor (PAI), leptin, p-selectin, angiogenic and antiangiogenic factors such as placental growth factor (PlGF), vascular endothelial growth factor (VEGF), fms-like tyrosine kinase receptor-1 (sFlt-1), endoglin
Others	Antithrombin-III(AT-3), atrial natriuretic peptide (ANP), β_2-microglobulin, haptoglobin, transferrin, ferritin, 25-hydroxyvitamin D, genetic markers, cell-free fetal DNA, serum and urine proteomics and metabolomic markers, hepatic aminotransferases

ADAM12 = ADAM metallopeptidase domain 12; MMP = matrix metalloproteinase.

Adapted from Conde-Agudelo, 2015, Duckworth, 2016.

Overall, these efforts have resulted in testing strategies with poor sensitivity and with poor positive-predictive values for preeclampsia (Conde-Agudelo, 2015; Odibo, 2013). *Currently, no screening tests for preeclampsia are predictably reliable, valid, and economical.* However, combinations of tests, some yet to be adequately evaluated, may be promising (Gallo, 2016; Olsen, 2012).

Vascular Resistance Testing and Placental Perfusion

Most tests in this category are cumbersome, time consuming, and overall inaccurate. To evaluate blood pressure changes, three tests assess the blood pressure rise in response to a stimulus. In one, women at 28 to 32 weeks' gestation rest in the left lateral decubitus position and then roll to the supine position. With this *roll-over test,* increased blood pressure with this maneuver signifies a positive test. The *isometric exercise test* employs the same principle by squeezing a handball. The *angiotensin II infusion test* is performed by giving incrementally increasing doses intravenously, and the hypertensive response is quantified. In an updated metaanalysis, sensitivities of all three tests were reported to range from 55 to 70 percent, and specificities approximated 85 percent (Conde-Agudelo, 2015).

Uterine artery Doppler velocimetry is posited to reflect faulty trophoblastic invasion of the spiral arteries. This failure results in diminished placental perfusion and upstream greater uterine artery resistance. Increased uterine artery velocimetry determined by Doppler ultrasound in the first two trimesters might provide indirect evidence of this process and thus serve as a predictive test for preeclampsia (Dar, 2010; Groom, 2009). Elevated flow resistance results in an abnormal vessel waveform represented by an exaggerated *diastolic notch.* These findings have value for prediction of fetal-growth restriction but not preeclampsia (American College of Obstetricians and Gynecologists, 2015). Several flow velocity waveforms have been investigated for preeclampsia prediction, however, none is suitable for clinical use (Conde-Agudelo, 2015; Kleinrouweler, 2012; Myatt, 2012a).

Fetal-Placental Unit Endocrine Function

Several serum analytes have been proposed to help predict preeclampsia (see Table 40-5). Newer ones are continually added. In general, none of these tests are clinically beneficial for hypertension prediction.

Renal Function Tests

Hyperuricemia likely results from reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption, and decreased secretion. Cnossen and coworkers (2006) reported that its sensitivity to detect preeclampsia ranged from 0 to 55 percent, and specificity was 77 to 95 percent.

Isolated gestational proteinuria is a risk factor for preeclampsia (Jayaballa, 2015; Morgan, 2016; Yamada, 2016). As a predictive test for preeclampsia, microalbuminuria has sensitivities that range from 7 to 90 percent and specificities that span 29 to 97 percent (Conde-Agudelo, 2015).

Endothelial Dysfunction and Oxidant Stress

Endothelial activation and inflammation are major participants in the pathophysiology of the preeclampsia syndrome. As a result, compounds such as those listed in Table 40-5 are found to be elevated in circulating blood of affected women, and some have been assessed for their predictive value.

First, fibronectins are high-molecular-weight glycoproteins released from endothelial cells and extracellular matrix following endothelial injury. However, in one systematic review, neither cellular nor total fibronectin levels were clinically useful to predict preeclampsia (Leeflang, 2007).

Thrombocytopenia and platelet dysfunction are integral features of preeclampsia. Platelet activation causes augmented destruction and lower concentrations. Mean platelet volume rises because of platelet immaturity (Kenny, 2015). Although markers of coagulation activation, described earlier (Maternal Thrombocytopenia), are elevated, the substantive overlap with levels in normotensive pregnant women stultifies their predictive value.

Markers of oxidative stress were also hoped to predict preeclampsia. Namely, associated higher levels of lipid peroxides coupled with decreased antioxidant activity raised this possibility. Other markers include iron, transferrin, and ferritin; resistin; hyperhomocysteinemia; blood lipids, including triglycerides, free fatty acids, and lipoproteins; and antioxidants such as ascorbic acid and vitamin E (Christiansen, 2015; Conde-Agudelo, 2015; D'Anna, 2004; Mackay, 2012; Mignini, 2005). However, these have not been found to be predictive.

Last, an imbalance in antiangiogenic factors is linked to preeclampsia etiopathogenesis. For example, serum levels of VEGF and PlGF begin to drop before clinical preeclampsia develops. And, recall from Figure 40-4 that at the same time, levels of some antiangiogenic factors, such as sFlt-1 and sEng, begin to rise (Karumanchi, 2016a; Maynard, 2008). With some of these factors, sensitivities for all cases of preeclampsia ranged from 30 to 50 percent, and specificity approximated 90 percent (Conde-Agudelo, 2015). Their predictive accuracy is higher for early-onset preeclampsia (Redman, 2015b; Tsiakkas, 2016). Determination of the sFlt-1/PlGF ratio in women admitted near 37 weeks' gestation to exclude preeclampsia was useful as a predictive factor (Baltajian, 2016; Zeisler, 2016a,b). These results suggest a clinical role for preeclampsia prediction, especially later in pregnancy (Duckworth, 2016; Gallo, 2016). They may also predict adverse pregnancy outcomes in women with lupus and comorbid antiphospholipid antibodies (Kim, 2016).

Other Markers

As discussed in Chapter 13 (Fetal DNA in the Maternal Circulation), cell-free DNA (cfDNA) can be detected in maternal plasma. It is hypothesized that cfDNA is released in preeclampsia by accelerated apoptosis of cytotrophoblasts (DiFederico, 1999). One MFMU Network study found no correlation between total cfDNA levels and preeclampsia (Silver, 2017).

Proteomic, metabolomic, and transcriptomic technologies can be employed to study serum and urinary proteins and cellular metabolites. These have opened new vistas for preeclampsia prediction, and preliminary studies indicate that these may become useful (Bahado-Singh, 2013; Carty, 2011; Ma, 2014; Myers, 2013).

PREVENTION

Various strategies used to prevent or modify preeclampsia severity have been evaluated. Some are listed in Table 40-6. In general, none of these has been found to be convincingly and reproducibly effective.

TABLE 40-6

Some Methods to Prevent Preeclampsia That Have Been Evaluated in Randomized Trials

Dietary manipulation—low-salt diet, calcium or fish oil supplementation
Exercise—physical activity, stretching
Cardiovascular drugs—diuretics, antihypertensive drugs
Antioxidants—ascorbic acid (vitamin C), α-tocopherol (vitamin E), vitamin D
Antithrombotic drugs—low-dose aspirin, aspirin/dipyridamole, aspirin + heparin, aspirin + ketanserin

Modified from Staff, 2015.

Dietary and Lifestyle Modifications

Dietary "treatment" for preeclampsia has produced some interesting abuses (Chesley, 1978). A *low-salt diet* was one of the earliest research efforts to prevent preeclampsia (De Snoo, 1937). This was followed by years of inappropriate diuretic therapy. Although these practices were discarded, it ironically was not until relatively recently that the first randomized trial was done and showed that a sodium-restricted diet was ineffective in preventing preeclampsia (Knuist, 1998).

Regular exercise during pregnancy is linked to a lower risk of developing preeclampsia (Barakat, 2016; Morris, 2017). Also, in one systematic review, a trend toward risk reduction with exercise was noted (Kasawara, 2012). Only a few studies have been randomized, and thus, more research is needed (Staff, 2015).

Somewhat related, Abenhaim and coworkers (2008) reported a retrospective cohort study of 677 nonhypertensive women hospitalized for bed rest because of threatened preterm delivery. When outcomes of these women were compared with those of the general obstetrical population, bed rest was associated with a

significantly reduced relative risk—0.27—of developing preeclampsia. From two small randomized trials, prophylactic bed rest for 4 to 6 hours daily at home was successful in significantly lowering the incidence of preeclampsia in women with normal blood pressures (Meher, 2006).

Calcium supplementation has been studied in several trials, including one by the National Institute of Child Health and Human Development (NICHD) that included more than 4500 low-risk nulliparas (Levine, 1997). Calcium supplementation did not prevent preeclampsia or pregnancy-associated hypertension. In one metaanalysis, increased calcium intake in high-risk women lowered the risk for preeclampsia (Patrelli, 2012). However, in aggregate, most of these trials have shown that unless women are calcium deficient, supplementation has no salutary effects (Sanchez-Ramos, 2017; Staff, 2015).

Cardioprotective fatty acids found in some fatty fishes are plentiful in diets of Scandinavians and American Eskimos. Because supplementation with these fatty acids likely prevents inflammatory-mediated atherogenesis, it was posited that they might also prevent preeclampsia. Unfortunately, randomized trials conducted thus far have shown no such benefits from fish oil supplementation (Makrides, 2006; Olafsdottir, 2006; Zhou, 2012).

Antihypertensive Drugs

Because of the putative effects of sodium restriction for preeclampsia prevention, diuretic therapy became popular with the introduction of chlorothiazide in 1957 (Finnerty, 1958; Flowers, 1962). In one metaanalysis of nine randomized trials with more than 7000 pregnancies, women given diuretics had a lower incidence of edema and hypertension but not of preeclampsia (Churchill, 2007). Because women with chronic hypertension are at high risk for preeclampsia, several randomized trials have evaluated various antihypertensive drugs to reduce the incidence of superimposed preeclampsia (Chap. 50, Management During Pregnancy). A critical analysis of these trials by Staff and coworkers (2015) failed to demonstrate benefits for this goal.

Antioxidants

Data imply that an imbalance between oxidant and antioxidant activity plays a role in preeclampsia pathogenesis. Thus, naturally occurring antioxidants—vitamins C, D, and E—might reduce such oxidation. Several randomized studies have assessed antioxidant vitamin supplementation for women at high risk for preeclampsia (Poston, 2006; Rumbold, 2006; Villar, 2009). The Combined Antioxidant and Preeclampsia Prediction Studies (CAPPS) by the MFMU Network included almost 10,000 low-risk nulliparas (Roberts, 2010). None of these studies showed reduced preeclampsia rates in women provided vitamins C and E compared with those given placebo.

Statins were proposed to prevent preeclampsia because they stimulate hemoxygenase-1 expression, which inhibits sFlt-1 release. Preliminary animal data suggest that statins may prevent hypertensive disorders of pregnancy (Lewis, 2017). The MFMU Network plans a randomized trial to test pravastatin for this purpose (Costantine, 2013, 2016).

Metformin inhibits *hypoxic inducible factor 1α* by lowering mitochondrial electron transport chain activity. It reduces sFlt-1 and sEng activity and thus has potential to prevent preeclampsia (Brownfoot, 2016). However, clinical studies are lacking.

Antithrombotic Agents

As noted earlier (Pathogenesis), preeclampsia is characterized by vasospasm, endothelial cell dysfunction, and inflammation, as well as activation of platelets and the coagulation-hemostasis system. Other sequelae include placental infarction and spiral artery thrombosis (Nelson, 2014b). Thus, antithrombotic agents have been evaluated to reduce the incidence of preeclampsia.

Low-molecular-weight heparin for prophylaxis has been studied in several randomized trials. Rodger and colleagues (2016) performed a metaanalysis using individual patient data from 963 women. The risk for recurrent preeclampsia, abruption, or fetal-growth restriction was similar in women receiving heparin or placebo.

Aspirin, in low oral doses of 50 to 150 mg daily, effectively inhibits platelet thromboxane A_2 biosynthesis but has minimal effects on vascular prostacyclin production (Wallenburg, 1986). Still, several clinical trials have shown limited benefits in preeclampsia prevention. For example, a randomized trial from the MFMU Network found that risks for adverse outcomes were not significantly reduced with aspirin therapy (Caritis, 1998). Some combined reports, however, are more favorable. The Paris Collaborative Group performed a metaanalysis that included 31 randomized trials involving 32,217 women (Askie, 2007). For women assigned to receive antiplatelet agents, the relative risk for preeclampsia, superimposed preeclampsia, preterm delivery, or any adverse pregnancy outcome was significantly decreased by 10 percent. Other metaanalyses report marginal benefits of low-dose aspirin for prevention of severe preeclampsia (Roberge, 2012; Villa, 2013). Recently, one randomized trial of more than 1600 women at high risk for preterm preeclampsia provided low-dose aspirin from 11 to 14 weeks' gestation until 36 weeks to prevent recurrence. The rate of preterm recurrence was 1.6 percent in the aspirin group compared with 4.3 percent in the placebo arm (Rolnik, 2017).

In recent dueling metaanalyses, Roberge and colleagues (2017) found that aspirin prophylaxis initiated before 16 weeks' gestation was associated with a significant risk reduction—about 60 percent–for preeclampsia and fetal-growth restriction. Moreover, they found a dose-response effect. At the same time, Meher and associates (2017) performed an individual participant data metaanalysis and reported a much lower—about 10 percent—risk reduction that was significant whether therapy was initiated before or after 16 weeks.

Meanwhile, the U.S. Preventive Services Task Force recommends low-dose aspirin prophylaxis for women at high risk for preeclampsia (Henderson, 2014). Because of this, the American College of Obstetricians and Gynecologists (2016b) issued a Practice Advisory that recommends low-dose aspirin be given between 12 and 28 weeks' gestation to help prevent preeclampsia in high-risk women. This includes those with a history of preeclampsia and those with twins, chronic hypertension, overt diabetes, renal disease, and autoimmune disorders. These results have also raised the question as to whether *all* pregnant women should be given aspirin (Mone, 2017). At this time, our answer is "no."

Low-dose aspirin coupled with heparin mitigates thrombotic sequelae in women with lupus anticoagulant (Chap. 59, Adverse Pregnancy Outcomes). Because of a similarly high prevalence of placental thrombotic lesions found with severe preeclampsia, trials have assessed the possible merits of such treatments for women with prior preeclampsia. In two randomized trials, women with a history of early-onset preeclampsia were given an aspirin therapy or an enoxaparin plus aspirin regimen (Groom, 2017; Haddad, 2016). Outcomes were similar. From their reviews, Sergis and associates (2006) reported better pregnancy outcomes in women with prior severe preeclampsia given low-molecular-weight heparin plus low-dose aspirin compared with those given low-dose aspirin alone. Similar findings were reported by de Vries and coworkers (2012).

PREECLAMPSIA

Pregnancy complicated by gestational hypertension is managed based on its severity, presence of preeclampsia, and gestational age. Preeclampsia cannot always be diagnosed definitively. Thus, the Task Force (2013) recommends more frequent prenatal visits if preeclampsia is "suspected." *Increases in systolic and diastolic blood pressure can be either normal physiological changes or signs of developing pathology*. Heightened surveillance permits more prompt recognition of ominous changes in blood pressure, critical laboratory findings, and clinical signs and symptoms (Macdonald-Wallis, 2015).

The basic management objectives for any pregnancy complicated by preeclampsia are: (1) termination of pregnancy with the least possible trauma to mother and fetus, (2) birth of a healthy newborn that subsequently thrives, and (3) complete restoration of health to the mother. In many women with preeclampsia, especially those at or near term, all three objectives are served equally well by induction of labor. *One of the most important clinical questions for successful management is precise knowledge of fetal age.*

Early Diagnosis of Preeclampsia

Traditionally, the frequency of prenatal visits is increased during the third trimester, and this aids early detection of preeclampsia. *Women without overt hypertension, but in whom early developing preeclampsia is suspected during routine prenatal visits, are seen more frequently*. For many years at Parkland Hospital, women with new-onset diastolic blood pressures >80 mm Hg but <90 mm Hg or with sudden abnormal weight gain of more than 2 pounds per week have, at minimum, returned for visits at 7-day intervals. Outpatient surveillance is continued unless overt hypertension, proteinuria, headache, visual disturbances, or epigastric pain supervenes.

Women with overt new-onset hypertension—either diastolic pressures ≥90 mm Hg or systolic pressures ≥140 mm Hg—are admitted to determine if the increase is due to preeclampsia, and if so, to evaluate its severity.

Evaluation

With hospitalization, a systematic evaluation is instituted to include:

Detailed examination, which is coupled with daily scrutiny for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain

Daily weight measurement

Quantification of proteinuria or urine protein:creatinine ratio on admittance and at least every 2 days thereafter

Blood pressure readings with an appropriate-size cuff every 4 hours, except between 2400 and 0600 unless previous readings are elevated

Measurements of plasma or serum creatinine and hepatic transaminase levels and a hemogram that includes a platelet count. The frequency of testing is determined by hypertension severity. Although some recommend measurement of serum uric acid and lactate dehydrogenase levels and coagulation studies, their value has been questioned (Conde-Agudelo, 2015; Thangaratinam, 2006).

Evaluation of fetal size and well-being and amnionic fluid volume, by either physical examination or sonography.

Reduced physical activity throughout much of the day is likely beneficial, but as the 2013 Task Force concluded, absolute bed rest is not desirable. Ample protein and calories are included in the diet, and sodium and fluid intake are not limited or forced.

In sum, goals of evaluation include early identification of preeclampsia or worsening of the syndrome and development of a management plan for timely delivery. Fortunately, many cases are sufficiently mild and near enough to term that they can be managed conservatively until labor commences spontaneously or until the cervix becomes favorable for labor induction. *Complete abatement of all signs and symptoms, however, is uncommon until after delivery*. If severe preeclampsia is diagnosed using the criteria in Table 40-2, further management is subsequently described.

Consideration for Delivery

Termination of pregnancy is the only cure for preeclampsia. Headache, visual disturbances, or epigastric pain are indicative that convulsions may be imminent, and oliguria is another ominous sign. Severe preeclampsia demands anticonvulsant and often antihypertensive therapy, followed by delivery. Treatment for eclampsia is identical. The prime objectives are to forestall convulsions, to prevent intracranial hemorrhage and serious damage to other vital organs, and to deliver a healthy newborn.

This is true even when the cervix is unfavorable (Tajik, 2012). Labor induction is carried out, usually with preinduction cervical ripening with a prostaglandin or osmotic dilator (Chap. 26, Preinduction Cervical Ripening).

Concerns stemming from an unfavorable cervix, a perceived sense of urgency because of preeclampsia severity, and a need to coordinate neonatal intensive care have led some to advocate cesarean delivery. Alexander and colleagues (1999) reviewed 278 singleton liveborn neonates weighing 750 to 1500 g delivered of women with severe preeclampsia at Parkland Hospital. In half of the women, labor was induced, and the remainder underwent cesarean delivery without labor. Induction was successful in accomplishing vaginal delivery in a third, and it was not harmful to very-low-birthweight neonates. Others have reported similar observations (Alanis, 2008; Roland, 2017). However, whenever it appears that induction almost certainly will not succeed or attempts have failed, then cesarean delivery is indicated.

For a woman near term, with a soft, partially effaced cervix, even a milder degree of preeclampsia probably carries more risk to the mother and her fetus-newborn than does induction of labor (Tajik, 2012). A randomized trial of 756 women with mild preeclampsia supported delivery after 37 weeks' gestation (Koopmans, 2009).

When the fetus is preterm, the tendency is to temporize in the hope that additional weeks in utero will reduce the risk of neonatal death or serious morbidity from prematurity. Such a policy certainly is justified in milder cases. Assessments of fetal well-being and placental function are performed, especially when the fetus is immature. Most recommend frequent performance of nonstress testing or biophysical profiles to assess fetal well-being (American College of Obstetricians and Gynecologists, 2016a). Several tests can be used to provide evidence of lung maturity (Chap. 34, Necrotizing Enterocolitis). An sFlt-1/PlGF ratio <38 is predictive of the short-term absence of preeclampsia, but this ratio testing is still investigational (Zeisler, 2016a,b). Also, women with higher ratios tend to have more adverse outcomes (Baltajian, 2016).

The decision to deliver late-preterm fetuses is less clear. Barton and coworkers (2011) reported excessive neonatal morbidity in women delivered before 38 weeks despite having stable, mild, nonproteinuric hypertension. The Netherlands study of 4316 newborns delivered between $34^{0/7}$ and $36^{6/7}$ weeks also described substantive neonatal morbidity in these cases (Langenveld, 2011). Another Dutch study—HYPITAT-II—randomly assigned women with nonsevere hypertension between 34 and 37 weeks to immediate delivery or to expectant management (Broekhuijsen, 2015). Immediate delivery reduced the risks for adverse maternal outcomes—1.1 versus 3.1 percent. However, it increased the risk for neonatal respiratory distress syndrome—5.7 versus 1.7 percent.

Hospitalization versus Outpatient Management

For women with mild-to-moderate stable hypertension—whether or not preeclampsia has been confirmed—monitoring is continued. During surveillance, reduced physical activity throughout much of the day, at least intuitively, seems beneficial. That said, complete bed rest is not recommended by the 2013 Task Force. First, this is pragmatically unachievable because of the severe restrictions it places on otherwise well women. Also, it likely predisposes to thromboembolism (Knight, 2007). To reduce activity, several studies have addressed the benefits of inpatient care and outpatient management.

The concept of prolonged hospitalization for women with hypertension arose during the 1970s. At Parkland Hospital, an inpatient antepartum unit was established in 1973 by Dr. Peggy Whalley in large part to provide care for such women. Initial results from this unit were reported by Hauth (1976) and Gilstrap (1978) and their coworkers. Most hospitalized women have a beneficial response characterized by amelioration or improvement of hypertension. *These women are not "cured," and nearly 90 percent have recurrent hypertension before or during labor.* By 2016, more than 10,000 nulliparas with mild-to-moderate, early-onset hypertension during pregnancy had been managed successfully in this unit. Provider costs—*not charges*—for this relatively simple physical facility, modest nursing care, no drugs other than iron and folate supplements, and few essential laboratory tests are minimal compared with the cost of neonatal intensive care for a preterm neonate. Importantly, none of these women have suffered thromboembolic disease.

Many clinicians believe that further hospitalization is not warranted if hypertension abates within a few days, and this has legitimized third-party payers to deny hospitalization reimbursement. Consequently, many women with mild-to-moderate hypertension are managed at home. Outpatient management may continue as long as preeclampsia syndrome does not worsen and fetal jeopardy is not suspected. Sedentary activity throughout the greater part of the day is recommended. These women are instructed in detail to report symptoms. Home blood pressure and urine protein monitoring or frequent evaluations by a visiting nurse may prove beneficial.

To assess this approach, 1182 nulliparas with mild gestational hypertension—20 percent had proteinuria—were managed with home health care (Barton, 2002). Their mean gestational ages were 32 to 33 weeks at enrollment and 36 to 37 weeks at delivery. Severe preeclampsia developed in approximately 20 percent, about 3 percent developed HELLP syndrome, and two women had eclampsia. Perinatal outcomes were generally good. In approximately 20 percent, there was fetal-growth restriction, and the perinatal mortality rate was 4.2 per 1000 births.

Several studies have compared continued hospitalization and outpatient care. In a pilot study from Parkland Hospital, 72 nulliparas with new-onset hypertension from 27 to 37 weeks were assigned either to continued hospitalization or to outpatient care (Horsager, 1995). The only significant difference was that women in the home care group developed severe preeclampsia significantly more frequently than hospitalized women—42 versus 25 percent. In another trial, after hospital evaluation, 218 women with mild gestational nonproteinuric hypertension were similarly divided (Crowther, 1992). As shown in Table 40-7, the mean hospital duration was 22.2 days for women with inpatient management compared with only 6.5 days in the home care group. Preterm delivery before 34 and before 37 weeks' gestation was increased twofold in the outpatient group. However, maternal and newborn outcomes were otherwise similar.

TABLE 40-7

Randomized Clinical Trials Comparing Hospitalization versus Routine Care for Women with Mild Gestational Hypertension or Preeclampsia

	Maternal Characteristics—Admission					Maternal Characteristics—Delivery				Perinatal Outcomes		
Study Groups	No.	$Para_0$ (%)	Chronic HTN (%)	EGA (wk)	Prot (%)	EGA (wk)	<37 wk (%)	< 34 wk (%)	Mean Hosp (d)	Mean BW (g)	SGA (%)	PMR (%)
Crowther (1992)	218[a]											
Hospitalization	110	13	14	35.3	0	38.3	12	1.8	22.2	3080	14	0
Outpatient	108	13	17	34.6	0	38.2	22	3.7	6.5	3060	14	0
Tuffnell (1992)	54											
Day Unit	24	57	23	36	0	39.8	—	—	1.1	3320	—	0
Usual Care	30	54	21	36.5	21	39	—	—	5.1	3340	—	0
Turnbull (2004)	374[b]											
Hospitalization	125	63	0	35.9	22	39	—	—	8.5	3330	3.8	0
Day Unit	249	62	0	36.2	22	39.7	—	—	7.2	3300	2.3	0

[a]Excluded women with proteinuria at study entry.

[b]Included women with ≤1+ proteinuria.

BW = birthweight; EGA = estimated gestational age; HTN = hypertension; $Para_0$= nulliparas; PMR = perinatal mortality rate; Prot = proteinuria; SGA = small for gestational age.

Another approach, popular in Europe, is day care (Milne, 2009). In one study, 54 women with hypertension after 26 weeks' gestation were assigned to either day care or routine outpatient management (see Table 40-7) (Tuffnell, 1992). Progression to overt preeclampsia and labor inductions were significantly greater in the routine outpatient management group. In another, 395 women participated in either day care or inpatient management (Turnbull, 2004). Almost 95 percent had mild-to-moderate hypertension. Of enrolled women, 288 lacked proteinuria, and 86 had ≥1+ proteinuria. There were no perinatal deaths, and none of the women developed eclampsia or HELLP syndrome. Costs for either scheme were not significantly different, and general satisfaction favored day care.

In sum, either inpatient or close outpatient management is appropriate for a woman with mild de novo hypertension, including those with nonsevere preeclampsia. Most of these studies were carried out in academic centers with dedicated management teams. That said, the key to success is close surveillance and a conscientious patient with good home support.

Antihypertensive Therapy for Mild-to-Moderate Hypertension

The use of antihypertensive drugs to prolong pregnancy or modify perinatal outcomes in pregnancies complicated by various hypertensive disorders has been of considerable interest. Treatment for women with chronic hypertension complicating pregnancy is discussed in detail in Chapter 50 (Management During Pregnancy).

Drug treatment for early mild preeclampsia has been disappointing (Table 40-8). Sibai and colleagues (1987a) reported that women given labetalol had significantly lower mean blood pressures. However, mean pregnancy prolongation, gestational age at delivery, and birthweight did not differ between groups. The cesarean delivery rate and the number of newborns admitted to special-care nurseries were also similar. *The frequency of growth-restricted neonates was doubled in women given labetalol—19 versus 9 percent.* The three other studies listed in Table 40-8 compared labetalol or the calcium-channel blockers nifedipine and isradipine against placebo. Except for fewer episodes of severe hypertension, none of these studies showed any benefits from antihypertensive treatment (Magee, 2015). Similar conclusions were reached by Abalos and associates (2014), who reviewed 49 randomized trials of active antihypertensive therapy compared with either no treatment or placebo given to women with mild-to-moderate gestational hypertension.

TABLE 40-8

Randomized Placebo-Controlled Trials of Antihypertensive Therapy for Early Mild Gestational Hypertension

Study	Study Drug (No.)	Pregnancy Prolonged (d)	Severe HTN[a] (%)	Cesarean Delivery (%)	Placental Abruption (%)	Mean Birthweight (g)	Growth Restriction (%)	Neonatal Deaths (No.)
Sibai (1987a)[a] 200 inpatients	Labetalol (100)	21.3	5	36	2	2205	19[c]	1
	Placebo (100)	20.1	15[c]	32	0	2260	9	0
Sibai (1992)[b] 200 outpatients	Nifedipine (100)	22.3	9	43	3	2405	8	0
	Placebo (100)	22.5	18[c]	35	2	2510	4	0
Pickles (1992) 144 outpatients	Labetalol (70)	26.6	9	24	NS	NS	NS	NS
	Placebo (74)	23.1	10	26	NS	NS	NS	NS
Wide-Swensson (1995)	Isradipine (54)	23.1	22	26	NS	NS	NS	0
111 outpatients	Placebo (57)	29.8	29	19	NS	NS	NS	0

[a]All women had preeclampsia.

[b]Includes postpartum hypertension.

[c]$p < .05$ when study drug compared with placebo.

HTN = hypertension; NS = not stated.

Delayed Delivery

Up through the early 1990s, the prevailing practice was that women with severe preeclampsia were usually delivered without delay. However, another approach for women with preterm severe preeclampsia has also been advocated. This approach calls for “conservative” or “expectant” management with the aim of improving neonatal outcome without compromising maternal safety. Aspects of such management always include careful daily—and usually more frequent—inpatient monitoring of the mother and her fetus.

Expectant Management of Preterm Severe Preeclampsia

Theoretically, antihypertensive therapy has potential application when severe preeclampsia develops before intact neonatal survival is likely. Such management is controversial, and it may be dangerous. In one of the first studies, Sibai and the Memphis group (1985) attempted to prolong pregnancy because of fetal immaturity in 60 women with severe preeclampsia between 18 and 27 weeks. The results were disastrous. *The perinatal mortality rate was 87 percent. Although no mothers died, 13 suffered placental abruption, 10 had eclampsia, three developed renal failure, two had hypertensive encephalopathy, one had an intracerebral hemorrhage, and another had a ruptured hepatic hematoma.*

Because of their early study, the Memphis group redefined criteria and performed a randomized trial of aggressive versus expectant management for 95 women who had severe preeclampsia but with more advanced gestations of 28 to 32 weeks (Sibai, 1994). *Women with HELLP syndrome were excluded from this trial.* Aggressive management included glucocorticoid administration for fetal lung maturation followed by delivery in 48 hours. Expectantly managed women were observed at bed rest and given either labetalol or nifedipine orally for severe hypertension. In this study, pregnancy was prolonged for a mean of 15.4 days in the expectant management group. An overall improvement in neonatal outcomes was also reported.

Following these experiences, expectant management became more commonly practiced, but with the caveat that women with HELLP syndrome or growth-restricted fetuses were usually excluded. But in a subsequent follow-up observational study, the Memphis group compared outcomes in 133 preeclamptic women with and 136

without HELLP syndrome who presented between 24 and 36 weeks (Abramovici, 1999). Women were subdivided into three study groups. The first group included those with *complete HELLP syndrome*. The second group included women with *partial HELLP syndrome*—defined as either one or two but not all three of the defining laboratory values. The third group included women who had severe preeclampsia without HELLP syndrome. Perinatal outcomes were similar in each group, and importantly, outcomes were not improved with procrastination. Despite this, the investigators concluded that women with partial HELLP syndrome and those with severe preeclampsia alone could be managed expectantly. Those with fetal-growth restriction generally have shorter interval-to-delivery durations (McKinney, 2016).

Sibai and Barton (2007b) reviewed expectant management of severe preeclampsia from 24 to 34 weeks. More than 1200 women were included, and although the average time gained ranged from 5 to 10 days, the maternal morbidity rates were formidable. Serious complications in some of these and in later studies included placental abruption, HELLP syndrome, pulmonary edema, renal failure, and eclampsia (Table 40-9). Moreover, perinatal mortality rates averaged 90 per 1000 births. Fetal-growth restriction was common, and in the studies from The Netherlands, it was an astounding 94 percent (Ganzevoort, 2005a,b). Perinatal mortality rates are disproportionately high in these growth-restricted neonates, but maternal outcomes are not appreciably different (Haddad, 2007; Shear, 2005). The MEXPRE Latin Study was a multicenter trial that randomly assigned 267 women with severe preeclampsia at 28 to 32 weeks to prompt delivery or to expectant management (Vigil-De Gracia, 2013). The perinatal mortality rate approximated 9 percent in each group, the composite neonatal morbidity outcome was not improved with expectant management. On the other hand, fetal-growth restriction—22 versus 9 percent—and placental abruption—7.6 versus 1.5 percent—were significantly higher in the group managed expectantly.

TABLE 40-9

Maternal and Perinatal Outcomes Reported since 2005 with Expectant Management of Severe Preeclampsia from 24 to 34 Weeks

			Maternal Outcomes (%)					Perinatal Outcomes (%)	
Study	**No.**	**Days Gained**	**Placental Abruption**	**HELLP**	**Pulm. Edema**	**AKI**	**Eclampsia**	**FGR**	**PMR**
Oettle (2005)	131[a]	11.6	23	4.6	0.8	2.3	2.3	NS	13.8
Shear (2005)	155	5.3	5.8	27	3.9	NS	1.9	62	3.9
Ganzevoort (2005a, b)	216	11	1.8	18	3.6	NS	1.8	94	18
Bombrys (2009)	66	5	11	8	9	3	0	27	1.5
Abdel-Hady (2010)	211	12	3.3	7.6	0.9	6.6	0.9	NS	48
Vigil-De Gracia (2013)	131	10.3	7.6	14	1.5	4.5	0.8	22	8.7
Range	910	5–12	1.8–23	4.6–27	0.9–3.9	2.3–6.6	0.9–18	27–94	1.5–48

[a]Includes one maternal death.

AKI = acute kidney injury; EGA = estimated gestational age; FGR = fetal-growth restriction; HELLP = hemolysis, elevated liver enzyme levels, low platelet count syndrome; NS = not stated; PMR = perinatal mortality rate; Pulm. = pulmonary.

Expectant Management of Midtrimester Severe Preeclampsia

Several small studies have focused on expectant management of severe preeclampsia syndrome *before 28 weeks*. In their review, Bombrys and coworkers (2008) found eight such studies that included nearly 200 women with severe preeclampsia with an onset <26 completed weeks. Maternal complications were common. Because no neonates survived when delivered before 23 weeks, the Task Force (2013) recommends pregnancy termination in these cases. For women with slightly more advanced pregnancies, however, the decision is less clear. For example, at 23 weeks' gestation, the perinatal survival rate was 18 percent, but long-term perinatal morbidity is yet unknown. For women with pregnancies at 24 to 26 weeks, perinatal survival approached 60 percent, and it averaged almost 90 percent for those at 26 weeks.

At least five observational studies of women with severe midtrimester preeclampsia who were managed expectantly have been published since 2005 (Abdel-Hady, 2010; Belghiti, 2011; Bombrys, 2008; Budden, 2006; Gaugler-Senden, 2006). Maternal complications developed in 60 percent, and there was one maternal death. The perinatal mortality rate was 650 per 1000 births. At this time, no comparative studies attest to perinatal benefits of such expectant treatment versus early delivery in the face of serious maternal complications, which approach rates of 50 percent. We do not recommend such management.

Glucocorticoids for Lung Maturation

To enhance fetal lung maturation, glucocorticoids have been administered to women with severe hypertension who are remote from term. Treatment does not seem to worsen maternal hypertension, and a lower incidence of respiratory distress and improved fetal survival rates have been cited. That said, only one randomized trial has evaluated corticosteroids given to hypertensive women for fetal lung maturation. This trial included 218 women with severe preeclampsia between 26 and 34 weeks' gestation who were randomly assigned to betamethasone or placebo administration (Amorim, 1999). Rates of neonatal complications that included respiratory distress, intraventricular hemorrhage, and death were reduced significantly when betamethasone was given compared with placebo. *On the heavily*

weighted negative side, there were two maternal deaths and 18 stillbirths. We add these findings to buttress our unenthusiastic acceptance of attempts to prolong gestation in many of these women (Alexander, 2015; Bloom, 2003).

Expectant Management Recommendations

Taken in toto, these studies do not show overwhelming benefits compared with maternal risks for expectant management of severe preeclampsia in women with gestations from 24 to 32 weeks. Despite these caveats, the Society for Maternal-Fetal Medicine (2011) has determined that such management is a reasonable alternative in selected women with severe preeclampsia before 34 weeks (Fig. 40-14). The Task Force (2013) supports this recommendation. As shown in Table 40-10, such management calls for in-hospital maternal and fetal surveillance with delivery prompted by evidence for worsening severe preeclampsia or maternal or fetal compromise. Although attempts are made for vaginal delivery in most cases, the likelihood of cesarean delivery rises with decreasing gestational age.

FIGURE 40-14

Clinical management algorithm for severe preeclampsia at <34 weeks. HELLP = hemolysis, elevated liver enzyme levels, low platelet count; L&D = labor and delivery; $MgSO_4$= magnesium sulfate; UOP = urine output. (Adapted from the Society for Maternal-Fetal Medicine, 2011.)

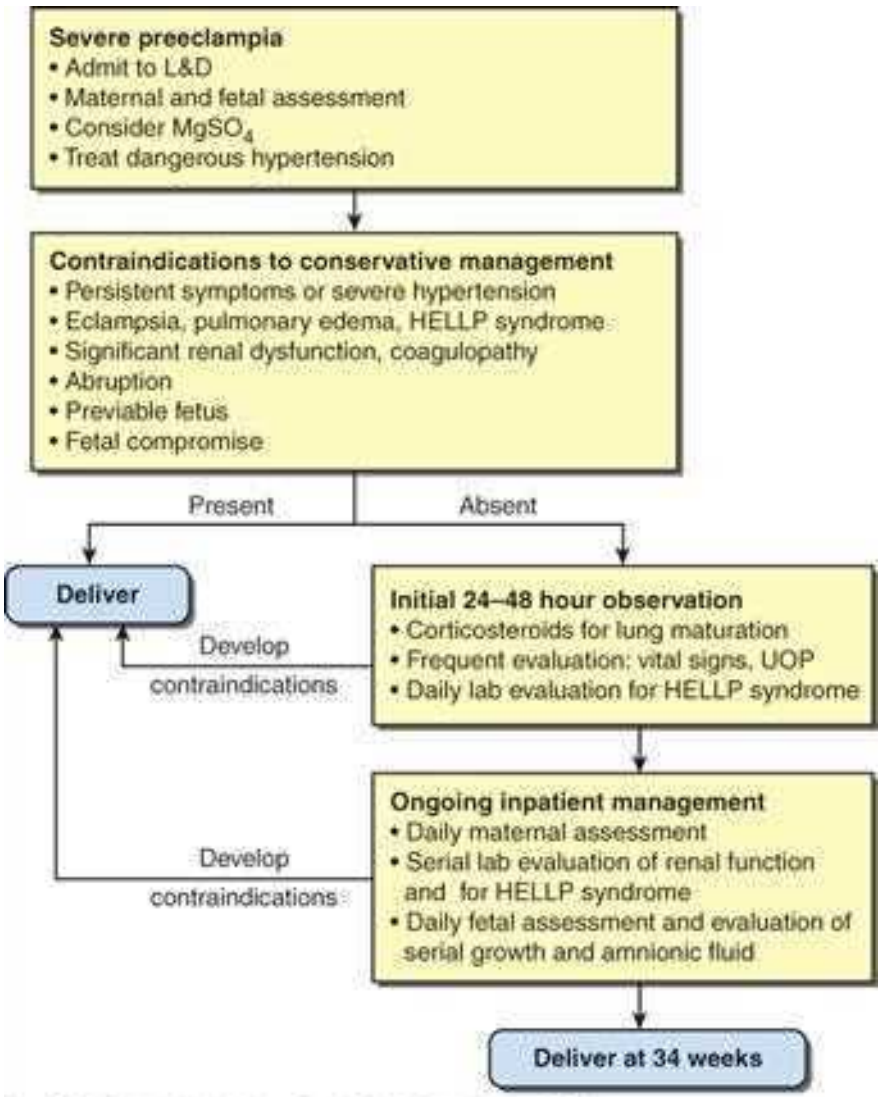


TABLE 40-10

Indications for Delivery in Women <34 Weeks' Gestation Managed Expectantly

Corticosteroid Therapy for Lung Maturation[a] and Delivery after Maternal Stabilization:
Uncontrolled severe hypertension
Eclampsia
Pulmonary edema
Placental abruption
Disseminated intravascular coagulation
Nonreassuring fetal status
Fetal demise
Corticosteroid Therapy for Lung Maturation—Delay Delivery 48 hr If Possible:
Preterm ruptured membranes or labor
Thrombocytopenia <100,000/μL
Hepatic transaminase levels twice upper limit of normal
Fetal-growth restriction
Oligohydramnios
Reversed end-diastolic Doppler flow in umbilical artery
Worsening renal dysfunction

[a]Initial dose only, do not delay delivery.

From the Society for Maternal-Fetal Medicine, 2011, and the Task Force of the American College of Obstetricians and Gynecologists, 2013.

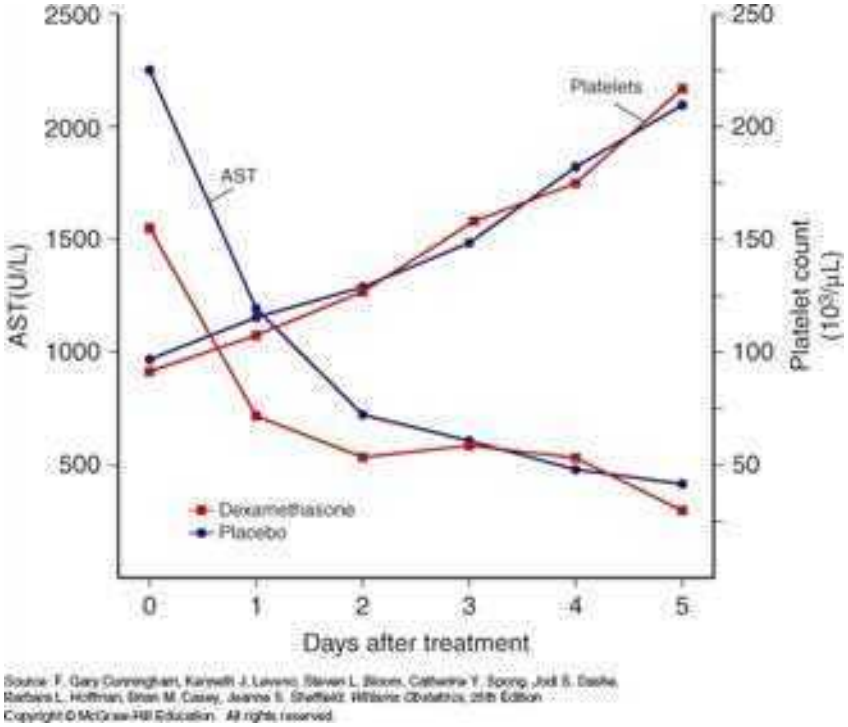
Our view is more conservative. Undoubtedly, the overriding reason to terminate pregnancies with severe preeclampsia is maternal safety. Indeed, it seems obvious that a delay to prolong gestation in women with severe preeclampsia may have serious maternal consequences (see Table 40-9). These observations are even more pertinent when considered with the absence of convincing evidence that perinatal outcomes are markedly improved by the average prolongation of pregnancy by approximately 1 week. If undertaken, the caveats that mandate delivery shown in Table 40-10 should be strictly heeded.

Corticosteroids to Ameliorate HELLP Syndrome

At least three randomized trials have evaluated the benefits of glucocorticoids given to improve the laboratory abnormalities associated with HELLP syndrome. First, Fonseca and associates (2005) randomly assigned 132 women with HELLP syndrome to either dexamethasone or placebo administration. Outcomes assessed included hospitalization length, recovery time of abnormal laboratory test results, resolution of clinical parameters, and complications that included acute renal failure, pulmonary edema, eclampsia, and death. None of these was significantly different between the two groups. In another study, 105 postpartum women with HELLP syndrome were assigned to dexamethasone or placebo treatment (Katz, 2008). Outcomes were analyzed similarly to the Fonseca study, and no advantage to dexamethasone was found (Fig. 40-15). In the third study, preeclamptic women were given either placebo or methylprednisolone if their platelet count was between 50,000 and 150,000/μL (Pourrat, 2016). No benefits were gained from corticosteroid therapy. Because of these findings, the 2013 Task Force does not recommend corticosteroid treatment for thrombocytopenia with HELLP syndrome.

FIGURE 40-15

Recovery times for platelet counts and serum aspartate transaminase (AST) levels in women with HELLP syndrome assigned to receive treatment with dexamethasone or placebo. (Data from Katz, 2008.)



Experimental Therapies

In several preliminary studies, therapies have attempted to lower serum levels or mitigate the action of antiangiogenic factors. Some of these include *therapeutic apheresis*, done to lower sFlt-1 levels (Thadhani, 2016). *Pravastatin* has been given for preeclampsia prevention (Cleary, 2014). *Sildenafil citrate*, a phosphodiesterase inhibitor, has been provided to promote vasodilation (Trapani, 2016; Vigil-De Gracia, 2016). In a recent randomized trial of 120 women with early-onset preeclampsia, an *recombinant antithrombin infusion* compared with saline afforded the same interval-to-delivery timing (Sibai, 2017).

ECLAMPSIA

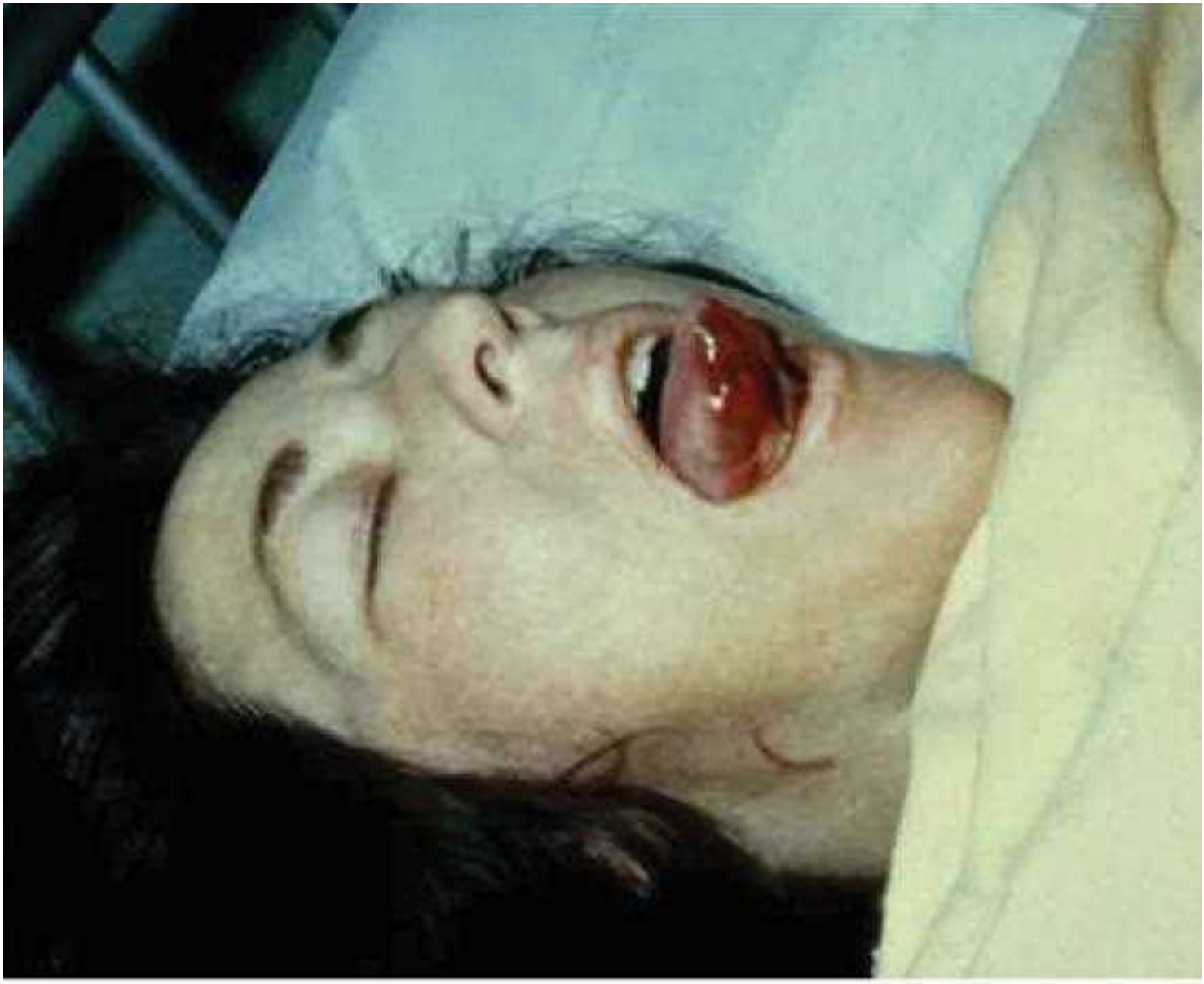
Preeclampsia complicated by generalized tonic-clonic convulsions appreciably raises the risk to both mother and fetus. In an earlier report, Mattar and Sibai (2000) described outcomes in 399 consecutive women with eclampsia from 1977 through 1998. Major maternal complications included placental abruption—10 percent, neurological deficits—7 percent, aspiration pneumonia—7 percent, pulmonary edema—5 percent, cardiopulmonary arrest—4 percent, and acute renal failure— 4 percent. Moreover, 1 percent of these women died. Several subsequent reports similarly described excessive maternal morbidity and mortality rates with eclampsia that also included HELLP syndrome, pulmonary embolism, and stroke (Andersgaard, 2006; Knight, 2007). In The Netherlands, there were three maternal deaths among 222 eclamptic women (Zwart, 2008). Data from Ireland and Australia are similar (O'Connor, 2013; Thornton, 2013). In perspective, this is a thousand-fold increase above the overall maternal death rates for these countries.

Almost without exception—but at times unnoticed—preeclampsia precedes the convulsion onset. Eclampsia is most common in the last trimester and becomes increasingly frequent as term approaches. In more recent years, the incidence of postpartum eclampsia has declined. This is presumably related to improved access to prenatal care, earlier detection of antepartum preeclampsia, and prophylactic use of magnesium sulfate (Chames, 2002). Importantly, other diagnoses should be considered in women with convulsions more than 48 hours postpartum or in women with focal neurological deficits, prolonged coma, or atypical eclampsia (Sibai, 2012).

Clinical Findings with Eclampsia

Eclamptic seizures may be violent, and the woman must be protected, especially her airway. So forceful are the muscular movements that the woman may throw herself out of her bed, and if not protected, her tongue is bitten by the violent action of the jaws (Fig. 40-16). This phase, in which the muscles alternately contract and relax, may last approximately a minute. Gradually, the muscular movements become smaller and less frequent, and finally the woman lies motionless.

FIGURE 40-16
Hematoma of tongue from laceration during an eclamptic convulsion. Thrombocytopenia may have contributed to the bleeding.

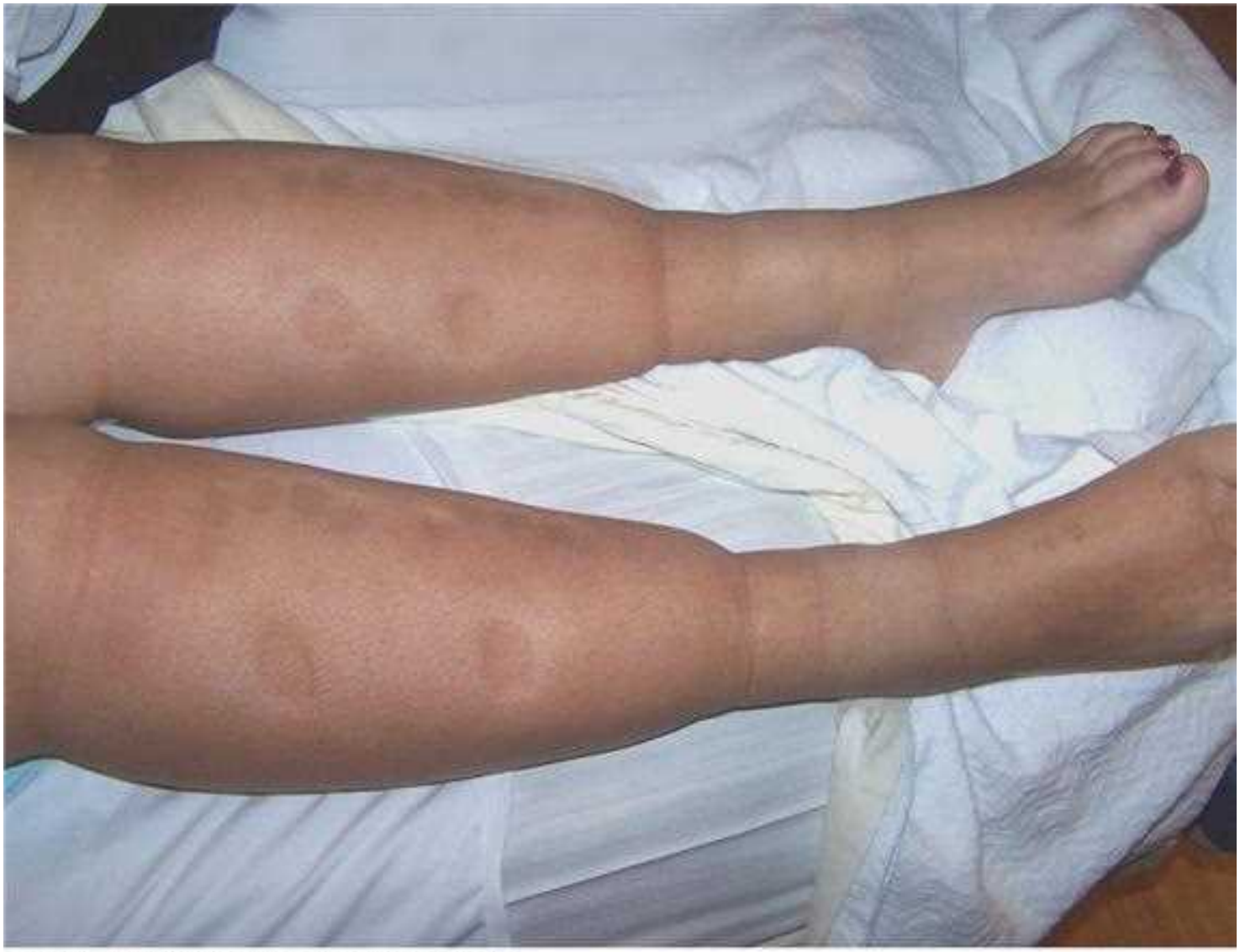


After a seizure, the woman is postictal, but in some, a coma of variable duration ensues. When the convulsions are infrequent, the woman usually recovers some degree of consciousness after each attack. As the woman arouses, a semiconscious combative state may ensue. In severe cases, coma persists from one convulsion to another, and death may result. In rare instances, a single convulsion may be followed by coma from which the woman may never emerge. As a rule, however, death does not occur until after frequent convulsions. Finally and also rarely, convulsions continue unabated—*status epilepticus*—and require deep sedation and even general anesthesia to obviate anoxic encephalopathy.

The respiratory rate after an eclamptic convulsion is usually increased and may reach 50 or more per minute in response to hypercarbia, lactic acidemia, and transient hypoxia. Cyanosis may be observed in severe cases. High fever is a grave sign as it likely emanates from cerebrovascular hemorrhage.

Proteinuria is usually, but not always, present as discussed earlier (Kidney). Urine output may be diminished appreciably, and occasionally anuria develops. There may be hemoglobinuria, but hemoglobinemia is rare. Often, facial and peripheral edema is pronounced, but it may be absent (Fig. 40-17).

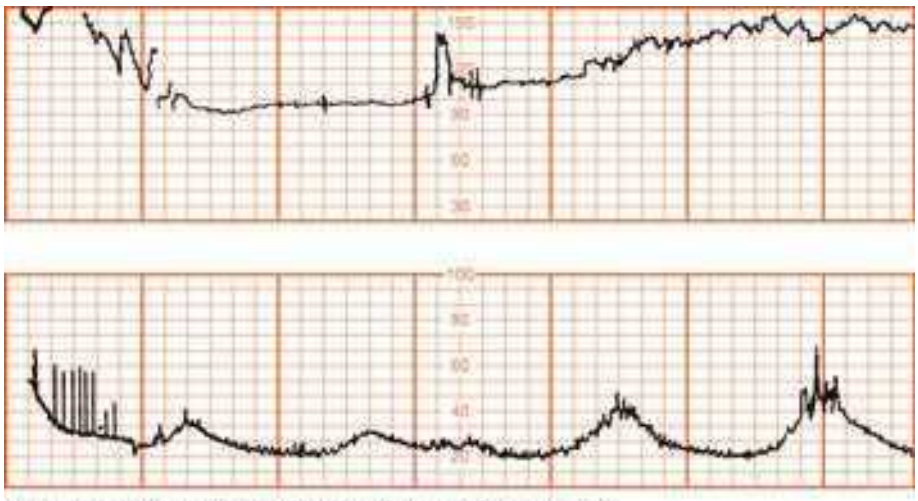
FIGURE 40-17
Severe edema in a young nullipara with antepartum preeclampsia. (Used with permission from Dr. Nidhi Shah.)



As with severe preeclampsia, urinary output rises after delivery and is usually an early sign of improvement. With renal dysfunction, serum creatinine levels are serially monitored. Proteinuria and edema ordinarily disappear within a week postpartum. In most cases, blood pressure returns to normal within a few days to 2 weeks after delivery (Berks, 2009). As subsequently discussed, persisting and severe hypertension likely predicts underlying chronic vascular disease (Podymow, 2010).

In antepartum eclampsia, labor may begin spontaneously shortly after convulsions ensue and may progress rapidly. If the convulsions occur during labor, contractions may increase in frequency and intensity, and the duration of labor may be shortened. Because of maternal hypoxemia and lactic acidemia caused by convulsions, fetal bradycardia often follows a seizure (Fig. 40-18). The fetal heart rate usually recovers within 2 to 10 minutes (Ambia, 2018). If it persists more than about 10 minutes, another cause of bradycardia, such as placental abruption or imminent delivery, should be considered.

FIGURE 40-18
Fetal heart rate tracing shows fetal bradycardia following an intrapartum eclamptic convulsion. Bradycardia resolved and beat-to-beat variability returned approximately 5 minutes following the seizure.



Pulmonary edema may follow shortly after eclamptic convulsions or up to several hours later. This usually is caused by aspiration pneumonitis from gastric-content inhalation during vomiting that frequently accompanies convulsions. In some women, pulmonary edema may be caused by ventricular failure from increased afterload that results from severe hypertension. Both pulmonary edema and hypertension can be further aggravated by vigorous intravenous fluid administration (Dennis, 2012b). Such pulmonary edema from ventricular failure is more common in morbidly obese women and in those with previously unappreciated chronic hypertension.

Occasionally, sudden death occurs synchronously with an eclamptic convulsion, or it follows shortly thereafter. Most often in these cases, a massive cerebral hemorrhage is the cause (see Fig. 40-10). Hemiplegia may result from sublethal hemorrhage. Cerebral hemorrhages are more likely in older women with underlying chronic hypertension.

In approximately 10 percent of eclamptic women, some degree of blindness follows a seizure. The causes of blindness or impaired vision were discussed earlier (Uteroplacental Perfusion). Blindness with severe preeclampsia without convulsions usually stems from retinal detachment (Vigil-De Gracia, 2011). Conversely, blindness with eclampsia is typically due to occipital lobe edema (Cunningham, 1995). In both instances, however, the prognosis for return to normal function is good and is usually complete within 1 to 2 weeks postpartum.

Up to 5 percent of women with eclampsia have substantively altered consciousness, including persistent coma, following a seizure. This is due to extensive cerebral edema, and associated transtentorial herniation may cause death (Cerebrovascular Pathophysiology).

Rarely, eclampsia is followed by psychosis, and the woman becomes violent. This may last for several days to 2 weeks. The prognosis for return to normal function is good, provided there was no preexisting mental illness. It is presumed to be similar to postpartum psychosis discussed in Chapter 61 (Anxiety Disorders). Antipsychotic medications have proven effective in the few cases of posteclampsia psychosis treated at Parkland Hospital.

Generally, eclampsia is more likely to be diagnosed too frequently rather than overlooked. Epilepsy, encephalitis, meningitis, brain tumor, neurocysticercosis, amnionic fluid embolism, postdural puncture cephalalgia, and ruptured cerebral aneurysm during late pregnancy or in the puerperium may simulate eclampsia. Until other such causes are excluded, however, all pregnant women with convulsions should be considered to have eclampsia.

Management of Eclampsia

Magnesium sulfate is highly effective to prevent convulsions in women with preeclampsia and to stop them in those with eclampsia. In his review, Chesley (1978) cited observational data by Pritchard and colleagues (1955, 1975) from Parkland Hospital and from his own institution. At that time, most eclampsia regimens in the United States adhered to a similar philosophy, and it is still in use today:

1. Control of convulsions using an intravenously administered loading dose of magnesium sulfate that is followed by a maintenance dose, usually intravenous, of magnesium sulfate
2. Intermittent administration of an antihypertensive medication to lower blood pressure whenever it is considered dangerously high
3. Avoidance of diuretics unless pulmonary edema is obvious, limitation of intravenous fluid administration unless fluid loss is excessive, and avoidance of hyperosmotic agents
4. Delivery of the fetus to resolve preeclampsia.

Magnesium Sulfate to Control Convulsions

Magnesium sulfate administered parenterally is an effective anticonvulsant that avoids producing central nervous system depression. It may be given intravenously by continuous infusion or intramuscularly by intermittent injection (Table 40-11). The dosages for severe preeclampsia are the same as for eclampsia. Because labor and delivery is a more likely time for convulsions to develop, women with preeclampsia-eclampsia usually are given magnesium sulfate during labor and for 24 hours postpartum.

TABLE 40-11

Magnesium Sulfate Dosage Schedule for Severe Preeclampsia and Eclampsia

Continuous Intravenous (IV) Infusion
Give 4- to 6-g loading dose of magnesium sulfate diluted in 100 mL of IV fluid administered over 15–20 min Begin 2 g/hr in 100 mL of IV maintenance infusion. Some recommend 1 g/hr Monitor for magnesium toxicity: Assess deep tendon reflexes periodically Some measure serum magnesium level at 4–6 hr and adjust infusion to maintain levels between 4 and 7 mEq/L (4.8 to 8.4 mg/dL) Measure serum magnesium levels if serum creatinine ≥1.0 mg/dL Magnesium sulfate is discontinued 24 hr after delivery
Intermittent Intramuscular Injections
Give 4 g of magnesium sulfate ($MgSO_4 \cdot 7H_2O$ USP) as a 20% solution intravenously at a rate not to exceed 1 g/min Follow promptly with 10 g of 50% magnesium sulfate solution, one half (5 g) injected deeply in the upper outer quadrant of each buttock through a 3-inch-long 20-gauge needle. (Addition of 1.0 mL of 2% lidocaine minimizes discomfort.) If convulsions persist after 15 min, give up to 2 g more intravenously as a 20% solution at a rate not to exceed 1 g/min. If the woman is large, up to 4 g may be given slowly. Every 4 hr thereafter, give 5 g of a 50% solution of magnesium sulfate injected deeply in the upper outer quadrant of alternate buttocks, but only after ensuring that: The patellar reflex is present, Respirations are not depressed, and Urine output the previous 4 hr exceeded 100 mL Magnesium sulfate is discontinued 24 hr after delivery

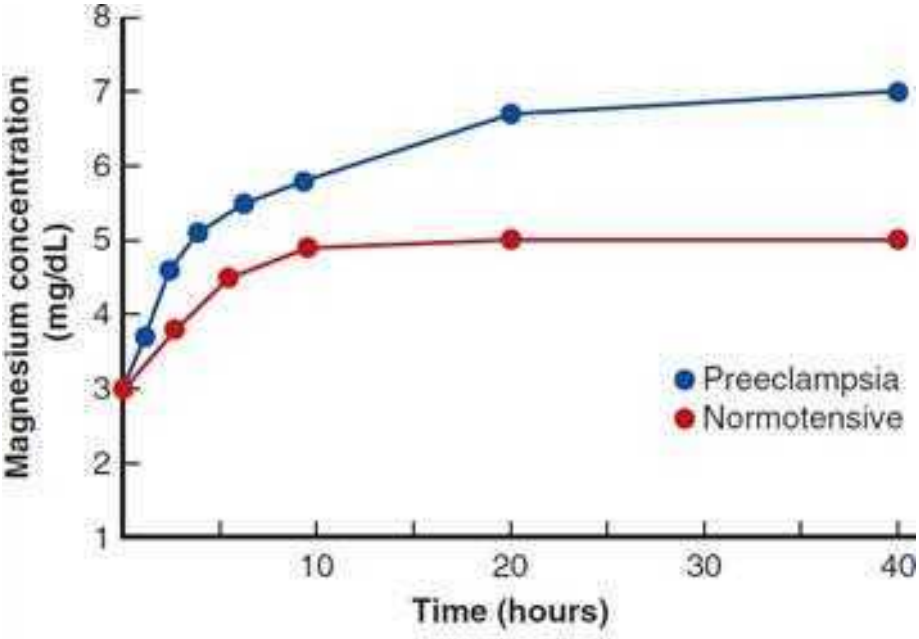
In the United States, magnesium sulfate is almost universally administered intravenously. Of concern, magnesium sulfate solutions, although inexpensive to prepare, are not readily available in all parts of the developing world. And even when the solutions are available, the technology to infuse them may not be. Therefore, it should not be overlooked that the drug can be administered intramuscularly and that this route is as effective as intravenous administration (Salinger, 2013). In two reports from India, intramuscular regimens were nearly equivalent in preventing recurrent convulsions and maternal deaths in women with eclampsia (Chowdhury, 2009; Jana, 2013). These observations comport with earlier ones from Parkland Hospital (Pritchard, 1975, 1984).

Magnesium sulfate is not given to treat hypertension. Magnesium most likely exerts a specific anticonvulsant action on the cerebral cortex. Typically, the mother stops convulsing after the initial 4-g loading dose. By an hour or two, she regains consciousness sufficiently to be oriented to place and time.

The magnesium sulfate dosage regimens presented in Table 40-11 usually result in plasma magnesium levels illustrated in Figure 40-19. When magnesium sulfate is given to arrest eclamptic seizures, 10 to 15 percent of women will have a subsequent convulsion. If so, an additional 2-g dose of magnesium sulfate in a 20-percent solution is slowly administered intravenously. In a small woman, this additional 2-g dose may be used once, but it can be given twice if needed in a larger woman. In only 5 of 245 women with eclampsia at Parkland Hospital was it necessary to use alternative supplementary anticonvulsant medication to control convulsions (Pritchard, 1984). For these, an intravenous barbiturate is given slowly. Midazolam or lorazepam may also be given in a small single dose, but prolonged use is avoided because it is associated with a higher mortality rate from aspiration pneumonia (Royal College of Obstetricians and Gynaecologists, 2006).

FIGURE 40-19

Serum magnesium concentration in normotensive and preeclamptic women following a 4-g loading dose of magnesium sulfate and 2 g/h infusion. (Data from Brookfield, 2016.)



Maintenance magnesium sulfate therapy has traditionally been continued for 24 hours after delivery. For eclampsia that develops postpartum, magnesium sulfate is administered for 24 hours after the onset of convulsions. A few investigators have truncated this therapy duration to 12 hours and found no seizures (Anjum, 2016; Ehrenberg, 2006; Kashanian, 2016). And more recently, Ludmir and colleagues (2017) described salutary outcomes when magnesium sulfate therapy was stopped after delivery. That said, these studies are small, and the abbreviated magnesium regimen needs further study before being routinely implemented.

Pharmacology and Toxicology

Using United States Pharmacopeia (USP) standards, magnesium sulfate USP is $MgSO_4 \cdot 7H_2O$, and it contains 8.12 mEq magnesium per 1 g. Parenterally administered magnesium is cleared almost totally by renal excretion, and magnesium intoxication is unusual when the glomerular filtration rate is normal or only slightly reduced. Adequate urine output *usually* correlates with preserved glomerular filtration rates. That said, magnesium excretion is not urine flow dependent, and urinary volume per unit time does not, per se, predict renal function. *Thus, serum creatinine levels must be measured to detect a decreased glomerular filtration rate.*

Eclamptic convulsions are almost always prevented or arrested by plasma magnesium levels maintained at 4 to 7 mEq/L, 4.8 to 8.4 mg/dL, or 2.0 to 3.5 mmol/L. But, one review of magnesium pharmacokinetics showed that most regimens result in much lower serum magnesium levels (Okusanya, 2016). This was especially true if only 1 g/hr was infused (Yefet, 2017). Importantly, the obesity epidemic has affected these observations (Cunningham, 2016). Tudela and colleagues (2013) described our observations from Parkland Hospital with magnesium administration to obese women. More than 60 percent of women whose body mass index (BMI) exceeded 30 kg/m^2 and who were receiving the 2 g/hr dose had subtherapeutic levels at 4 hours. Thus, obese women would require 3 g/hr to maintain effective plasma levels. That said, most currently do not recommend routine magnesium level measurements (American College of Obstetricians and Gynecologists, 2013; Royal College of Obstetricians and Gynaecologists, 2006).

Patellar reflexes disappear when the plasma magnesium level reaches 10 mEq/L—about 12 mg/dL—presumably because of a curariform action. This sign serves to warn of impending magnesium toxicity. When plasma levels rise above 10 mEq/L, breathing becomes weakened. At 12 mEq/L or higher levels, respiratory paralysis and respiratory arrest follow (Somjen, 1966). *Treatment with calcium gluconate or calcium chloride, 1 g intravenously, along with discontinuation of further magnesium sulfate, usually reverses mild-to-moderate respiratory depression.* One of these agents should be readily available whenever magnesium is being infused. Unfortunately, the effects of intravenously administered calcium may be short-lived if there is a steady-state toxic level. For severe respiratory depression and arrest, prompt tracheal intubation and mechanical ventilation are lifesaving. Direct toxic effects on the myocardium from high levels of magnesium are uncommon (McCubbin, 1981; Morisaki, 2000).

Because magnesium is cleared almost exclusively by renal excretion, the dosages described will become excessive if glomerular filtration is substantially decreased. The initial 4-g loading dose of magnesium sulfate can be safely administered regardless of renal function. It is important to administer the standard loading dose and not to reduce it under the mistaken conception that diminished renal function requires it. This is because after distribution, a loading dose *achieves* the desired therapeutic level, and the infusion *maintains* the steady-state level. *Thus, only the maintenance infusion rate should be altered with diminished glomerular filtration rate.* Renal function is estimated by measuring plasma creatinine. Whenever plasma creatinine levels are >1.0 mg/mL, serum magnesium levels are determined to guide the infusion rate.

After a 4-g intravenous dose administered over 15 minutes, mean arterial pressure falls slightly, accompanied by a 13-percent rise in cardiac index (Cotton, 1986b). Thus, magnesium lowers systemic vascular resistance and mean arterial pressure. At the same time, cardiac output is increased. These findings are coincidental with transient nausea and flushing, and the cardiovascular effects persist for only 15 minutes despite continued magnesium infusion.

Thurnau and associates (1987) showed that magnesium therapy led to a small but significant rise in the total magnesium concentration in the cerebrospinal fluid. The magnitude of the elevation was directly proportional to the corresponding serum concentration.

Other Effects

Magnesium has anticonvulsant and neuroprotective effects in several animal models. Some proposed mechanisms of action include: (1) reduced presynaptic release of the neurotransmitter glutamate, (2) blockade of glutamatergic *N*-methyl-d-aspartate (NMDA) receptors, (3) potentiation of adenosine action, (4) improved calcium buffering by mitochondria, and (5) blockage of calcium entry via voltage-gated channels (Arango, 2008; Wang, 2012).

In the uterus, relatively high serum magnesium concentrations depress myometrial contractility both in vivo and in vitro. With the suggested regimen, myometrial depression has not been observed, except for a transient decline in activity during and immediately after the initial intravenous loading dose (Leveno, 1998; Szal, 1999; Witlin, 1997). Blood loss at delivery is not increased by standard magnesium treatment (Graham, 2016). However, inhibition of uterine contractility is magnesium dose dependent, and serum levels of at least 8 to 10 mEq/L are necessary to inhibit uterine contractions (Watt-Morse, 1995).

Fetal and Neonatal Effects

Magnesium administered parenterally promptly crosses the placenta to achieve equilibrium in fetal serum and less so in amnionic fluid (Hallak, 1993). Levels in amnionic fluid rise with the duration of maternal infusion (Gortzak-Uzan, 2005). Magnesium sulfate has small but significant effects on the fetal heart rate pattern—specifically beat-to-beat variability (Hallak, 1999). Duffy and associates (2012) reported a lower heart rate baseline that was within the normal range; decreased variability; and fewer prolonged decelerations. They noted no adverse outcomes.

Overall, maternal magnesium therapy appears safe for perinates (Drassinower, 2015). One MFMU Network study of more than 1500 exposed preterm neonates found no association between the need for neonatal resuscitation and cord blood magnesium levels (Johnson, 2012). Still, a few neonatal adverse events are associated with its use. In a Parkland Hospital study of 6654 mostly term, exposed newborns, 6 percent had hypotonia (Abbassi-Ghanavati, 2012). In addition, exposed neonates had lower 1- and 5-minute Apgar scores, a higher intubation rate, and more admissions to the special care nursery. The study showed that neonatal depression occurs only if hypermagnesemia at delivery is severe.

Observational studies suggest a protective effect of magnesium against the development of cerebral palsy in very-low-birthweight newborns (Nelson, 1995; Schendel, 1996). At least five randomized trials have also assessed neuroprotective effects in preterm neonates. These findings are discussed in detail in Chapter 42 (Magnesium Sulfate for Neuroprotection). Nguyen and colleagues (2013) expanded this possibility to include term newborn neuroprotection, but data were insufficient to draw conclusions.

Last, in cases of preterm labor, magnesium has been given for several days for tocolysis (Chap. 42, β-Adrenergic Receptor Agonists). Administration in these instances has been associated with neonatal osteopenia (American College of Obstetricians and Gynecologists, 2016c).

Maternal Safety and Efficacy

The multinational Eclampsia Trial Collaborative Group study (1995) involved 1687 women with eclampsia randomly allocated to one of three different anticonvulsant regimens: magnesium sulfate, diazepam, or phenytoin (Table 40-12). In aggregate, magnesium sulfate therapy was associated with a significantly lower incidence of recurrent seizures (9.7 percent) compared with women given phenytoin (28 percent) or diazepam (17 percent). Importantly, the aggregate maternal death rate of 3.2 percent with magnesium sulfate was significantly lower than that of 5.2 percent for the other two regimens.

TABLE 40-12

Randomized Comparative Trials of Magnesium Sulfate Versus Phenytoin and Diazepam to Prevent Recurrent Eclamptic Convulsions

	Magnesium Sulfate	Phenytoin	Diazepam
Recurrent seizures[a]	60/453 (13%)	126/452 (28%)	—
	22/388 (5.6%)	—	66/389 (17%)
Maternal deaths[b]	10/388 (2.6%)	20/387 (5.2%)	—
	17/453 (3.8%)	—	24/452 (5.3%)

[a]All comparisons $p < 0.01$.

[b]Individual comparisons nonsignificant, combined comparison $p < .05$.

Data from Eclampsia Trial Collaborative Group, 1995.

In their review of more than 9500 treated women, Smith and coworkers (2013) reported the overall rate of absent patellar tendon reflexes to be 1.6 percent; respiratory depression, 1.3 percent; and calcium gluconate administration, 0.2 percent. Only one mother died due to magnesium toxicity. Our experiences are similar. In the more than 60 years of magnesium use at Parkland Hospital, only one woman has died from an overdose (Pritchard, 1984).

MANAGEMENT CONSIDERATIONS

Severe Hypertension Management

Dangerous hypertension can cause cerebrovascular hemorrhage and hypertensive encephalopathy, and it can trigger eclamptic convulsions in women with preeclampsia. Other complications include placental abruption and congestive heart failure induced by elevated hypertensive afterload.

Because of these serious sequelae, the working group for the National High Blood Pressure Education Program (NHBPEP)(2000) and the 2013 Task Force recommend treatment to lower systolic pressures to or below 160 mm Hg and diastolic pressures to or below 110 mm Hg. Martin and associates (2005, 2016) reported provocative observations that highlight the importance of treating systolic hypertension. They described 28 selected women with severe preeclampsia who suffered an associated stroke. Most (93 percent) were hemorrhagic strokes, and all women had systolic pressures >160 mm Hg before suffering their stroke. By contrast, only 20 percent of these same women had diastolic pressures >110 mm Hg.

From other observations, it seems likely that at least half of serious hemorrhagic strokes associated with preeclampsia are in women with chronic hypertension (Cunningham, 2005). Long-standing hypertension results in development of *Charcot-Bouchard aneurysms* in the deep penetrating arteries of the lenticulostriate branch of the middle cerebral arteries. These vessels supply the basal ganglia, putamen, thalamus, and adjacent deep white matter, as well as the pons and deep cerebellum. These unique aneurysmal weakenings predispose these small arteries to rupture during sudden hypertensive episodes.

Several drugs are available to rapidly lower dangerously elevated blood pressure in women with pregnancy-associated hypertension. The three most commonly employed are hydralazine, labetalol, and nifedipine. For years, parenteral hydralazine was the only one of these three available. But when parenteral labetalol was later introduced, it was proven to be equally effective for obstetrical use. Orally administered nifedipine has since also gained popularity. All three of these are recommended as first-line agents by the American College of Obstetricians and Gynecologists (2017a).

Hydralazine

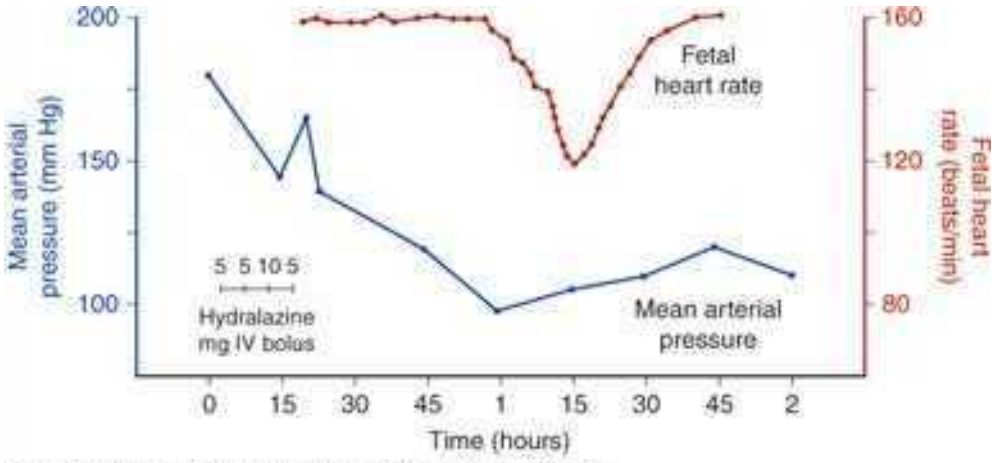
This is probably still the most commonly used antihypertensive agent in the United States for treatment of women with severe gestational hypertension. Hydralazine is administered intravenously with a 5- to 10-mg initial dose, and this is followed by 10-mg doses at 15- to 20-minute intervals until a satisfactory response is achieved. Although we will administer a third dose, the American College of Obstetricians and Gynecologists (2017a) recommends labetalol therapy if severe hypertension persists after the second dose. Antepartum or intrapartum, the target response is a decline in systolic pressure to <160 mm Hg and diastolic blood pressure to 90 to 110 mm Hg. Lower diastolic pressures risk compromised placental perfusion. Hydralazine has proven remarkably effective to prevent cerebral hemorrhage. Its onset of action can be as rapid as 10 minutes. Although repeated administration every 15 to 20 minutes may theoretically lead to undesirable hypotension, this has not been our experience when given in these 5- to 10-mg increments.

At Parkland Hospital, between 5 and 10 percent of all women with intrapartum hypertensive disorders are given a parenteral antihypertensive agent. Antepartum, we usually give hydralazine as described. We do not limit the total dose, and seldom is a second antihypertensive agent needed. We estimate that nearly 6000 women have been so treated at our facility during the past 50 years. Although less popular in Europe, hydralazine is used in some centers according to the Royal College of Obstetricians and Gynaecologists (2006).

For higher blood pressures, there is a tendency to give a larger initial dose of hydralazine. But, this must be avoided. The response to even 5- to 10-mg doses cannot be predicted by hypertension severity. Thus, our protocol is to always administer 5 mg as the initial dose. An adverse response to exceeding this initial dose is shown in Figure 40-20. This woman had chronic hypertension complicated by severe superimposed preeclampsia, and hydralazine was injected more frequently than recommended. Her blood pressure in less than 1 hour dropped from 240–270/130–150 mm Hg to 110/80 mm Hg. Fetal heart rate decelerations characteristic of uteroplacental insufficiency became evident. Decelerations persisted until her blood pressure was increased with rapid crystalloid infusion. In some cases, this fetal response to diminished uterine perfusion may be confused with placental abruption and may result in unnecessary and potentially dangerous emergency cesarean delivery.

FIGURE 40-20

Hydralazine was given at 5-minute intervals instead of 15-minute intervals. The mean arterial pressure dropped from 180 to 90 mm Hg within 1 hour and was associated with fetal bradycardia. Rapid crystalloid infusion raised the mean pressure to 115 mm Hg, and the fetus recovered.



Labetalol

This effective intravenous antihypertensive agent is an α- and nonselective β-blocker. Some prefer its use over hydralazine because of fewer side effects. At Parkland Hospital, we give 10 mg intravenously initially. If the blood pressure has not decreased to the desirable level in 10 minutes, then 20 mg is given. The next 10-minute incremental dose is 40 mg and is followed by another 40 mg if needed. If a salutary response is not achieved, then an 80-mg dose is given. Sibai (2003) recommends 20 to 40 mg every 10 to 15 minutes as needed and a maximum dose of 220 mg per treatment cycle. The American College of Obstetricians and Gynecologists (2017a)

recommends starting with a 20-mg intravenous bolus. If not effective within 10 minutes, this is followed by 40 mg, then 80 mg every 10 minutes. If hypertension persists, hydralazine is then given.

Comparative studies of hydralazine versus labetalol show equivalent results (Umans, 2015). In one trial, labetalol lowered blood pressure more rapidly, and associated tachycardia was minimal. But, hydralazine lowered mean arterial pressures to safe levels more effectively (Mabie, 1987). In another trial, maternal and neonatal outcomes were similar (Vigil-De Gracia, 2007). Hydralazine causes significantly more maternal tachycardia and palpitations, whereas labetalol more frequently leads to maternal hypotension and bradycardia. Both drugs have been associated with a reduced frequency of fetal heart rate accelerations (Cahill, 2013). Labetalol is not given to asthmatic women.

Nifedipine

This orally administered calcium-channel blocking agent has become popular because of its efficacy to control acute pregnancy-related hypertension. The American College of Obstetricians and Gynecologists (2017a), the NHBPEP Working Group (2000), and the Royal College of Obstetricians and Gynaecologists (2006) recommend a 10-mg initial immediate-release oral dose to be followed in 20 to 30 minutes with 10 to 20 mg if necessary. If not satisfactory, this is followed by labetalol. *Nifedipine given sublingually is no longer recommended.* This route is associated with dangerously rapid and extensive effects. Randomized trials that compared nifedipine with labetalol found neither drug definitively superior, but nifedipine lowered blood pressure more quickly (Scardo, 1999; Shekhar, 2016; Vermillion, 1999). Finally, nifedipine does not potentiate magnesium-related effects (Magee, 2015).

Other Antihypertensive Agents

A few other generally available antihypertensive agents have been tested in clinical trials but are not widely used (Umans, 2015). These include verapamil, nitroglycerin, nitroprusside, ketanserin, nicardipine, and nimodipine (Belfort, 1990, 2003; Bolte, 2001; Cornette, 2016). There are also experimental antihypertensive drugs that may become useful for preeclampsia treatment (Lam, 2013).

Diuretics

Potent loop diuretics can further compromise placental perfusion. Immediate effects include redistribution of the intravascular volume, which most often is already reduced in severe preeclampsia (Blood Volume). Therefore, before delivery, diuretics are not used to lower blood pressure (Zeeman, 2009; Zondervan, 1988). We use *antepartum* furosemide or similar drugs solely to treat pulmonary edema.

Fluid Therapy

Lactated Ringer solution is administered routinely at a rate between 60 and 125 mL per hour, unless fluid loss is unusual from vomiting, diarrhea, or diaphoresis, or, more likely, excessive blood loss with delivery. Oliguria is common with severe preeclampsia. Thus, coupled with the knowledge that maternal blood volume is likely constricted compared with that of normal pregnancy, it is tempting to administer intravenous fluids more vigorously. But controlled, conservative fluid administration is preferred for the typical woman with severe preeclampsia who already has excessive extracellular fluid that is inappropriately distributed between intravascular and extravascular spaces. Infusion of large fluid volumes enhances the maldistribution and thereby appreciably elevates the risk of pulmonary and cerebral edema (Dennis, 2012a; Sciscione, 2003; Zinaman, 1985). Thus, for preeclamptic women with anuria, small incremental boluses can be given to maintain urine output above 30 mL per hour. Diminished intravascular volume from hemorrhage or fluid loss from vomiting or fever can similarly be replaced by gradual incremental boluses. For labor analgesia with neuraxial analgesia, crystalloid solutions are infused slowly in graded amounts (Chap. 25, Safety).

Pulmonary Edema

Women with severe preeclampsia who develop pulmonary edema most often do so postpartum (Cunningham, 1986, 2012; Zinaman, 1985). With suspected pulmonary edema in the eclamptic woman, aspiration of gastric contents, which may be the result of convulsions, anesthesia, or oversedation, should be excluded. There are three common causes of pulmonary edema in women with severe preeclampsia syndrome—pulmonary capillary permeability edema, cardiogenic edema, or a combination of the two.

Some women with severe preeclampsia—especially if given vigorous fluid replacement—will have mild pulmonary congestion secondary to permeability edema. This is caused by normal pregnancy changes magnified by the preeclampsia syndrome. Importantly, plasma oncotic pressure drops appreciably in normal term pregnancy because of decreased serum albumin concentration, and oncotic pressure falls even more with preeclampsia (Zinaman, 1985). Moreover, both increased extravascular fluid oncotic pressure and increased capillary permeability are found in women with preeclampsia (Brown, 1989; Øian, 1986).

Invasive Hemodynamic Monitoring

Knowledge concerning cardiovascular and hemodynamic pathophysiological alterations associated with severe preeclampsia-eclampsia has accrued from studies done using invasive monitoring and a flow-directed pulmonary artery catheter (see Fig. 40-5). Two conditions frequently cited as indications are preeclampsia associated with oliguria and that associated with pulmonary edema (Clark, 2010). Somewhat ironically, it is usually vigorous treatment of the former that results in most cases of the latter. The Task Force (2013) recommends against routine invasive monitoring. Such monitoring is best reserved for severely preeclamptic women with accompanying cardiac disease, renal disease, or both or with refractory hypertension, oliguria, and pulmonary edema.

Plasma Volume Expansion

Because the preeclampsia syndrome is associated with hemoconcentration, some have infused various fluids, starch polymers, albumin concentrates, or combinations thereof to expand blood volume (Ganzevoort, 2004). Older observational studies describe serious complications—especially pulmonary edema—with volume expansion (Benedetti, 1985; López-Llera, 1982; Sibai, 1987b).

The Amsterdam randomized study reported by Ganzevoort and coworkers (2005a,b) was a well-designed investigation done to evaluate volume expansion. A total of 216 women with severe preeclampsia were enrolled between 24 and 34 weeks' gestation. The study included women whose preeclampsia was complicated by HELLP syndrome, eclampsia, or fetal-growth restriction. In the group randomly assigned to volume expansion, each woman was given 250 mL of 6-percent

hydroxyethyl starch infused over 4 hours twice daily. Their outcomes were compared with a control group, and none of these outcomes were significantly different (Table 40-13). Importantly, serious maternal morbidity and a substantive perinatal mortality rate accompanied their "expectant" management (see Table 40-9).

TABLE 40-13

Maternal and Perinatal Outcomes after Enrollment in a Randomized Trial of Plasma Volume Expansion versus Saline Infusion in 216 Women with Severe Preeclampsia between 24 and 34 Weeks

Outcomes	Control Group[a] (n = 105)	Treatment Group[a] (n = 111)
Maternal Outcomes (%)		
Eclampsia	1.9	1.8
HELLP	19.0	17.0
Pulmonary edema	2.9	4.5
Placental abruption	3.8	1.0
Perinatal Outcomes		
Fetal deaths (%)	7	12
Prolongation of pregnancy (mean)	11.6 d	6.7 d
EGA at death (mean)	26.7 wk	26.3 wk
Birthweight (mean)	625 g	640 g
Live births (%)	93	88
Prolongation of pregnancy (mean)	10.5 d	7.4 d
EGA at delivery (mean)	31.6 wk	31.4 wk
RDS (%)	30	35
Neonatal death (%)	7.6	8.1
Perinatal mortality rate (n per 1000)	142/1000	207/1000

[a]All comparisons $p > 0.05$.

EGA = estimated gestational age; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; RDS = respiratory distress syndrome.

Data from Ganzevoort, 2005a, b.

Neuroprophylaxis—Prevention of Seizures

Several randomized trials have tested the efficacy of seizure prophylaxis for women with gestational hypertension, with or without proteinuria. In most of these, magnesium sulfate was compared with another anticonvulsant or with a placebo. *In all studies, magnesium sulfate was reported to be superior to the comparator agent to prevent eclampsia*. Four of the larger studies are summarized in Table 40-14. In the study from Parkland Hospital, magnesium sulfate therapy was superior to phenytoin to prevent eclamptic seizures in women with gestational hypertension or preeclampsia (Lucas, 1995). In another, magnesium sulfate and nimodipine—a calcium-channel blocker with specific cerebral vasodilator activity—were compared in 1650 women with severe preeclampsia (Belfort, 2003). The rate of eclampsia was more than threefold higher for women allocated to the nimodipine group—2.6 versus 0.8 percent.

TABLE 40-14

Randomized Comparative Trials of Prophylaxis with Magnesium Sulfate and Placebo or Another Anticonvulsant in Women with Gestational Hypertension

	No. with Seizures/Total No. Treated (%)		
Study/Inclusions	**Magnesium Sulfate**	**Control**	**Comparison[a]**
Lucas et al (1995)		Phenytoin	
Gestational hypertension[b]	0/1049 (0)	10/1089 (0.9)	$p < 0.001$
Coetzee et al (1998)		Placebo	
Severe preeclampsia	1/345 (0.3)	11/340 (3.2)	RR = 0.09 (0.1–0.69)
Magpie Trial (2002)[c]		Placebo	
Severe preeclampsia	40/5055 (0.8)	96/5055 (1.9)	RR = 0.42 (0.26–0.60)
Belfort et al (2003)		Nimodipine	
Severe preeclampsia	7/831 (0.8)	21/819 (2.6)	RR = 0.33 (0.14–0.77)

[a]All comparisons significant $p < 0.05$.

[b]Included women with and without proteinuria and those with all severities of preeclampsia.

[c]Magpie Trial Collaboration Group, 2002.

RR = relative risk.

The largest comparative study was *Magnesium Sulfate for Prevention of Eclampsia* reported by the Magpie Trial Collaboration Group (2002). More than 10,000 women with severe preeclampsia from 33 countries were randomly allocated to treatment with magnesium sulfate or placebo. Women given magnesium had a 58-percent significantly lower risk of eclampsia than those given placebo. In follow-up data of infants born to these mothers given magnesium sulfate, child behavior at approximately 18 months did not differ in those exposed compared with those not exposed to magnesium sulfate (Smyth, 2009).

Who Should Be Given Magnesium Sulfate?

Magnesium will prevent proportionately more seizures in women with correspondingly worse disease. However, severity is difficult to quantify, and thus deciding which individual woman might benefit most from neuroprophylaxis is difficult. *The 2013 Task Force recommends that women with either eclampsia or severe preeclampsia should be given magnesium sulfate prophylaxis.* Again, criteria that establish "severity" are not totally uniform (see Table 40-2). At the same time, however, the 2013 Task Force suggests that women with "mild" preeclampsia do not need magnesium sulfate neuroprophylaxis. The conundrum is whether or not to give neuroprophylaxis to any of these women with "nonsevere" gestational hypertension or preeclampsia (Alexander, 2006).

In most other countries, and principally following dissemination of the Magpie Trial Collaboration Group (2002) study results, magnesium sulfate is now recommended for women with severe preeclampsia. In some, however, debate continues concerning whether therapy should be reserved for women who have an eclamptic seizure. We believe that eclamptic seizures are dangerous (Brain and Renal Sequelae). Maternal mortality rates of up to 5 percent have been reported even in recent studies. Moreover, perinatal mortality rates are substantially increased (Abd El Aal, 2012; Knight, 2007; Ndaboine, 2012; Schutte, 2008; von Dadelszen, 2012). Finally, the possibility of adverse long-term neuropsychological and vision-related sequelae of eclampsia have raised additional concerns that eclamptic seizures are not "benign."

Selective versus Universal Prophylaxis

Because of the foregoing, there is uncertainty about which women with *nonsevere* gestational hypertension should be given magnesium sulfate neuroprophylaxis. An opportunity to address these questions was afforded by a change in our prophylaxis protocol at Parkland Hospital. Before this time, the risk of eclampsia without magnesium prophylaxis was approximately 1 in 100 for women with *mild preeclampsia* (Lucas, 1995). Up until 2000, all women with gestational hypertension were given magnesium prophylaxis intramuscularly. After 2000, we instituted a standardized protocol for intravenously administered magnesium sulfate (Alexander, 2006). At the same time, we also changed our practice of universal seizure prophylaxis for all women with gestational hypertension to one of selective prophylaxis given only to women who met our criteria for severe gestational hypertension. These criteria, shown in Table 40-15, included women with ≥2+ proteinuria measured by dipstick in a catheterized urine specimen.

TABLE 40-15

Selective versus Universal Magnesium Sulfate Prophylaxis: Parkland Hospital Criteria to Define Severe Gestational Hypertension or Preeclampsia

In a woman with new-onset proteinuric hypertension, at least one of the following criteria is required:
Systolic BP ≥160 or diastolic BP ≥110 mm Hg
Proteinuria ≥2+ by dipstick in a catheterized urine specimen
Serum creatinine >1.1 mg/dL
Platelet count <100,000/μL
Aspartate aminotransferase (AST) elevated two times above upper limit of normal range
Persistent headache or scotomata
Persistent midepigastric or right-upper quadrant pain

BP = blood pressure.

Criteria based on those from National High Blood Pressure Education Program Working Group, 2000; American College of Obstetricians and Gynecologists, 2012; cited by Alexander, 2006.

Following this protocol change, 60 percent of 6518 women with gestational hypertension during a 4½-year period were given magnesium sulfate neuroprophylaxis. The remaining 40 percent with nonsevere hypertension were not treated, and of these, 27 women developed eclamptic seizures—1 in 92. The seizure rate was only 1 in 358 for 3935 women with criteria for severe disease who were given magnesium sulfate, and thus these cases were treatment failures.

To assess morbidity, outcomes in 87 eclamptic women were compared with outcomes in all 6431 noneclamptic severely hypertensive women (Alexander, 2006). Although most maternal outcomes were similar, almost a fourth of women with eclampsia who underwent emergent cesarean delivery required general anesthesia. This is a great concern because eclamptic women have laryngotracheal edema and are at a higher risk for failed intubation, gastric acid aspiration, and death. Neonatal outcomes were also a concern because the composite morbidity was increased tenfold in eclamptic compared with noneclamptic women—12 versus 1 percent, respectively. These outcomes included cord artery pH <7.0; 5-minute Apgar score <4; or unanticipated admission of a term newborn to an intensive care nursery.

Thus, if one uses the Parkland criteria for nonsevere gestational hypertension, approximately 1 of 100 such women who are not given magnesium sulfate prophylaxis can be expected to have an eclamptic seizure. A fourth of these women likely will require emergent cesarean delivery with attendant maternal and perinatal morbidity and mortality from general anesthesia. From this, the major question regarding management of nonsevere gestational hypertension remains whether it is acceptable to avoid unnecessary treatment of 99 women to risk eclampsia in one? The answer appears to be yes as suggested by the 2013 Task Force. At Parkland Hospital, we only give magnesium neuroprophylaxis to women with severe criteria.

Analgesia and Anesthesia

During the past 20 years, the use of conduction analgesia for women with preeclampsia syndrome has proven ideal. Initial problems with this method included hypotension and diminished uterine perfusion caused by sympathetic blockade in preeclamptic women, with already attenuated hypervolemia. But pulmonary edema was mitigated by techniques that used slow induction of epidural analgesia with dilute solutions of anesthetic agents. This countered the need for rapid infusion of large volumes of crystalloid or colloid to correct maternal hypotension from neural blockade (Hogg, 1999; Wallace, 1995). These techniques are described in detail in Chapter 25 (Safety). Importantly, epidural blockade avoids general anesthesia, in which the stimulation of tracheal intubation may cause sudden severe hypertension. Such blood pressure spikes, in turn, can cause pulmonary edema, cerebral edema, or intracranial hemorrhage. Finally, tracheal intubation may be particularly difficult and thus hazardous in women with airway edema due to preeclampsia (American College of Obstetricians and Gynecologists, 2017b).

At least three randomized studies have been performed to compare these methods of analgesia and anesthesia. Wallace and colleagues (1995) studied 80 women at Parkland Hospital with severe preeclampsia who were to undergo cesarean delivery. They had not been given labor epidural analgesia and were randomly assigned to receive general anesthesia, epidural analgesia, or combined spinal-epidural analgesia. Their average preoperative blood pressures approximated 170/110 mm Hg, and all had proteinuria. Maternal and perinatal outcomes in each group were similar. Maternal hypotension resulting from regional analgesia was managed with judicious intravenous fluid administration. In women undergoing general anesthesia, maternal blood pressure was managed to avoid severe hypertension. There were no serious maternal or fetal complications attributable to any of the three anesthetic methods. It was concluded that all three are acceptable for use in women with pregnancies complicated by severe preeclampsia if steps are taken to ensure a careful approach to the selected method.

Another randomized study included 70 women with severe preeclampsia receiving spinal analgesia versus general anesthesia for cesarean delivery (Dyer, 2003). Their maternal and fetal outcomes were equivalent. In a third study, 116 women with severe preeclampsia received either epidural or patient-controlled intravenous meperidine analgesia during labor (Head, 2002). More women—9 percent—from the group assigned to epidural analgesia required ephedrine for hypotension. As

expected, pain relief was superior in the epidural group. Maternal and neonatal complications were similar between groups, and one woman in each group developed pulmonary edema. Importantly, epidural analgesia is not considered *treatment* of preeclampsia (Lucas, 2001; Ray, 2017).

Judicious fluid administration is essential in severely preeclamptic women who receive regional analgesia. Vigorous crystalloid infusion with epidural blockade in women with severe preeclampsia elevates pulmonary capillary wedge pressures (Newsome, 1986). Aggressive volume replacement in preeclamptic women raises their risk for pulmonary edema, especially in the first 72 hours postpartum (Clark, 1985; Cotton, 1986a). Finally, most cases of pharyngolaryngeal edema are related to aggressive volume therapy (Heller, 1983).

Blood Loss at Delivery

Hemoconcentration or lack of normal pregnancy-induced hypervolemia is an almost predictable feature of severe preeclampsia-eclampsia (see Fig. 40-7) (Zeeman, 2009). *These women, who consequently lack normal pregnancy hypervolemia, are much less tolerant of even normal blood loss than are normotensive pregnant women.* Importantly, an appreciable fall in blood pressure soon after delivery most often means excessive blood loss and not sudden resolution of vasospasm and endothelial damage. When oliguria follows delivery, the hematocrit should be evaluated frequently to help detect excessive blood loss. If identified, hemorrhage should be treated appropriately by crystalloid and blood transfusion.

Persistent Severe Postpartum Hypertension

Although severe postpartum hypertension usually follows labor and delivery complicated by hypertension, 8 percent of women develop de novo hypertension postpartum (Goel, 2015). In either case, if difficulty arises in controlling severe hypertension or if intravenous hydralazine or labetalol are being used repeatedly, then oral regimens can be given. Examples include labetalol or another β-blocker, or nifedipine or another calcium-channel blocker (Sharma, 2017). Women so treated are less likely to require readmission (Hirshberg, 2016). Persistent or refractory hypertension is likely aggravated by mobilization of pathological interstitial fluid and redistribution into the intravenous compartment, underlying chronic hypertension, or usually both (Sibai, 2012; Tan, 2002). Chronic, but not sporadic, administration of some nonsteroidal antiinflammatory drugs, namely ibuprofen, may aggravate postpartum hypertension in those with preeclampsia (Vigil-De Gracia, 2017; Viteri, 2017). In women with chronic hypertension and left-ventricular hypertrophy, severe postpartum hypertension can cause pulmonary edema from cardiac failure (Cunningham, 1986, 2012; Sibai, 1987a).

Furosemide

Because persistence of severe hypertension corresponds to the onset and length of diuresis and extracellular fluid mobilization, it seems logical that furosemide-augmented diuresis might serve to hasten blood pressure control. One randomized trial included 264 postpartum preeclamptic women who, after onset of spontaneous diuresis, were assigned to 20-mg oral furosemide given daily or to no therapy (Ascarelli, 2005). Women with mild disease had similar blood pressure control regardless of whether they received treatment or placebo. However, after 2 days, women with severe preeclampsia who were treated, compared with those receiving placebo, had a lower mean systolic blood pressure—142 versus 153 mm Hg. They also less frequently required supplemental antihypertensive therapy during the remainder of hospitalization—14 versus 26 percent, respectively. In a recent randomized study, Veena and colleagues (2017) treated severe postpartum eclampsia with nifedipine plus furosemide or nifedipine alone. They reported that this prophylactic therapy significantly lowered the need for an additional antihypertensive—26 versus 8 percent, respectively.

We use a simple method to estimate excessive extracellular/interstitial fluid. The *postpartum weight* is compared with the most recent *prenatal weight*, either from the last clinic visit or on admission for delivery. Typically, soon after delivery, maternal weight should be reduced by at least 10 to 15 pounds depending on newborn and placental weight, amnionic fluid volume, and blood loss. Because of various interventions, especially intravenous crystalloid infusions given with labor epidural analgesia or during operative vaginal or cesarean delivery, women with severe preeclampsia often have an immediate postpartum weight *in excess of their last prenatal weight*. If this weight increase is associated with severe persistent postpartum hypertension, then diuresis with intravenous furosemide is usually helpful in controlling blood pressure.

Plasma Exchange

Occasionally, women have an atypical syndrome in which severe preeclampsia-eclampsia persists despite delivery. Martin and colleagues (1995) described 18 such women whom they encountered during a 10-year period. They advocate single or multiple plasma exchange for these women. In some cases, 3 L of plasma was exchanged three times—a 36- to 45-donor unit exposure for each patient—before a response was forthcoming. Others have described plasma exchange performed in postpartum women with HELLP syndrome (Förster, 2002; Obeidat, 2002). In all of these cases, however, the distinction between HELLP syndrome and thrombotic thrombocytopenic purpura or hemolytic uremic syndrome was not clear (Tsai, 2016).

In our experiences with more than 50,000 women with gestational hypertension among nearly 450,000 pregnancies cared for at Parkland Hospital through 2017, we have encountered very few women with persistent postpartum hypertension, thrombocytopenia, and renal dysfunction who were diagnosed as having a thrombotic microangiopathy (Dashe, 1998). These latter syndromes complicating pregnancy were reviewed by Martin (2008) and George (2013) and their colleagues, who conclude that a rapid diagnostic test for ADAMTS-13 enzyme activity might be helpful to differentiate most of these syndromes.

Reversible Cerebral Vasoconstriction Syndrome

This is another cause of persistent hypertension, “thunderclap” headaches, seizures, and central nervous system findings. It is a form of postpartum angiopathy. *Reversible cerebral vasoconstriction syndrome* is characterized by diffuse segmental constriction of cerebral arteries and may be associated with ischemic and hemorrhagic strokes. This syndrome has several inciting causes that include pregnancy, and particularly preeclampsia (Ducros, 2012). It is more common in women, and in some cases, vasoconstriction may be so severe as to cause cerebral ischemia and infarction. The appropriate management is not known at this time (Edlow, 2013).

LONG-TERM CONSEQUENCES

Future Pregnancies

Defective remodeling of the spiral arteries in some placentas is posited as a cause of at least one preeclampsia phenotype. Specifically, lack of deep placentation is linked with preeclampsia, placental abruption, fetal-growth restriction, and preterm birth (Wikström, 2011). With this type of "overlap syndrome," hypertensive disorders may serve as markers for subsequent preterm labor and fetal-growth restriction. For example, even in subsequent nonhypertensive pregnancies, women who had preterm preeclampsia are at higher risk for preterm birth and growth-restricted neonates (Bramham, 2011; Connealy, 2014; Palatnik, 2016).

In addition, women who have had either gestational hypertension or preeclampsia risk developing hypertension in future pregnancies (Lykke, 2009b). Generally, the earlier preeclampsia is diagnosed during the index pregnancy, the greater the likelihood of recurrence. And, the recurrence risk for preeclampsia is elevated further in women with the metabolic syndrome (Stekkinger, 2015). Sibai and colleagues (1986, 1991) found that nulliparas diagnosed with preeclampsia before 30 weeks had a recurrence risk as high as 40 percent during a subsequent pregnancy. In a prospective study of 500 women previously delivered for preeclampsia at 37 weeks, the recurrence rate in a subsequent gestation was 23 percent (Bramham, 2011).

As perhaps expected, women with HELLP syndrome have a substantive risk for recurrence in subsequent pregnancies. In two studies, the risk ranged from 5 to 26 percent, but the true recurrence risk likely lies between these two extremes (Habli, 2009; Sibai, 1995). Even if HELLP syndrome does not recur with subsequent pregnancies, again incidences of preterm delivery, fetal-growth restriction, placental abruption, and cesarean delivery are increased (Habli, 2009; Hnat, 2002).

Long-Term Morbidity and Mortality

Evidence has accrued that the preeclampsia syndrome is a marker for subsequent long-term cardiovascular and related morbidity and mortality (Table 40-16). Thus, women with hypertension identified during pregnancy should be evaluated during the first several months postpartum. The working group of the NHBPEP (2000) concluded that hypertension attributable to pregnancy should resolve within 12 weeks of delivery. Hypertension persisting beyond this time is considered chronic (Chap. 50, Definition and Classification). The Magpie Trial Follow-Up Collaborative Group (2007) reported that 20 percent of 3375 preeclamptic women seen at a median of 26 months postpartum had hypertension. Importantly, even if hypertension does not persist in the short term, convincing evidence suggests a higher risk for long-term cardiovascular morbidity.

TABLE 40-16

Some Long-Term Consequences in Women with Preeclampsia Syndrome

Cardiovascular
Chronic hypertension
Ischemic heart disease
Atherosclerosis
Coronary artery calcification
Cardiomyopathy
Thromboembolism
Neurovascular
Stroke
Retinal detachment
Diabetic retinopathy
Metabolic
Type 2 diabetes
Metabolic syndrome
Dyslipidemia
Obesity
Renal
Glomerular dysfunction
Proteinuria
Central nervous system
White-matter lesions
Cognitive dysfunction
Retinopathy

Cardiovascular Morbidity

Any hypertension during pregnancy is a risk marker for morbidity and mortality in later life (American College of Obstetricians and Gynecologists, 2013; Bellamy, 2007). In a case-control study from Iceland, Arnadottir and associates (2005) reported the prevalences of *ischemic heart disease*—24 versus 15 percent, and *stroke*—9.5 versus 6.5 percent, were significantly increased in women who had gestational hypertension compared with normotensive controls. In a Swedish population study of more than 400,000 women, those with recurrent preeclampsia have systolic dysfunction and a greater incidence of ischemic heart disease (Valensise, 2016). Diastolic dysfunction is also more common (Bokslag, 2017). Preeclampsia is also a risk for coronary artery calcification and idiopathic cardiomyopathy (Behrens, 2016; White, 2016).

Lykke and associates (2009a) cited findings from a Danish registry of more than 780,000 nulliparas. After a mean follow-up of almost 15 years, the incidence of *chronic hypertension* was fivefold higher in those who had gestational hypertension, 3.5-fold greater after mild preeclampsia, and sixfold higher after severe preeclampsia. After two hypertensive pregnancies, this incidence rose sixfold. Moreover, these women with pregnancy-associated hypertension are at increased risk for *type 2 diabetes* (Rice, 2016). And, preeclampsia is a risk factor for later diabetic retinopathy and retinal detachment (Auger, 2017; Beharier, 2016).

As emphasized by several investigators, other cofactors or comorbidities are related to acquisition of these long-term adverse outcomes (Gastrich, 2012; Harskamp, 2007; Hermes, 2012; Spaan, 2012b). These include the metabolic syndrome, diabetes, obesity, dyslipidemia, and atherosclerosis (Kajantie, 2017; Orabona, 2016; Stekkinger, 2015).

Individuals who are born preterm have greater ventricular mass later in life (Lewandowski, 2013). And, women who have preeclampsia and who develop chronic hypertension later in life have an increased ventricular mass index before they become hypertensive (Ghossein-Doha, 2013). Finally, in at least some of these women, hypertensive cardiovascular pathologies appear to have begun near the time of *their own* births. A similar phenomenon is associated with preterm birth and with fetal-growth disorders.

Renal Sequelae

Preeclampsia is also a marker for subsequent renal disease. Almost 15 percent of previously preeclamptic women have renal dysfunction (Lopes van Balen, 2017). In a 40-year study of Norwegian birth and end-stage renal disease linked registries, although the absolute risk of renal failure was small, preeclampsia was associated with a fourfold greater risk (Vikse, 2008). Women with recurrent preeclampsia had an even higher risk. These data need to be considered in light of the findings that 15 to 20 percent of women with preeclampsia who undergo renal biopsy have evidence of chronic renal disease (Chesley, 1978). In another long-term study, Spaan and coworkers (2009) compared formerly preeclamptic women with a cohort of women who were normotensive at delivery. At 20 years following delivery, preeclamptic women were significantly more likely to be chronically hypertensive—55 versus 7 percent—compared with control women. They also had higher peripheral vascular and renovascular resistance and decreased renal blood flow. These data do not permit conclusions as to cause versus effect.

Central Nervous System Sequelae

Until recently, eclamptic seizures were believed to have no significant long-term sequelae. However, this may not be the case (Theilen, 2016). Recall that almost all eclamptic women have multifocal areas of perivascular edema, and approximately a fourth also have areas of cerebral infarction (Zeeman, 2004a).

In several long-term follow-up studies in women with severe preeclampsia and eclampsia, brain white-matter lesions that followed eclamptic convulsions persist (Aukes, 2007, 2009, 2012). Specifically, when studied with MR imaging at a mean of 7 years, 40 percent of formerly eclamptic women had more numerous and larger aggregate white matter lesions compared with 17 percent of normotensive control women. These investigators later also observed these white-matter lesions in preeclamptic women without convulsions (Aukes, 2012). And, Siepmann and associates (2017) documented temporal lobe white matter changes and reduced cortical volume in previously preeclamptic women. In studies designed to assess clinical relevance, formerly eclamptic women had subjectively impaired cognitive functioning (Postma, 2014). Wiegman and associates (2012) reported that formerly eclamptic women at approximately 10 years had lower vision-related quality of life compared with control subjects. This likely coincides with an elevated risk for retinopathy described by Auger and colleagues (2017). Because no baseline studies were done before these women suffered from preeclampsia or eclampsia, the investigators appropriately concluded that a cause versus an effect of these white-matter lesions remains unknown.

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CHAPTER 41: Obstetrical Hemorrhage

A profuse hemorrhage occurring prior to or shortly after the birth of the child is always dangerous and not infrequently a fatal complication.

—J. Whitridge Williams (1903)

INTRODUCTION

As in Williams' time, obstetrical hemorrhage continues along with hypertension and infection to be one part of the infamous "triad" of maternal death causes. It also is a leading reason for admission of pregnant women to intensive care units (Chantry, 2015; Crozier, 2011; De Greve, 2016; Guntupalli, 2015). Hemorrhage was a direct cause of 11.4 percent of 5367 pregnancy-related maternal deaths from 2006 to 2013 in the United States (Creanga, 2015, 2017). Similarly, 16 percent of 1102 maternal deaths recorded in the Nationwide Inpatient Sample were caused by hemorrhage (Kuriya, 2016). In developing countries, hemorrhage's contribution is even more striking, and it is the single most important cause of maternal death worldwide (Goffman, 2016; Oladapo, 2016; Thomas, 2016). Despite these numbers, a declining maternal mortality rate from hemorrhage in the United States has been a seminal achievement. But, as discussed in Chapter 1 (Maternal Mortality), it seems unlikely that deaths from hemorrhage have reached an irreducible minimum.

GENERAL CONSIDERATIONS

Mechanisms of Normal Hemostasis

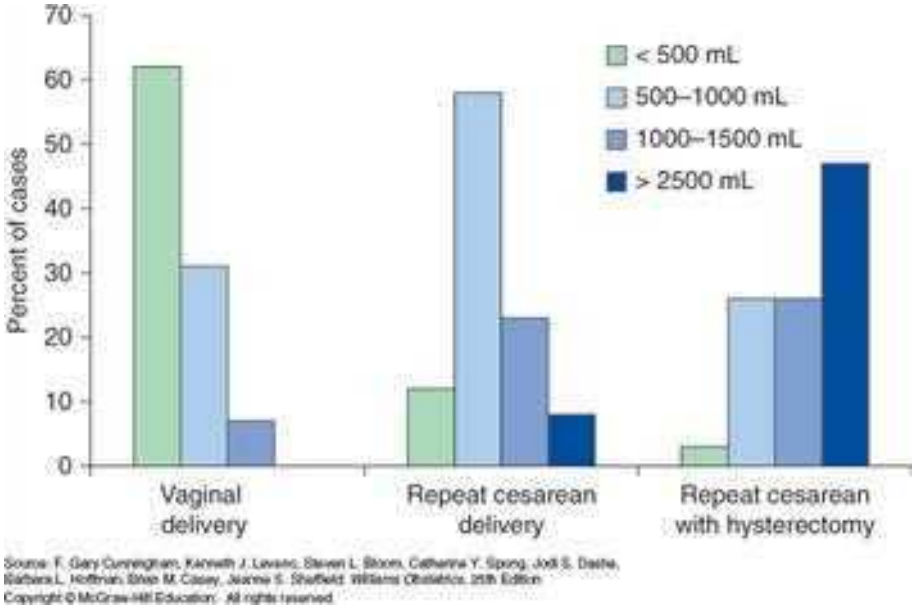
A major concept in understanding the pathophysiology and management of obstetrical hemorrhage is the mechanism by which hemostasis is achieved after normal delivery. Recall that near term an incredible amount of blood—at least 600 mL/min—flows through the intervillous space (Pates, 2010). This prodigious flow circulates through the spiral arteries, which average 120 in number. Also, recall that these vessels have no muscular layer because of their remodeling by trophoblasts, which creates a low-pressure system. With placental separation, these vessels at the implantation site are avulsed, and hemostasis is achieved first by myometrial contraction, which compresses this formidable number of large vessels. Compression is followed by clotting and obliteration of vessel lumens.

If, after delivery, the myometrium contracts vigorously, fatal hemorrhage from the placental implantation site is unlikely. *Importantly, an intact coagulation system is not necessary for postpartum hemostasis unless there are lacerations in the uterus, birth canal, or perineum.* At the same time, however, fatal postpartum hemorrhage can result from uterine atony despite normal coagulation.

Definition and Incidence

Traditionally, postpartum hemorrhage is defined as the loss of ≥500 mL of blood after completion of the third stage of labor. This is problematic because almost half of all women delivered vaginally shed that amount of blood or more when losses are carefully measured (Pritchard, 1962). These results are depicted in Figure 41-1 and show further that approximately 5 percent of women delivering vaginally lose more than 1000 mL of blood. According to the American College of Obstetricians and Gynecologists (2017d), postpartum hemorrhage is defined as cumulative blood loss >1000 mL accompanied by signs and symptoms of hypovolemia. And, almost a third of women undergoing cesarean delivery have blood loss that exceeds 1000 mL. *These studies show that estimated blood loss is commonly only approximately half the actual loss*. Because of this, estimated blood loss in excess of "average" should alert the obstetrician to possible excessive bleeding. Whether quantification of blood loss improves accuracy is controversial (Hamm, 2017; Toledo, 2007).

FIGURE 41-1
Blood loss associated with vaginal delivery, repeat cesarean delivery, and repeat cesarean delivery plus hysterectomy. (Data from Pritchard, 1962.)



The blood volume of a pregnant woman with normal pregnancy-induced hypervolemia usually rises by half, but individual increases range from 30 to 60 percent, that is, 1500 to 2000 mL for an average-sized woman (Pritchard, 1965). The equation to calculate blood volume is shown in Table 41-1. It is axiomatic that a normal pregnant woman tolerates, without any decrease in postpartum hematocrit, blood loss at delivery that approaches the volume of blood that she added during pregnancy. Thus, if blood loss is less than the pregnancy-added volume, the hematocrit remains the same acutely and during the first several days postpartum. It then rises as nonpregnant plasma volume normalizes during the next week or so. *Whenever the postpartum hematocrit is lower than one obtained on admission for delivery, blood loss can be estimated as the sum of the calculated pregnancy-added volume plus 500 mL for each 3 volume percent decline of the hematocrit.*

TABLE 41-1

Calculation of Maternal Total Blood Volume

Nonpregnant blood volume[a]: $\frac{[\text{Height (inches)} \times 50] + [\text{Weight (pounds)} \times 25]}{7} = \text{Blood volume (mL)}$
Pregnancy blood volume:
Average increase is 30 to 60 percent of calculated nonpregnant volume
Increases across gestational age and plateaus at approximately 34 weeks
Usually larger with low normal-range hematocrit (~30) and smaller with high normal-range hematocrit (~40)
Average increase is 40 to 80 percent with multifetal gestation
Average increase is less with preeclampsia—volumes vary inversely with severity
Postpartum blood volume with serious hemorrhage:
Assume acute return to nonpregnant total volume after fluid resuscitation
Pregnancy hypervolemia cannot be restored postpartum

[a]Formula arrived at by measuring blood volume and blood loss in more than 100 women using ^{51}Cr-labeled erythrocytes.

Data from Hernandez, 2012.

Excessive blood loss has been estimated by several methods. Sosa and colleagues (2009) used specially constructed drapes and reported that 10.8 percent of women had hemorrhage in excess of 500 mL with vaginal delivery, whereas 1.9 percent lost >1000 mL. Compared with the findings of Figure 41-1, these estimates likely are too low. Tita and associates (2012) used a 6-volume percent drop in the postpartum hematocrit to define clinically significant blood loss with vaginal delivery. This decline easily signifies a >1000-mL blood loss in the averaged-sized woman. They documented this amount in a fourth of women, which agrees with Figure 41-1.

Another marker used to estimate hemorrhage incidence is the transfusion rate. In the study by Tita just cited, more than 6 percent of women who delivered vaginally underwent blood transfusions. In a study of more than 66,000 women delivered at Parkland Hospital, 2.3 percent overall were given blood transfusions for hypovolemia (Hernandez, 2012). Half of these women had undergone cesarean delivery. Importantly, for those transfused, these investigators calculated blood loss to average approximately 3500 mL! Finally, Green and coworkers (2016) reported that the incidence of *massive transfusion* for postpartum hemorrhage was 23 per 100,000 births.

From the foregoing, it is apparent that significant blood loss accompanies up to a fourth of vaginal deliveries. The amounts and proportions for cesarean delivery are much greater. And, hemorrhage is underreported. For example, data from the National Hospital Discharge Summary database reported postpartum hemorrhage

incidences of only 2.0 and 2.6 percent for two epochs in the United States (Berg, 2009). Similar incidences have been reported by others (Kramer, 2013; Mehrabadi, 2013; Patterson, 2014).

Risks

Numerous clinical circumstances raise the risks for obstetrical hemorrhage. The imposing list shown in Table 41-2 illustrates that hemorrhage can manifest at any time throughout pregnancy, delivery, and the puerperium. Thus, any description of obstetrical hemorrhage should include gestational age. Contributions to maternal death from some of these causes of are shown in Figure 41-2.

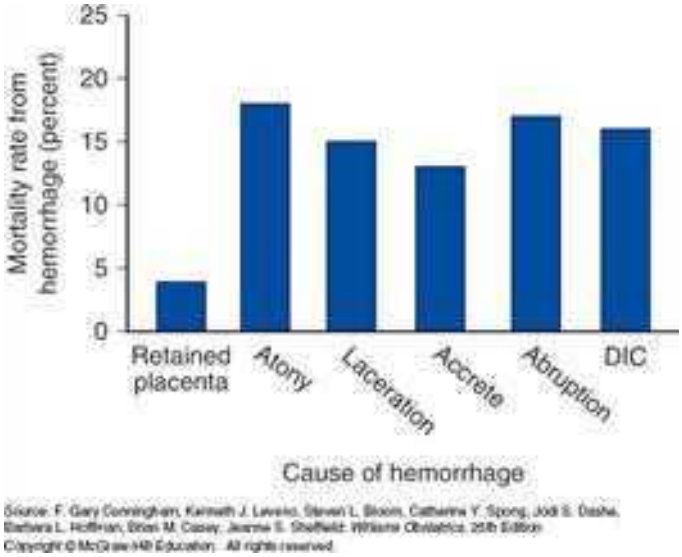
TABLE 41-2

Obstetrical Hemorrhage: Causes, Predisposing Factors, and Vulnerable Patients

Abnormal Placentation	**Uterine Atony**
Placenta previa	Uterine overdistention
Placental abruption	Large fetus
Morbidly adherent placenta	Multiple fetuses
Ectopic pregnancy	Hydramnios
Hydatidiform mole	Retained clots
Injuries to the Birth Canal	Labor induction
Episiotomy and lacerations	Anesthesia or analgesia
Forceps or vacuum delivery	Halogenated agents
Cesarean delivery or hysterectomy	Conduction analgesia with hypotension
Uterine rupture	Labor abnormalities
Previously scarred uterus	Rapid labor
High parity	Prolonged labor
Hyperstimulation	Augmented labor
Obstructed labor	Chorioamnionitis
Intrauterine manipulation	Previous uterine atony
Midforceps rotation	Parity: primiparity, high parity
Breech extraction	**Coagulation Defects—Intensify Other Causes**
Obstetrical Factors	Massive transfusions
Obesity	Placental abruption
Previous postpartum hemorrhage	Sepsis syndrome
Early preterm pregnancy	Severe preeclampsia syndrome
Sepsis syndrome	Acute fatty liver
Preeclampsia/eclampsia	Anticoagulant treatment
Vulnerable Patients	Congenital coagulopathies
Chronic renal insufficiency	Amnionic fluid embolism
Constitutionally small size	Prolonged retention of dead fetus
	Saline-induced abortion

FIGURE 41-2

Contributions to maternal death from various causes of obstetrical hemorrhage. Percentages are approximations because of different classification schemata used. DIC = disseminated intravascular coagulopathy. (Data from Al-Zirqi, 2008; Berg, 2010; Creanga, 2015; Zwart, 2008.)



Timing

Antepartum Hemorrhage

Obstetrical hemorrhage is traditionally classified as *antepartum*—such as with placenta previa or placental abruption, or as *postpartum*—commonly caused by uterine atony or genital tract lacerations. In individual women, however, these terms are nonspecific, and it is reasonable to specify the cause and gestational age as descriptors.

Bleeding during various times in gestation may give a clue to its cause. Many aspects of bleeding during the first half of pregnancy from abortion or ectopic pregnancy are covered in Chapters 18 and 19. Discussions that follow concern pregnancies with a viable-size fetus. *In these cases, rapid assessment should always consider the deleterious fetal effects of maternal hemorrhage.*

During active labor, slight vaginal bleeding is common. This “bloody show” is the consequence of effacement and dilation of the cervix, with tearing of small vessels. Uterine bleeding above the cervix, however, is concerning. It may follow some separation of a placenta previa implanted in the immediate vicinity of the cervical canal, or it may be from a placental abruption or uterine tear. In some women, especially with a placenta previa, cervical varicosities may bleed (O’Brien, 2013). Rarely, there may be velamentous insertion of the umbilical cord, and the involved placental vessels may overlie the cervix—*vasa previa.* In this case, serious fetal hemorrhage follows laceration of these vessels at the time of membrane rupture (Swank, 2016).

Near term in many women, the source of uterine bleeding is not identified, bleeding ceases, and no apparent anatomical cause is found at delivery. In most of these cases, bleeding likely originated from a slight marginal placental separation. *Despite this, any pregnancy with antepartum bleeding remains at higher risk for an adverse outcome even though bleeding has stopped and placenta previa has been excluded sonographically.*

Bleeding after midpregnancy is associated with several adverse outcomes. The Canadian Perinatal Network described 806 women with hemorrhage between 22 and 28 weeks’ gestation (Sabourin, 2012). Placental abruption (32 percent), previa (21 percent), and cervical bleeding (6.6 percent) were the most frequent causes identified. In a third, no cause was found. Of all women, 44 percent were delivered before 29 weeks’ gestation. In more than 68,000 women in Scotland, the incidence of antepartum hemorrhage after the first trimester was 11 percent (Bhandari, 2014). These women were at significantly higher risk for preterm birth, labor induction, and postpartum hemorrhage.

Postpartum Hemorrhage

In most cases, the source of postpartum hemorrhage can and should be determined. Frequent causes are uterine atony with placental site bleeding, genital tract trauma, or both. Postpartum hemorrhage is usually obvious. Important exceptions are unrecognized intrauterine and intravaginal blood accumulation and uterine rupture with intraperitoneal or retroperitoneal bleeding. Another consideration is an expanding vulvar or vaginal hematoma (Puerperal Hematomas). Initial evaluation attempts to differentiate uterine atony from genital tract lacerations. For this, risk factors are sought, the lower genital tract is examined, and uterine tone is assessed. Atony is identified by a boggy, soft uterus during bimanual examination and by expression of clots and hemorrhage during uterine massage.

Persistent bleeding despite a firm, well-contracted uterus suggests that hemorrhage most likely is from lacerations. Bright red blood further suggests arterial bleeding. *To confirm that lacerations are a source of bleeding, careful inspection of the vagina, cervix, and uterus is essential.* Sometimes bleeding may be caused by both atony and trauma, especially after forceps or vacuum-assisted vaginal delivery. Examination is easier if conduction analgesia was given. If there are no lower genital tract lacerations and the uterus is contracted, yet supracervical bleeding persists, then manual exploration of the uterus is done to exclude a uterine tear (Kaplanoglu, 2016). This also is completed routinely after internal podalic version, breech extraction, or successful vaginal birth after cesarean.

Late postpartum hemorrhage describes bleeding after the first 24 hours. Found in up to 1 percent of women, it may be serious and is discussed in Chapter 37 (American College of Obstetricians and Gynecologists, 2017d).

Blood Loss Estimation

As noted, visual estimates are notoriously inaccurate, especially with excessive bleeding. Instead of sudden massive hemorrhage, postpartum bleeding is frequently steady. If atony persists, bleeding may appear to be only moderate at any given instant but may continue until serious hypovolemia develops. Bleeding from an episiotomy or a vaginal laceration can also appear to be only minimal to moderate. But, constant seepage can lead to enormous blood loss relatively quickly. In some cases, after placental separation, blood may not escape vaginally but instead may collect within the uterine cavity, which can become distended by 1000 mL or more of blood. In others, postpartum uterine massage is applied to a roll of abdominal fat mistaken for the uterus.

All of these factors can lead to an underappreciation of the magnitude of hemorrhage over time. The effects of hemorrhage depend to a considerable degree on the maternal nonpregnant blood volume and the corresponding degree of pregnancy-induced hypervolemia. For this and other reasons, hypovolemia may not be recognized until very late. *A treacherous feature of postpartum hemorrhage is the failure of the pulse and blood pressure to undergo more than moderate alterations until large amounts of blood have been lost.* The normotensive woman initially may actually become somewhat hypertensive from catecholamine release in response to hemorrhage. And importantly, women with preeclampsia may become “normotensive” despite remarkable hypovolemia.

Some gravidas may be particularly susceptible to hemorrhage because their blood volume expansion is less than expected. This situation is most commonly encountered in small women—even those with normal pregnancy-induced hypervolemia. Women with severe preeclampsia or eclampsia are also more vulnerable to hemorrhage because they frequently do not have a normal blood volume accrual. Specifically, Zeeman and associates (2009) documented a mean increase above nonpregnant volume of only 10 percent in *eclamptic* women (Chap. 40, Blood Volume). A third example is the moderate-to-severe curtailing of pregnancy-induced volume expansion in women with chronic renal insufficiency (Chap. 53, Chronic Kidney Disease). *When excessive hemorrhage is suspected in these high-risk women, crystalloid and blood are promptly administered for suspected hypovolemia.*

UTERINE ATONY

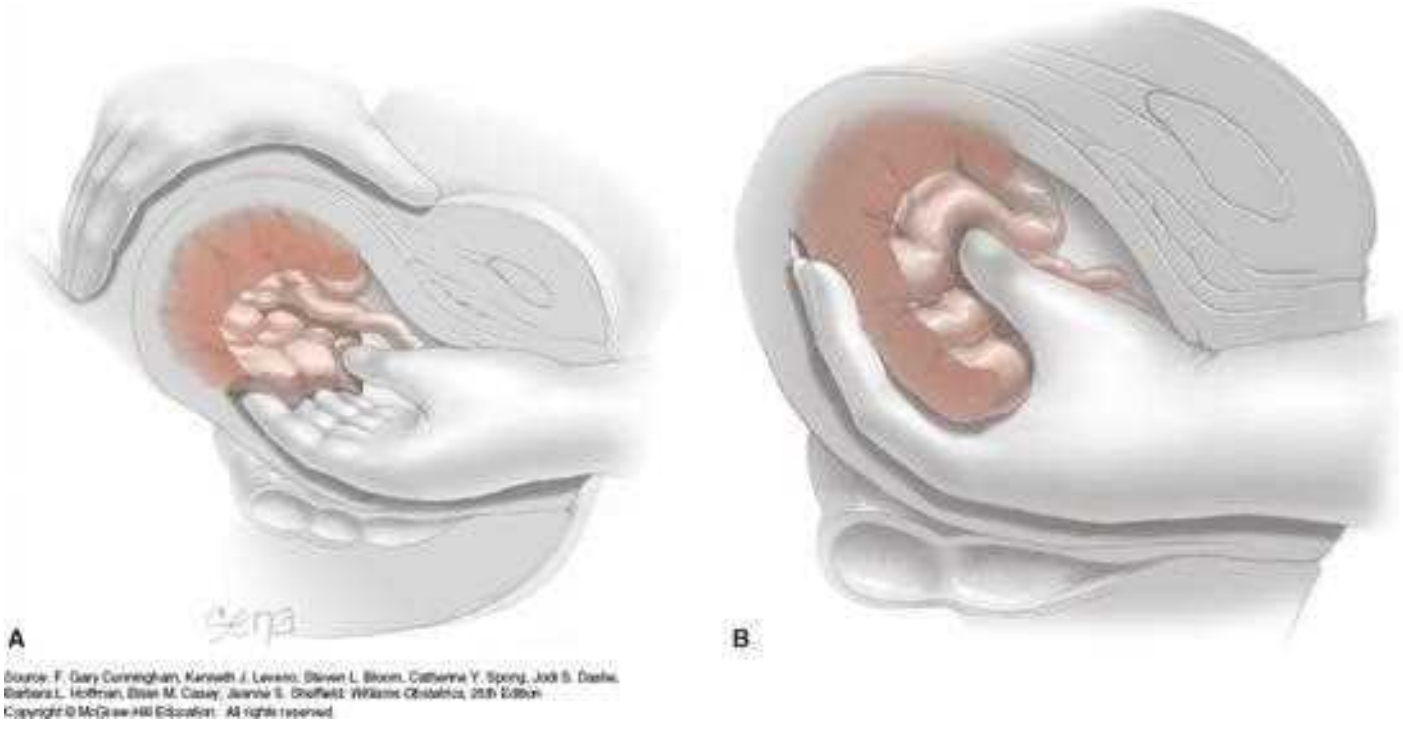
Third-Stage Labor Management

The most frequent cause of obstetrical hemorrhage is failure of the uterus to contract sufficiently after delivery and to arrest bleeding from vessels at the placental implantation site (General Considerations). That said, some bleeding is inevitable during third-stage labor as the placenta begins to separate. Blood from the implantation site may escape into the vagina immediately—the *Duncan mechanism* of placental separation, or it remains concealed behind the placenta and membranes until the placenta is delivered—the *Schultze mechanism.* After signs of placental separation, the uterus should be massaged if it is not contracted firmly, and placental descent is indicated by a slack umbilical cord. *Importantly, separation and delivery of the placenta by cord traction, especially when the uterus is atonic, may cause uterine inversion.*

If heavy bleeding persists after delivery of the newborn and while the placenta remains partially or totally attached, then manual placental removal is indicated (Cummings, 2016; Frolova, 2016). For this, adequate analgesia is mandatory, and aseptic surgical technique should be used. As illustrated in Figure 41-3, the fingertips of one hand, with fingers approximated, are insinuated between the uterine wall and placenta. A sweeping forward motion in this plane will peel the placenta off its uterine attachment. After its removal, trailing membranes are carefully teased free from the decidua using ring forceps as needed. Another method to clear membranes is to wipe out the uterine cavity with a gauze-wrapped hand. Most recommend ampicillin or cefazolin antimicrobial prophylaxis after manual removal (World Health Organization, 2015).

FIGURE 41-3

Manual removal of placenta. **A.** One hand grasps the fundus. The other hand is inserted into the uterine cavity, and the fingers are swept from side to side as they are advanced. **B.** When the placenta has become detached, it is grasped and removed.



The fundus is always palpated following placental delivery to confirm that the uterus is well contracted. If it is not firm, then vigorous fundal massage usually prevents postpartum hemorrhage from atony (Hofmeyr, 2013). Simultaneously, 20 units of oxytocin in 1000 mL of crystalloid solution will often be effective given intravenously at 10 mL/min for a dose of 200 mU/min. Higher concentrations are minimally more effective (Tita, 2012). *Oxytocin is never given as an undiluted bolus dose because serious hypotension or cardiac arrhythmias can develop.*

Risk Factors

In many women with known risks, uterine atony can at least be anticipated well in advance of delivery. In one study, however, up to half of women with atony after cesarean delivery had no risk factors (Rouse, 2006). The magnitude of risk for atony imposed by each of the factors shown in Table 41-2 varies considerably between reports. *Primiparity* and *high parity* are risk factors (Driessen, 2011). In one study, the incidence of postpartum hemorrhage rose from 0.3 percent in women of low parity to 1.9 percent with parity of four or greater. It was 2.7 percent with parity of seven or greater (Babinszki, 1999). The *overdistended uterus* is prone to hypotonia after delivery, and thus women with a large fetus, multiple fetuses, or hydramnios are at greater risk. *Labor abnormalities* predispose to atony and include hyper- or hypotonic labor. Similarly, *labor induction* or *augmentation* with either prostaglandins or oxytocin is more likely to be followed by atony (Driessen, 2011). The frequency of hemorrhage increases with prolongation of the third stage (Frolova, 2016). Finally, the woman who has had a *prior postpartum hemorrhage* is at risk for recurrence.

Evaluation and Management

With immediate postpartum hemorrhage, careful inspection is done to exclude birth canal laceration. Because bleeding can be caused by retained placental fragments, inspection of the placenta after delivery should be routine. If a defect is seen, the uterus should be manually explored and the fragment removed. Occasionally, retention of a *succenturiate lobe* may cause postpartum hemorrhage (Chap. 6, Shape and Size Variants). During examination for lacerations and causes of atony, the uterus is massaged and uterotonic agents are administered.

Uterotonic Agents

Several compounds can prompt the postpartum uterus to contract (Chap. 27, Immediate Postpartum Care). One of these is routinely selected and given to *prevent* postpartum bleeding by ensuring uterine contractions. Most of these same agents are also used to *treat* uterine atony with bleeding. Moreover, because many trials combine results from atony prophylaxis and treatment, their evaluation is problematic. For example, o*xytocin* has been used for more than 70 years, and in most cases, it is infused intravenously or given intramuscularly after placental delivery. Neither route has been shown to be superior (Dagdeviren, 2016). This or other uterotonics given prophylactically will prevent most cases of uterine atony.

To treat uterine atony, ergot alkaloids have been used for centuries. If atony persists despite oxytocin and other preventive measures, ergot derivatives can be used for second-line treatment. Ergot preparations include methylergonovine (Methergine) and ergonovine, however, only methylergonovine is currently manufactured in the United States. Given parenterally, these drugs rapidly stimulate tetanic uterine contractions and act for approximately 45 minutes (Schimmer, 2011). A common regimen is 0.2 mg of either drug given intramuscularly. Methergine can be repeated at 2- to 4-hour intervals as needed. *A caveat is that ergot agents, especially given intravenously, may cause dangerous hypertension, especially in women with preeclampsia.* Severe hypertension is also seen with concomitant use of protease inhibitors given for human immunodeficiency viral (HIV) infection. These adverse effects notwithstanding, it is speculative whether ergot derivatives offer superior therapeutic effects compared with oxytocin.

In cases of atony refractory to one agent, an agent from a different group can be added. At least two randomized studies have addressed combined ergot-oxytocin regimens. In one, ergometrine plus oxytocin was compared with ergometrine alone to prevent postpartum hemorrhage (Koen, 2016). The overall need for transfusion was significantly lower with the combination regimen. Another comparable study reaffirmed these findings (Şentürk, 2016).

During the past 40 years, other second-line agents for atony have included the E- and F-series prostaglandins. Carboprost tromethamine (Hemabate) is the 15-methyl derivative of prostaglandin $F_{2\alpha}$. It is approved for uterine atony treatment in a dose of 250 µg (0.25 mg) given intramuscularly. This dose can be repeated if necessary at 15- to 90-minute intervals up to a maximum of eight doses. Observational data indicate an 88-percent success rate (Oleen, 1990). Carboprost causes side effects in approximately 20 percent of women. These include, in descending order of frequency, diarrhea, hypertension, vomiting, fever, flushing, and tachycardia. Another pharmacological effect is pulmonary airway and vascular constriction. Thus, carboprost should not be used for asthmatic women and those with suspected amnionic fluid embolism (General Management). We have occasionally encountered severe hypertension with carboprost given to women with preeclampsia. It has also been reported to cause arterial oxygen desaturation that averaged 10 percent (Hankins, 1988). Relative contraindications to carboprost include renal, liver, and cardiac disease (American College of Obstetricians and Gynecologists, 2017d).

E-series prostaglandins can also prevent or treat atony. Dinoprostone—prostaglandin E_2—may be used off label and is given as a 20-mg suppository per rectum or per vaginum every 2 hours. It typically causes diarrhea, which is problematic for the rectal route, whereas vigorous vaginal bleeding may preclude its use per vaginum. Hypotension, which is commonly encountered with hemorrhage, is considered a contraindication by some. Intravenous prostaglandin E_2—*sulprostone*—is used in Europe, but it is not available in the United States (Schmitz, 2011).

Misoprostol—*Cytotec*—is a synthetic prostaglandin E_1 analogue that is used for prevention and treatment of atony (Abdel-Aleem, 2001; Ugwu, 2016). Most studies have addressed prevention and have conflicting conclusions. In a Cochrane review, Mousa and associates (2014) reported no added benefits for misoprostol use compared with oxytocin or ergonovine for treatment. Derman and coworkers (2006) compared a 600-µg oral dose given preventively at delivery against placebo. They found that the drug lowered the incidence of hemorrhage from 12 to 6 percent and that of severe hemorrhage from 1.2 to 0.2 percent. In another study, Gerstenfeld and Wing (2001) concluded that 400 µg misoprostol administered rectally was not superior to intravenous oxytocin given to prevent postpartum hemorrhage. From a systematic review, Villar (2002) found that oxytocin and ergot preparations administered after delivery were more effective than misoprostol for

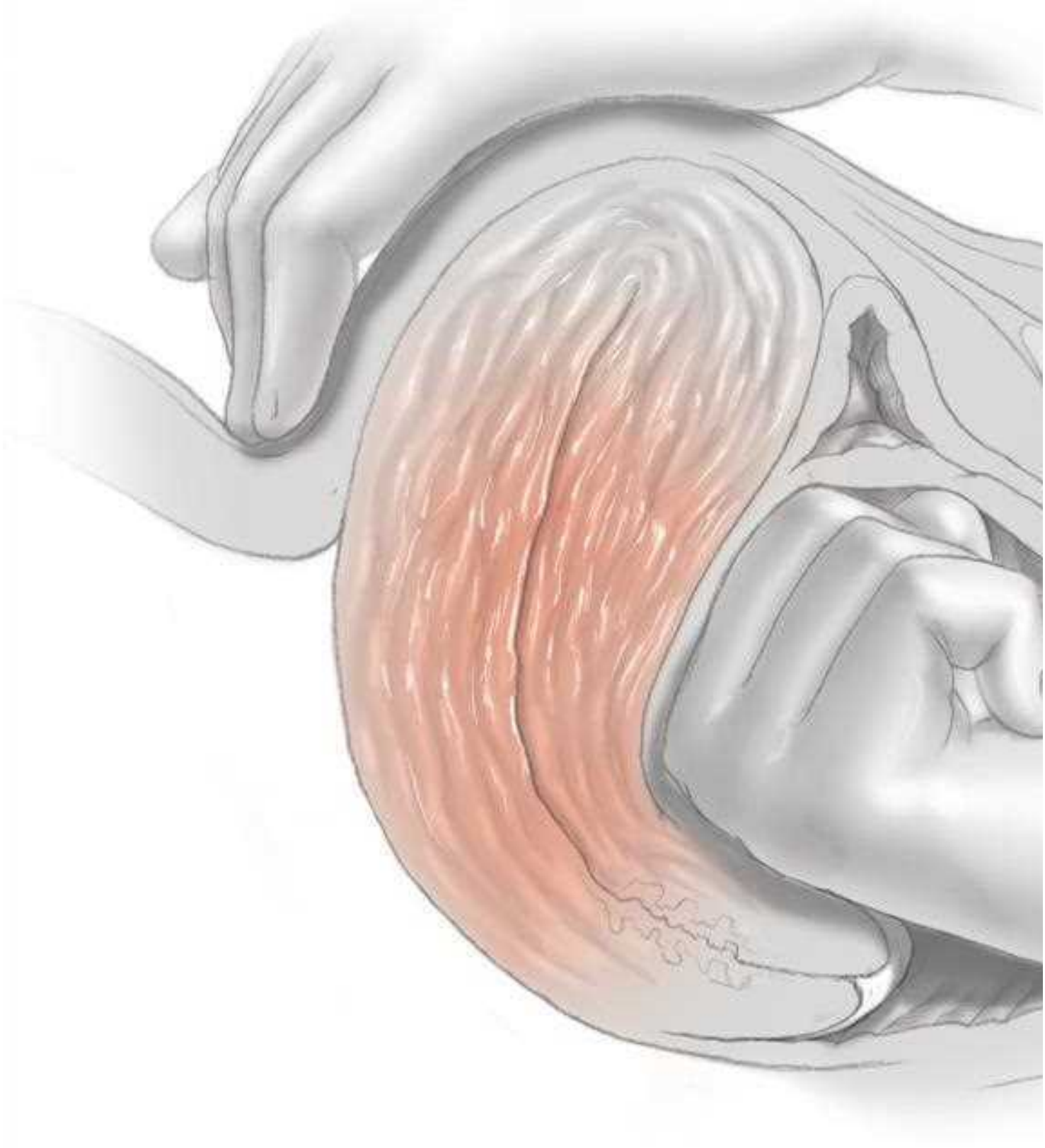
prevention of postpartum hemorrhage (Chap. 27, Immediate Postpartum Care). If misoprostol is used to treat atony, the American College of Obstetricians and Gynecologists (2017d) recommends a dose of 600 to 1000 µg rectally, orally, or sublingually.

Bleeding Unresponsive to Uterotonic Agents

If bleeding persists after initial measures for atony have been implemented, then the following management steps are performed immediately and simultaneously:

1. Begin bimanual uterine compression, which is easily done and controls most cases of continuing hemorrhage (Fig. 41-4). This technique is not simply fundal massage. The posterior uterine wall is massaged by one hand on the abdomen, while the other hand is made into a fist and placed into the vagina. This fist kneads the anterior uterine wall through the anterior vaginal wall and the uterus is also compressed between the two hands.
2. Immediately mobilize the emergent-care obstetrical team to the delivery room and call for whole blood or packed red cells.
3. Request urgent help from the anesthesia team.
4. Secure at least two large-bore intravenous catheters so that crystalloid with oxytocin can be continued simultaneously with blood products. Insert an indwelling Foley catheter for continuous urine output monitoring.
5. Begin volume resuscitation with rapid intravenous infusion of crystalloid (Hypovolemic Shock).
6. With sedation, analgesia, or anesthesia established and now with optimal exposure, once again manually explore the uterine cavity for retained placental fragments and for uterine abnormalities, including lacerations or rupture.
7. Thoroughly inspect the cervix and vagina again for lacerations that may have escaped attention.
8. If the woman is still unstable or if there is persistent hemorrhage, then blood transfusions are given (Hypovolemic Shock).

FIGURE 41-4
Bimanual compression for uterine atony. The uterus is positioned with the fist of one hand in the anterior fornix pushing against the anterior wall, which is held in place by the other hand on the abdomen. The abdominal hand is also used for uterine massage.



At this juncture, after causes other than atony have been excluded and after hypovolemia is reversed, several other measures are considered if bleeding continues. Their use depends on several factors such as parity, desire for sterilization, and experience with each method.

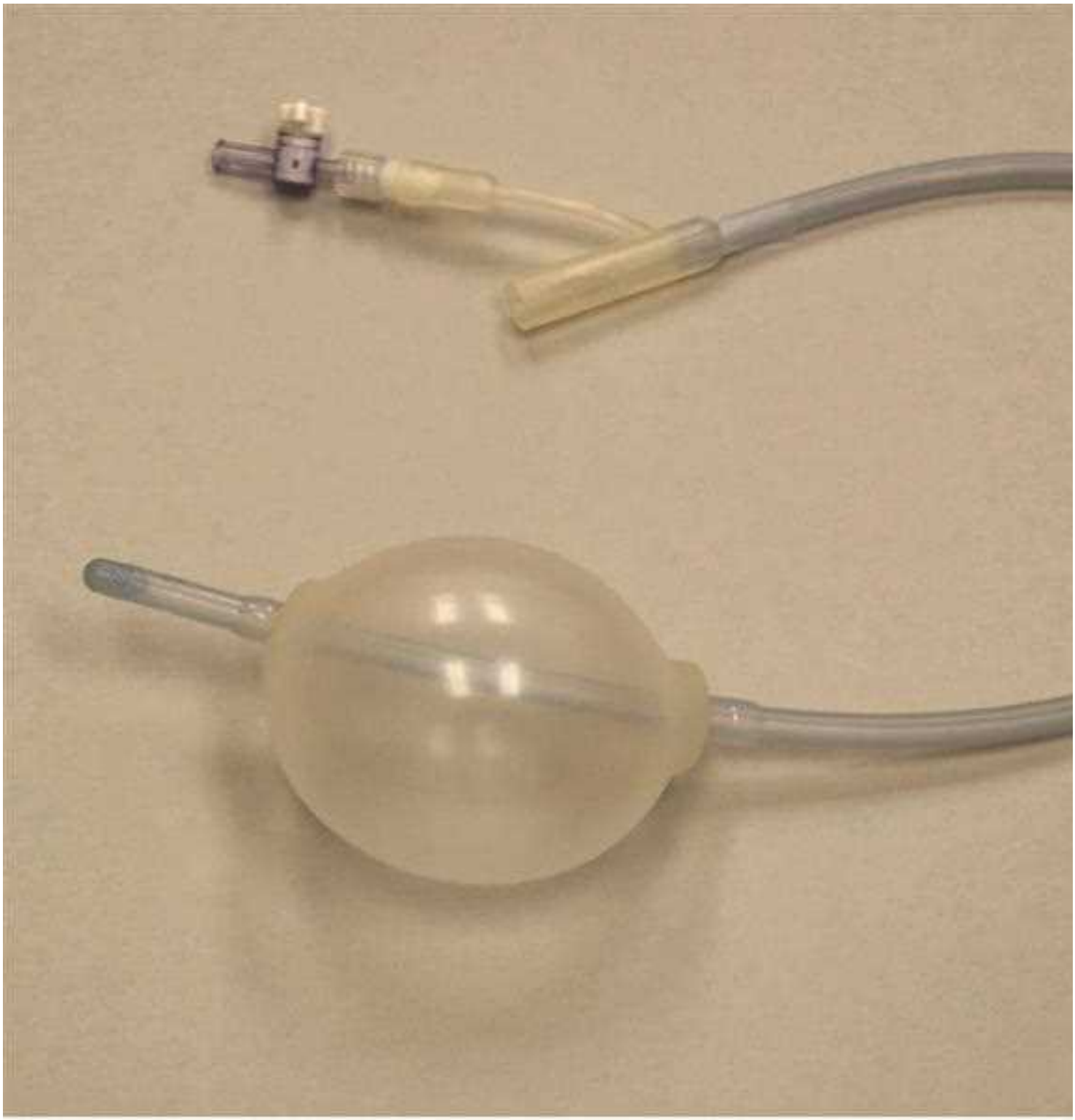
Balloon Tamponade

Uterine packing to treat refractory uterine atony fell from favor because of concerns regarding concealed bleeding and infection (Gilstrap, 2017). Newer techniques of balloon tamponade help alleviate some of these concerns (Sentilhes, 2016; Zelop, 2011). In one technique, the tip of a 24F to 30F Foley catheter with a 30-mL balloon is guided into the uterine cavity and filled with 60 to 80 mL of saline. The open tip permits continuous drainage of blood from the uterus. We have experienced balloon rupture when more than 50 mL was instilled into the balloon, thus a 34F Foley with a 60-ml balloon can be used. If bleeding subsides, the catheter is typically

removed after 12 to 24 hours. Similar devices for tamponade include Segstaken-Blakemore, Rusch, and ebb balloons and condom catheters (Antony, 2017; Georgiou, 2009).

Enthusiasm has developed for specially constructed intrauterine balloons to treat hemorrhage from uterine atony and other causes. A *Bakri Postpartum Balloon* or *BT-Cath* may be inserted and inflated to tamponade the endometrial cavity and stop bleeding (Fig. 41-5). Insertion requires two or three team members. The first performs abdominal sonography during the procedure. The second places the deflated balloon into the uterus and stabilizes it. The third member instills fluid to inflate the balloon, rapidly infusing at least 150 mL followed by further instillation over a few minutes for a total of 300 to 500 mL to arrest hemorrhage. It is reasonable to remove the balloon after approximately 12 hours (Einerson, 2017).

FIGURE 41-5
Intrauterine Bakri balloon for postpartum hemorrhage.



In prospective studies, nearly 150 women have been managed for postpartum hemorrhage with these uterine balloons (Grönvall, 2013; Kaya, 2016; Vintejoux, 2015). Perhaps a fourth of cases were caused by uterine atony. For all causes, the success rate was noted to be approximately 85 percent. Combinations of balloon tamponade and uterine compression sutures have also been described (Diemert, 2012; Yoong, 2012). Failures for all of these require various surgical methods including hysterectomy.

Surgical Procedures

These include uterine compression sutures, pelvic vessel ligation, angiographic embolization, and hysterectomy. These are discussed in Adjunctive Surgical Procedures.

UTERINE INVERSION

Puerperal inversion of the uterus is one of the classic hemorrhagic disasters encountered in obstetrics. Unless promptly recognized and managed appropriately, associated bleeding often is massive. Risk factors include alone or in combination: (1) fundal placental implantation, (2) uterine atony, (3) cord traction applied *before* placental separation, and (4) abnormally adhered placentation such as with the accrete syndromes (Morbidly Adherent Placenta).

Depending on which of these factors are contributory, the incidence and severity of uterine inversion varies. There is progressive severity of inversion as shown in Figure 41-6. The worst scenario is complete inversion with the uterus protruding from the birth canal (Fig. 41-7).

FIGURE 41-6
Progressive degrees of uterine inversion.

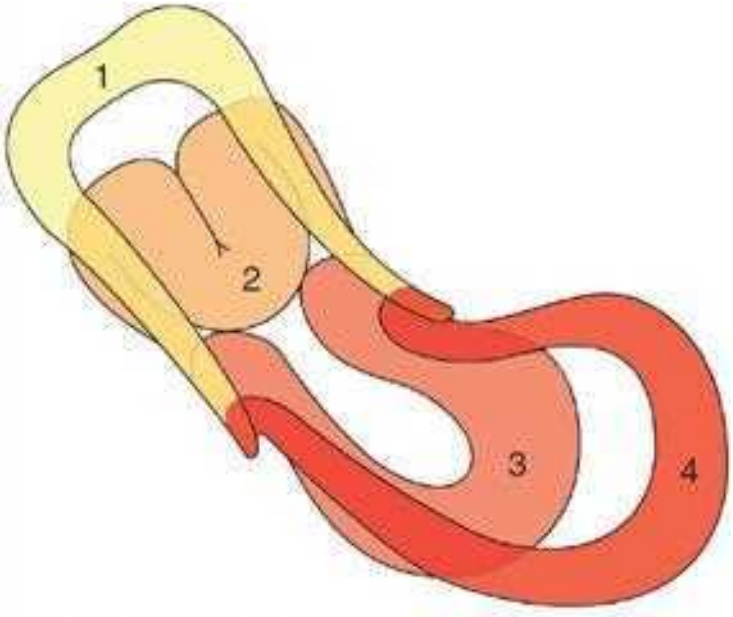
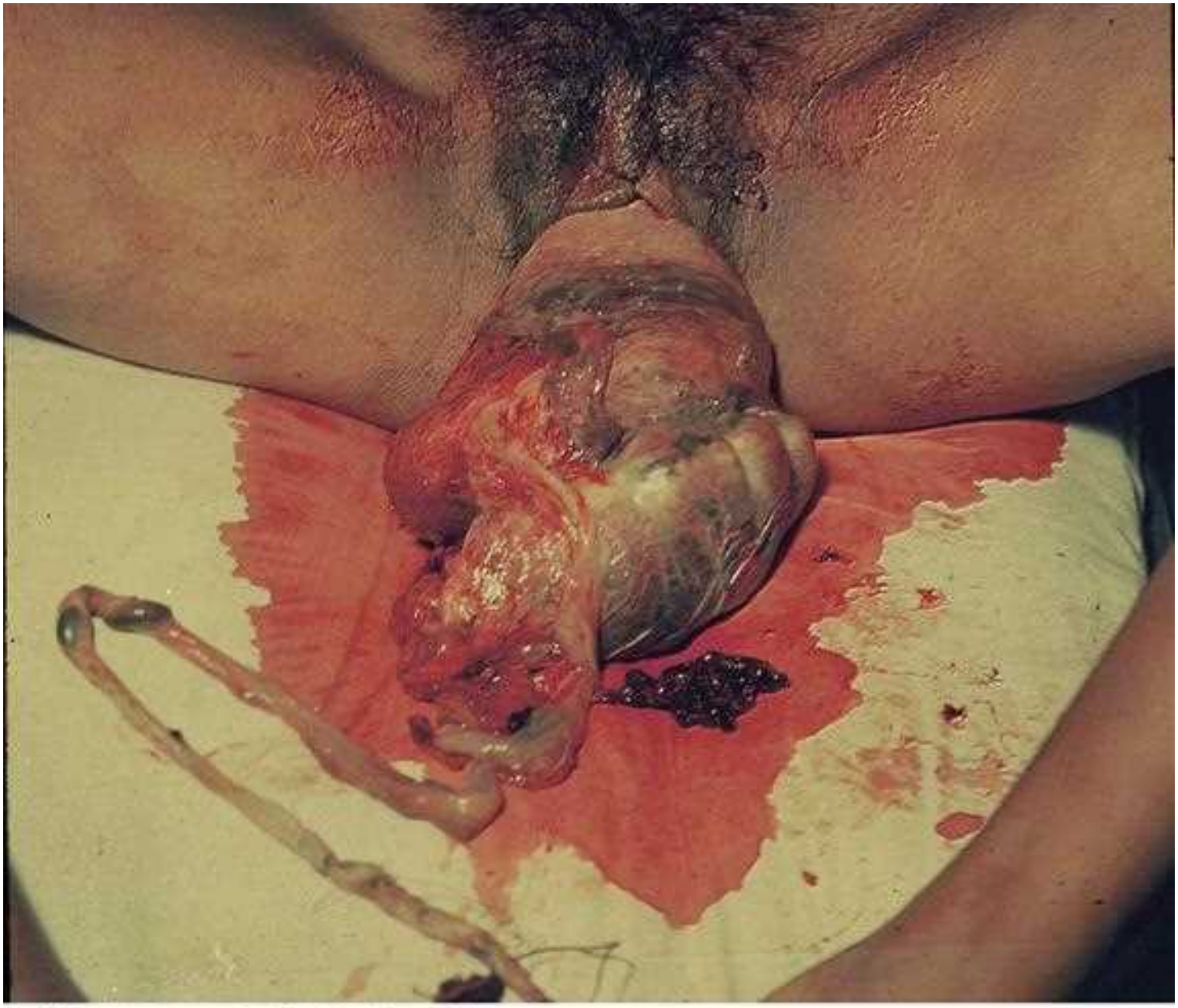


FIGURE 41-7
Maternal death during home delivery caused by exsanguination from uterine inversion and a fundally implanted placenta accreta.



The incidence of uterine inversion ranges from 1 in 2000 to 1 in 20,000 vaginal deliveries (Coad, 2017; Ogah, 2011; Rana, 2009; Witteveen, 2013). Our experiences at Parkland Hospital comport with the higher 1:2000 incidence. This is despite our policy of discouraging placental delivery by cord traction alone, and before certainty of its separation. It is unknown if *active management of third-stage labor* with cord traction applied ostensibly *after* signs of placental separation raises the likelihood of uterine inversion (Deneux-Tharaux, 2013; Gülmezoglu, 2012; Prick, 2013).

Recognition and Management

Immediate recognition of uterine inversion improves the chances of a quick resolution and good outcome (Furukawa, 2015b). If initially unrecognized, continued hemorrhage likely will prompt closer examination of the birth canal. Although complete inversion is usually evident, the partially inverted uterus can be mistaken for a uterine myoma, and sonography can aid differentiation (Pan, 2015; Smulian, 2013). Many cases are associated with immediate life-threatening hemorrhage, and a fourth require blood replacement (Coad, 2017).

Once any degree of uterine inversion is recognized, several steps must be implemented urgently and simultaneously:

1. Immediate assistance is summoned, including obstetrical and anesthesia personnel.
2. Blood is brought to the delivery suite for potential use.
3. The woman is evaluated for emergency general anesthesia. Large-bore intravenous infusion systems are secured to begin rapid crystalloid infusion to treat hypovolemia while awaiting arrival of blood products.

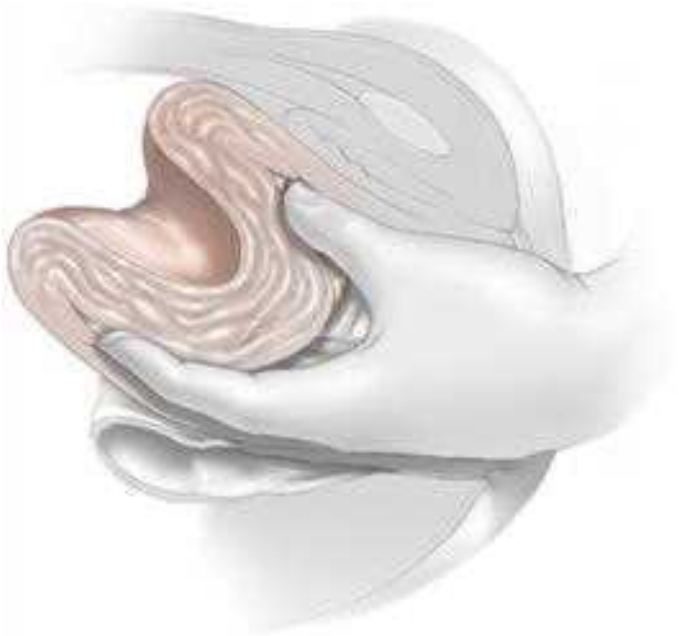
4. If the recently inverted uterus has not contracted and retracted completely and if the placenta has already separated, then the uterus may often be replaced simply by pushing up on the inverted fundus with the palm of the hand and fingers in the direction of the long axis of the vagina (Fig. 41-8). Some use two fingers rigidly extended to push the center of the fundus upward. *Care is taken not to apply so much pressure as to perforate the uterus with the fingertips.*

5. If the placenta is still attached, then attempts are made to reposition the uterus with the placenta in situ. Many recommend a trial of an intravenously administered tocolytic drug such as terbutaline, magnesium sulfate, or nitroglycerin for uterine relaxation and repositioning (You, 2006). If these fail to provide sufficient relaxation, then a rapidly acting halogenated inhalational agent is administered. After the uterus is replaced, the placenta is carefully manually removed.

6. If uterine repositioning fails with the placenta attached, then it is peeled off and steady pressure with the fist, palm, or fingers is applied to the inverted fundus in an attempt to push it up into and through the dilated cervix as described in Step 4.

7. Once the uterus is restored to its normal configuration, tocolysis is stopped. Oxytocin is then infused, and other uterotonics may be given as described for atony (Risk Factors). Meanwhile, the operator maintains the fundus in its normal anatomical position while applying bimanual compression to control further hemorrhage until the uterus is well contracted (see Fig. 41-4). The operator continues to monitor the uterus transvaginally for evidence of subsequent inversion. A Bakri balloon has been used to maintain the repositioned uterus (Haeri, 2015; Ida, 2015).

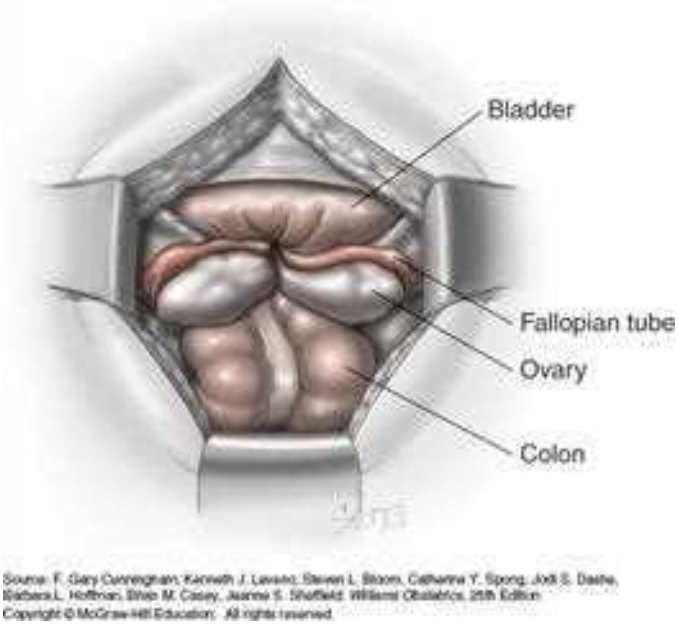
FIGURE 41-8
Incomplete uterine inversion repositioned by using the abdominal hand for palpation of the crater-like depression while simultaneously gently pushing the inverted fundus upward.



Surgical Intervention

In most cases, the inverted uterus can be restored to its normal position by the techniques just described. Occasionally, manual replacement fails. One cause is a dense myometrial constriction ring. At this point, laparotomy is imperative. The anatomical configuration found at surgery can be confusing as shown in Figure 41-9. With agents given for tocolysis, a combined effort is made to reposition the uterus by simultaneously pushing upward from below and pulling upward from above. Application of atraumatic clamps to each round ligament and upward traction may be helpful—the *Huntington procedure*. In some cases, placing a deep traction suture in the inverted fundus or grasping it with tissue forceps may be of aid. Either or both of these may be technically difficult. If a constriction ring still prohibits repositioning, a sagittal surgical cut—*Haultain incision*—is made posteriorly through the muscular ring to release it. The exposed fundus can then be reinverted (Sangwan, 2009). After uterine replacement, tocolytics are stopped, oxytocin and other uterotonics are given, and the uterine incision is repaired. Risks of separation of this posterior hysterotomy incision during subsequent pregnancy, labor, and delivery are unknown. Further illustration and discussion is found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Zahn, 2017).

FIGURE 41-9
Surgical anatomy of a completely inverted uterus viewed from above at laparotomy.



In some cases, the uterus will again invert almost immediately after repositioning. With this problem, uterine compression sutures can be used to prevent another inversion (Matsubara, 2009; Mondal, 2012). Occasionally, chronic puerperal uterine inversion may become apparent weeks after delivery.

INJURIES TO THE BIRTH CANAL

Childbirth is invariably associated with trauma to the birth canal, which includes the uterus and cervix, vagina, and perineum. Injuries sustained during labor and delivery range from minor mucosal tears to lacerations that create life-threatening hemorrhage or hematomas.

Vulvovaginal Lacerations

According to the American College of Obstetricians and Gynecologists (2016b), up to 80 percent of women sustain some type of laceration at vaginal delivery. These may lie proximally or distally along the lower genital tract.

First, small tears of the anterior vaginal wall near the urethra are relatively common. They are often superficial with little to no bleeding, but they occasionally require sutures for hemostasis. Those large enough to require extensive repair are typically associated with short-term voiding difficulty, and an indwelling bladder catheter will obviate this.

Deeper perineal lacerations are usually accompanied by varying degrees of injury to the outer third of the vaginal vault. Some extend to involve the anal sphincter or varying depths of the vaginal walls. Repair of these perineal lacerations is detailed in Chapter 27 (Laceration and Episiotomy Repairs).

Lacerations involving the middle or upper third of the vaginal vault usually are comorbid with injuries of the perineum or cervix. These sometimes are missed unless inspection is thorough. Those that extend upward usually are longitudinal. They may follow spontaneous delivery but frequently result from injuries sustained during operative vaginal delivery. Most involve deeper underlying tissues and thus usually cause significant hemorrhage, which is controlled by suture repair. For this, effective analgesia or anesthesia, clear visualization, capable assistance, and sufficient resuscitation of hypovolemia are mandatory.

Extensive vaginal or cervical tears should prompt a careful search for evidence of retroperitoneal hemorrhage or of peritoneal perforation with hemorrhage. Also, intrauterine exploration is considered to exclude uterine tears or rupture (Conrad, 2015). If peritoneal perforation or uterine rupture is strongly suspected, laparotomy is considered (Rafi, 2010). As discussed later (Angiographic Embolization), imaging and potential embolization may be suitable for large retroperitoneal hematomas.

Cervical Lacerations

Superficial lacerations of the cervix can be seen on close inspection in more than half of all vaginal deliveries. Most of these measure <0.5 cm and seldom require repair. Deeper lacerations are less frequent, but even these may be unnoticed. Due to ascertainment bias, variable incidences are described. For example, with close inspection, the incidence of cervical lacerations in the Consortium on Safe Labor database was 1 percent in nulliparas and 0.5 percent in multiparas (Landy, 2011). But, the overall incidence in a study of more than 81,000 Israeli women was only 0.16 percent (Melamed, 2009). Such lacerations are more likely to be associated with vacuum- or forceps-assisted vaginal delivery (Fong, 2014).

Cervical lacerations are not usually problematic unless they cause hemorrhage or extend to the vagina. Rarely, the cervix may be entirely or partially avulsed from the vagina in the anterior, posterior, or lateral fornices, an injury termed co*lporrhexis*. Another rare injury is when the entire vaginal portion of the cervix is avulsed—*annular* or *circular detachment*. These injuries sometimes follow forceps deliveries performed through an incompletely dilated cervix with the blades applied over the cervix. In some women, cervical tears reach into the lower uterine segment and involve the uterine artery and its major branches. They occasionally extend into the peritoneal cavity. More severe lacerations usually manifest as external hemorrhage or as a hematoma, however, they may occasionally be unsuspected. In the Israeli study just cited, almost 11 percent of women with a cervical laceration required blood transfusions (Melamed, 2009).

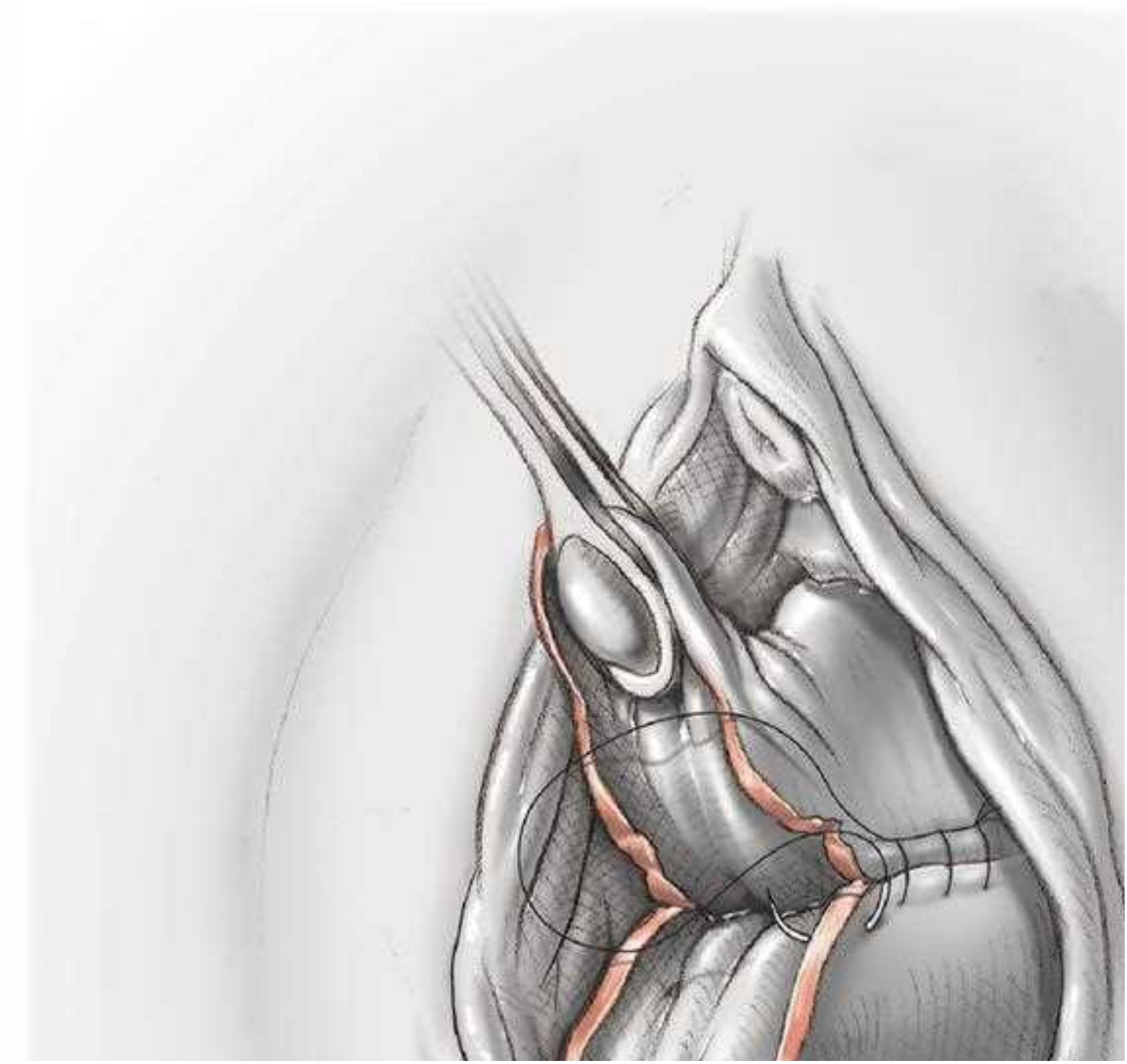
At times, the edematous anterior cervical lip is compressed between the fetal head and maternal symphysis pubis. This usually is of little consequence and resolves spontaneously. Rarely, this causes severe ischemia, and the anterior lip may undergo necrosis and subsequently separate from the rest of the cervix.

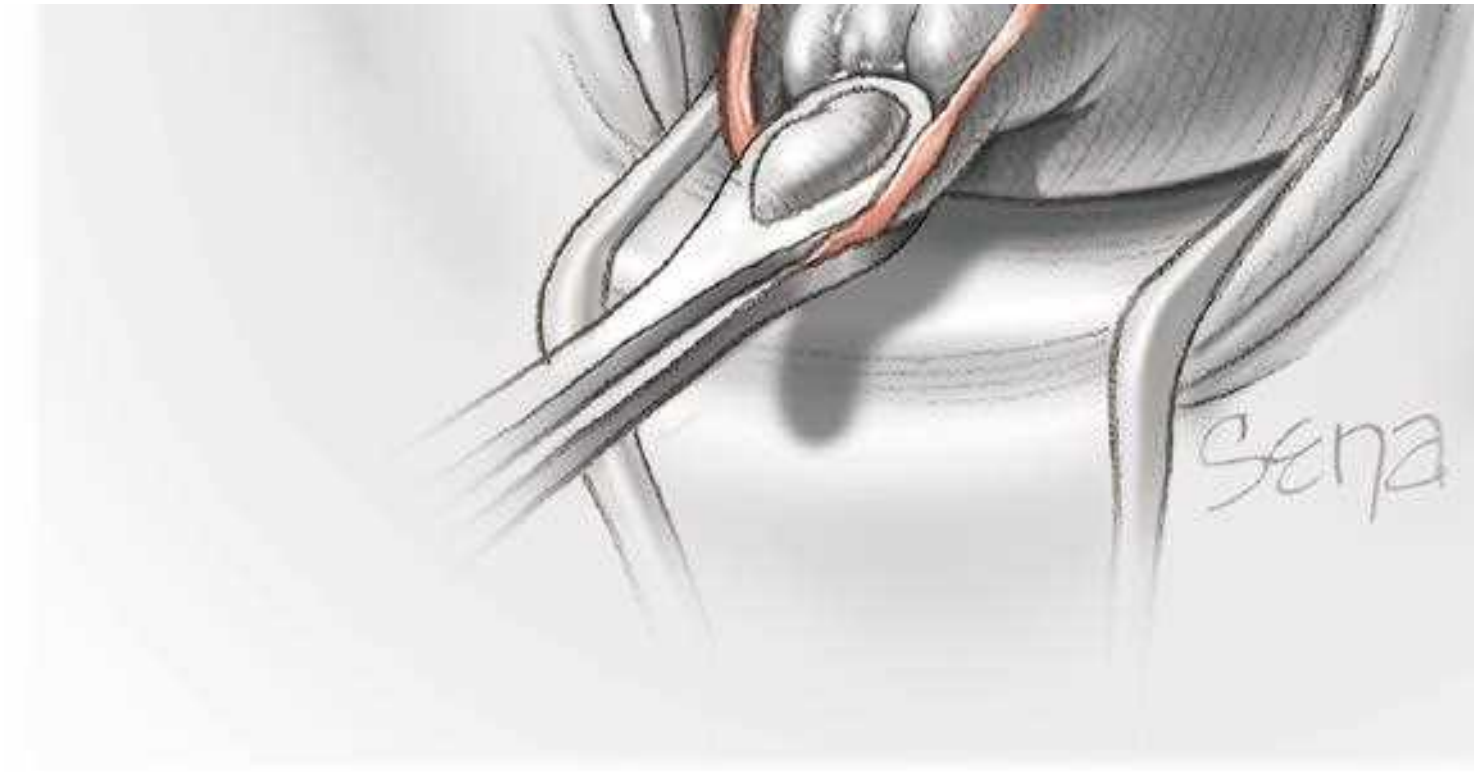
As with vulvovaginal lacerations, cervical tears can be more fully appreciated with adequate exposure, which may be best attained with transfer to an operating room. An assistant applies firm downward pressure on the uterus, while the operator exerts gentle traction on the lips of the cervix with ring forceps. A second assistant can provide even better exposure with right-angle vaginal wall retractors or Breisky vaginal retractors. Use of suction devices can also aid viewing.

In general, cervical lacerations of 1 and even 2 cm are not repaired unless they are bleeding. Such tears heal rapidly and ultimately create an irregular, sometimes stellate appearing, external cervical os that indicates previous delivery.

Deep cervical tears usually require surgical repair. When the laceration is limited to the cervix or even when it extends somewhat into the vaginal fornix, satisfactory results are obtained by suturing the cervix after bringing it into view as depicted in Figure 41-10. While cervical lacerations are repaired, any associated vaginal lacerations or an episiotomy may be tamponaded with gauze packs to arrest their bleeding. Because hemorrhage usually comes from the upper angle of the wound, the first suture using 2–0 chromic or polyglactin is placed in tissue above the angle. Subsequently, either interrupted or continuous locking sutures are serially placed outward toward the operator. If the uterus is involved and hemorrhage persists, some of the methods described later (Adjunctive Surgical Procedures) may be necessary to obtain hemostasis.

FIGURE 41-10
Repair of cervical laceration with appropriate surgical exposure. Continuous absorbable sutures are placed beginning at the upper angle of the laceration.



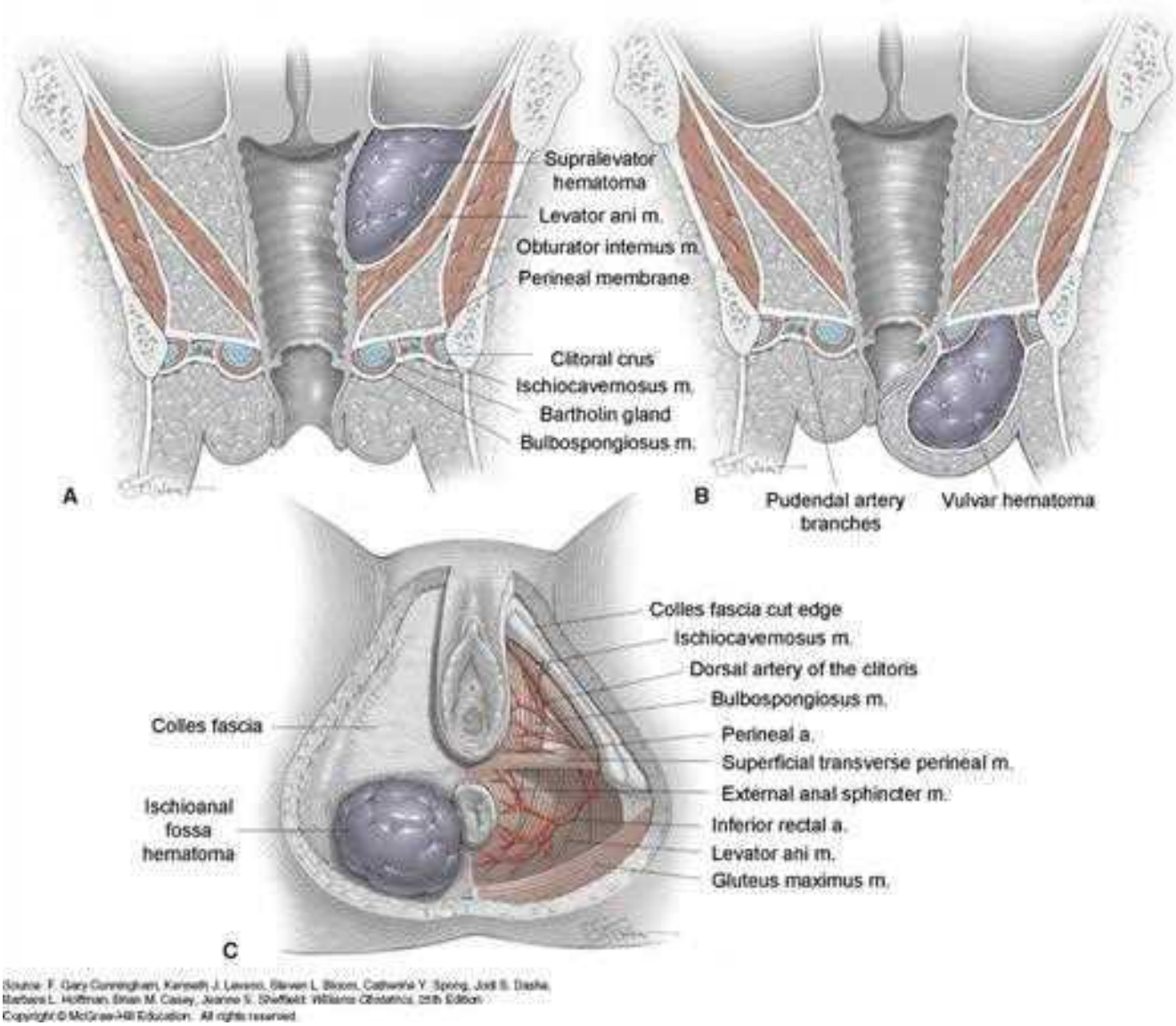


Puerperal Hematomas

Classification and Risks

Pelvic hematomas can have several anatomical manifestations following childbirth. One classification is anatomical and describes vulvar, vulvovaginal, paravaginal, and retroperitoneal hematomas. Vulvar hematomas may involve the vestibular bulb or branches of the pudendal artery, which are the inferior rectal, perineal, and clitoral arteries (Fig. 41-11). Paravaginal hematomas may involve the descending branch of the uterine artery. In some cases, a torn vessel lies above the pelvic fascia, and a supralevator hematoma develops. These can extend into the upper portion of the vaginal canal and may almost occlude its lumen. Continued bleeding may dissect retroperitoneally to form a mass palpable above the inguinal ligament. In some cases, it may even dissect up behind the ascending colon to the hepatic flexure (Rafi, 2010).

FIGURE 41-11
Schematic drawing showing types of puerperal hematomas. **A.** Coronal view showing a supralevator hematoma. **B.** Coronal view showing an anterior perineal triangle hematoma. **C.** Perineal view showing posterior perineal triangle anatomy and an ischioanal fossa hematoma. (Reproduced with permission from Cunningham FG: Genital tract lacerations and hematomas. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017a.)

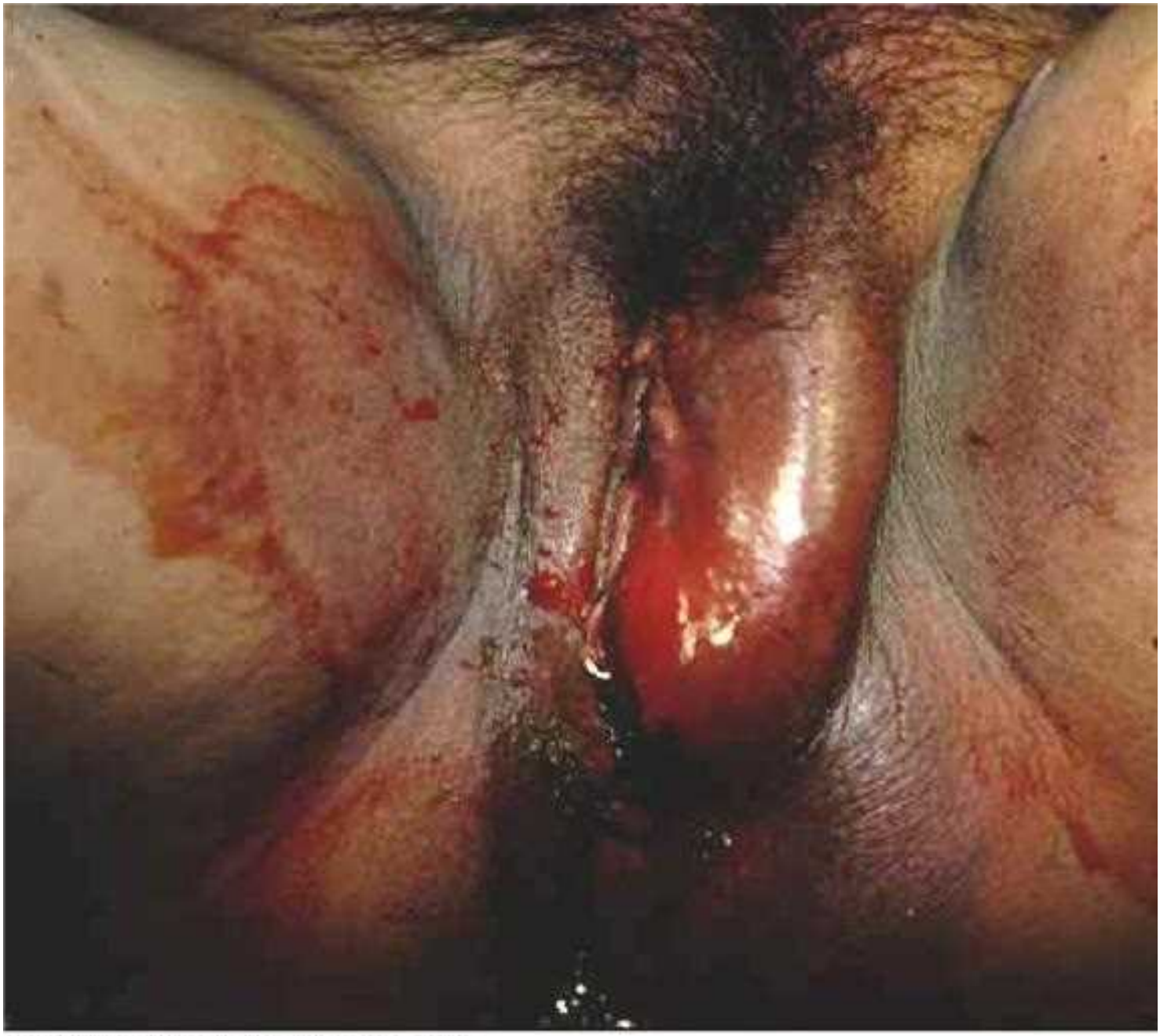


Risks for puerperal hematomas include vaginal or perineal laceration, episiotomy, or an operative delivery (Iskender, 2016). Any hematoma can also develop following stretch and rupture of a blood vessel without an associated laceration (Nelson, 2012). This may be especially true with forceps delivery. Occasionally, they are associated with an underlying coagulopathy (Obstetrical Coagulopathies).

Diagnosis

Perineal, vulvar, and paravaginal hematomas can develop rapidly and frequently cause excruciating pain (Fig. 41-12). A tense, tender swelling of varying size rapidly develops, encroaches on the vaginal lumen, and causes overlying skin or epithelium to become ecchymotic. A paravaginal hematoma may escape detection initially. However, symptoms of pelvic pressure, pain, or inability to void should prompt evaluation. Others may go undetected until other measures of hypovolemia become evident. When there is a supralevator extension, the hematoma extends upward in the paravaginal space and between the leaves of the broad ligament. The hematoma may escape detection until it can be felt on abdominal palpation or until hypovolemia develops. Imaging with sonography or computed tomographic scanning may be useful (Cichowski, 2017; Kawamura, 2014; Takeda, 2014).

FIGURE 41-12
Left-sided anterior perineal triangle hematoma associated with a vaginal laceration following spontaneous delivery in a woman with consumptive coagulopathy from acute fatty liver of pregnancy.



Clinical Course and Management

Small hematomas often remained contained and show minimal expansion. In others, the tissues overlying an expanding hematoma may rupture from pressure necrosis. In some, profuse hemorrhage may follow, but in other cases, the hematoma drains in the form of large clots and old blood. In those that involve the paravaginal space and extend above the levator sling, retroperitoneal bleeding may be massive and occasionally fatal. Finally, we have encountered a few that rebled up to 2 weeks postpartum (Cunningham, 2017a).

Vulvovaginal hematomas are managed according to their size, location, duration since delivery, and expansion. If bleeding ceases, then small- to moderate-sized hematomas may be treated expectantly until absorbed. But, if pain is severe or if the hematoma continues to enlarge, surgical exploration is preferable. *Blood loss with large puerperal hematomas is nearly always considerably more than the clinical estimate.* Hypovolemia is common, and transfusions are frequently required when surgical repair is necessary.

For repair, an incision is made at the point of maximal distention, blood and clots are evacuated, and bleeding points ligated. The cavity may then be obliterated with absorbable sutures. Often, no sites of bleeding are identified. Nonetheless, the evacuated hematoma cavity is surgically closed, and the vagina is packed for 12 to 24 hours. Supralevator hematomas are more difficult to treat. Although some can be evacuated by vulvar or vaginal incisions, laparotomy or interventional embolization, described next, is a consideration if bleeding continues.

Angiographic embolization has become popular for management of some puerperal hematomas. This is especially true for supralevator or retroperitoneal hematomas. Embolization can be used primarily, or more likely secondarily, if surgical attempts at hemostasis have failed or if the hematoma is difficult to access surgically (Distefano, 2013; Lee, 2012; Poujade, 2012). The use of a Bakri balloon for a paracervical hematoma has also been described (Gizzo, 2013; Grönvall, 2013). Finally, ultrasound-guided drainage of a recurrent supralevator hematoma has been reported (Mukhopadhyay, 2015).

Uterine Rupture

Predisposing Factors

Uterine rupture frequently is catastrophic. It may be *primary*, defined as occurring in a previously intact or unscarred uterus, or may be *secondary* and associated with a preexisting incision, injury, or anomaly of the myometrium. Some of the etiologies associated with uterine rupture are presented in Table 41-3. Importantly, the contribution of each of these underlying causes has changed remarkably during the past 50 years. Specifically, before 1960, when the cesarean delivery rate was much lower and women of great parity were numerous, primary uterine rupture predominated. As the incidence of cesarean delivery rose and especially as a subsequent trial of labor in these women became prevalent through the 1990s, uterine rupture through the cesarean hysterotomy scar became the preeminent cause (Gibbins, 2015; Mone, 2016). However, concurrent with the diminished enthusiasm for a trial of labor in women with a prior cesarean delivery, incidence trends for the two types of rupture have again changed. In a study of 3942 cases of uterine rupture in more than 15 million women, approximately half were in women with a prior cesarean delivery (Yao, 2017). In 40 cases of rupture at Parkland Hospital from 2009 to 2016, 15 events (37 percent) were primary, and 25 (63 percent) were secondary (Happe, 2017).

TABLE 41-3

Some Causes of Uterine Rupture

Preexisting Uterine Injury or Anomaly	Uterine Injury or Abnormality Incurred in Current Pregnancy
Surgery involving the myometrium:	**Before delivery:**
Cesarean delivery or hysterotomy	Persistent, intense, spontaneous contractions
Previously repaired uterine rupture	Labor stimulation—oxytocin or prostaglandins
Myomectomy incision through or to the endometrium	Intraamnionic instillation—saline or prostaglandins
Deep cornual resection of interstitial fallopian tube	Perforation by internal uterine pressure catheter
Metroplasty	External trauma—sharp or blunt
Coincidental uterine trauma:	External version
Abortion with instrumentation—sharp or suction curette, sounds	Uterine overdistention—hydramnios, multifetal pregnancy
Sharp or blunt trauma—assaults, vehicular accidents, bullets, knives	**During delivery:**
Silent rupture in previous pregnancy	Internal version second twin
Congenital:	Difficult forceps delivery
Pregnancy in undeveloped uterine horn	Rapid tumultuous labor and delivery
Defective connective tissue—Marfan or Ehlers-Danlos syndrome	Breech extraction
	Fetal anomaly distending lower segment
	Vigorous uterine pressure during delivery
	Difficult manual removal of placenta
	Acquired:
	Placental accrete syndromes
	Gestational trophoblastic neoplasia
	Adenomyosis
	Sacculation of entrapped retroverted uterus

Additional risks for rupture include other previous operations or manipulations that traumatize the myometrium. Examples are uterine curettage or perforation, endometrial ablation, myomectomy, or operative hysteroscopy (Kieser, 2002; Pelosi, 1997). In a study by Porreco and colleagues (2009), seven of 21 women without a prior cesarean delivery had undergone prior uterine surgery.

In developed countries, the incidence of rupture is 1 in 4800 deliveries (Getahun, 2012). During a 40-year period in Norway, the uterine rupture rate rose significantly to about 1 in 1560 deliveries (Al-Zirqi, 2016). The frequency of primary rupture, however, approximates 1 in 10,000 to 15,000 births (Porreco, 2009). As discussed, one reason is a decreased incidence of women of great parity. Another is that excessive or inappropriate uterine stimulation with oxytocin—previously a frequent cause—has mostly disappeared. Maggio and associates (2014) found no association between the number of Montevideo units and secondary uterine rupture. In addition, in a recent analysis of three trials comparing high- versus low-dose oxytocin regimens, the rate of uterine rupture did not differ between groups (Budden, 2014). The rate of rupture is elevated with sequential induction of labor with prostaglandins and oxytocin (Al-Zirqi, 2017). At Parkland Hospital, we too have encountered primary uterine rupture in a disparate number of women in whom labor was induced with prostaglandin E_1.

Blunt abdominal trauma can precipitate uterine rupture. Although the distended pregnant uterus is surprisingly resistant, pregnant women sustaining such trauma should be watched carefully for signs of a ruptured uterus (Chap. 47, Other Blunt Trauma). In one study of 13 cases of primary uterine rupture, trauma accounted for

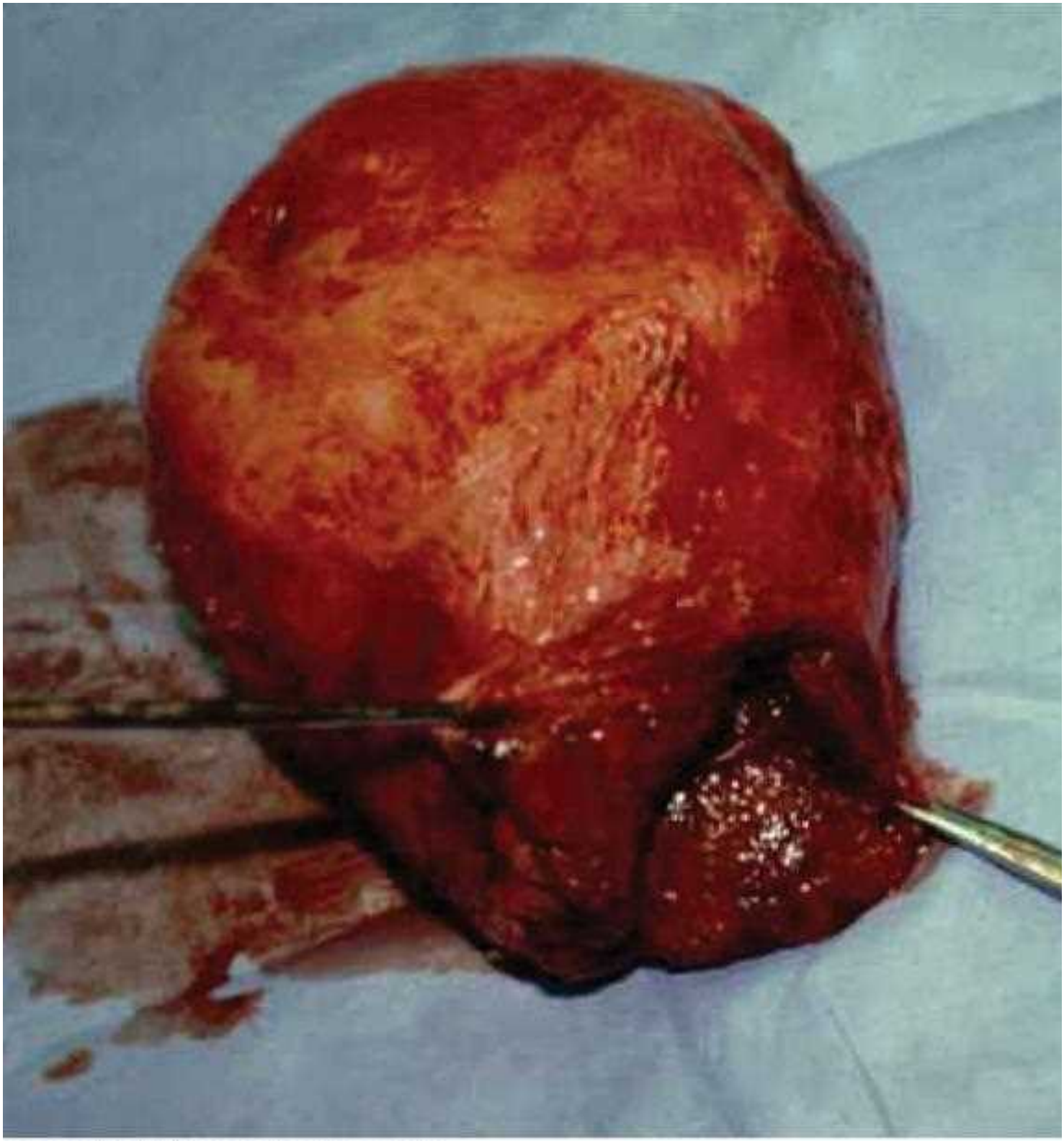
three cases (Miller, 1996). Other causes of traumatic rupture that are uncommon today are those due to internal podalic version and extraction, difficult forceps delivery, breech extraction, and unusual fetal enlargement such as with hydrocephaly.

Uncommon associations of rupture are uterine anomalies or multifetal pregnancy (Bankada, 2015; Tarney, 2013; Tola, 2014). Occasionally, focal inherent weakness in the myometrium predisposes to rupture. Examples include anatomical anomalies, leiomyomas, adenomyosis, choriocarcinoma, and connective-tissue defects such as Ehlers-Danlos syndrome (Arici, 2013; Nikolaou, 2013; Noh, 2013; Ramskill, 2014; Sun, 2016).

Pathogenesis

Rupture of the previously intact uterus during labor most often involves the thinned-out lower uterine segment. When the rent is in the immediate vicinity of the cervix, it frequently extends transversely or obliquely. When the rent forms in the portion of the uterus adjacent to the broad ligament, the tear is usually longitudinal. Although these tears develop primarily in the lower uterine segment, they can extend upward into the active segment or downward through the cervix and into the vagina (Fig. 41-13). In some cases, the bladder may also be lacerated. If the rupture is of sufficient size, the uterine contents will usually escape into the peritoneal cavity. If the presenting fetal part is firmly engaged, however, then only a portion of the fetus may be extruded from the uterus. Fetal prognosis is largely dependent on the degree of placental separation and magnitude of maternal hemorrhage and hypovolemia. In some cases, the overlying peritoneum remains intact, and this usually is accompanied by hemorrhage that extends into the broad ligament to cause a large retroperitoneal hematoma.

FIGURE 41-13
Supracervical hysterectomy specimen showing uterine rupture during spontaneous labor with a vertical tear at the left lateral edge of lower uterine segment.



Following vaginal delivery in an unscarred uterus, we and others have occasionally encountered cases of an incomplete tear on the inside of the uterus that extends vertically into the active segment and is a source of profuse hemorrhage (Conrad, 2015). These tears are usually not visible from below but are found at the time of hysterectomy for intractable bleeding despite a contracted uterus. Hemorrhage with this type of tear can be torrential, and bleeding is usually not slowed until the uterine artery pedicles are clamped bilaterally.

Management and Outcomes

The varied clinical presentations of uterine rupture and its management are discussed in detail in Chapter 31 (Uterine Scar Rupture). In the most recent maternal mortality statistics from the Centers for Disease Control and Prevention, uterine rupture accounted for almost 10 percent of deaths caused by hemorrhage (Creanga, 2015, 2017). Maternal morbidity includes hysterectomy that may be necessary to control hemorrhage. Rates of perinatal mortality and morbidity, which may include

severe neurological impairment, are also high (Gibbins, 2015; Porreco, 2009). Maternal obesity comorbid with uterine rupture is associated with increased rates of adverse neonatal outcomes (Yao, 2017).

PLACENTAL ABRUPTION

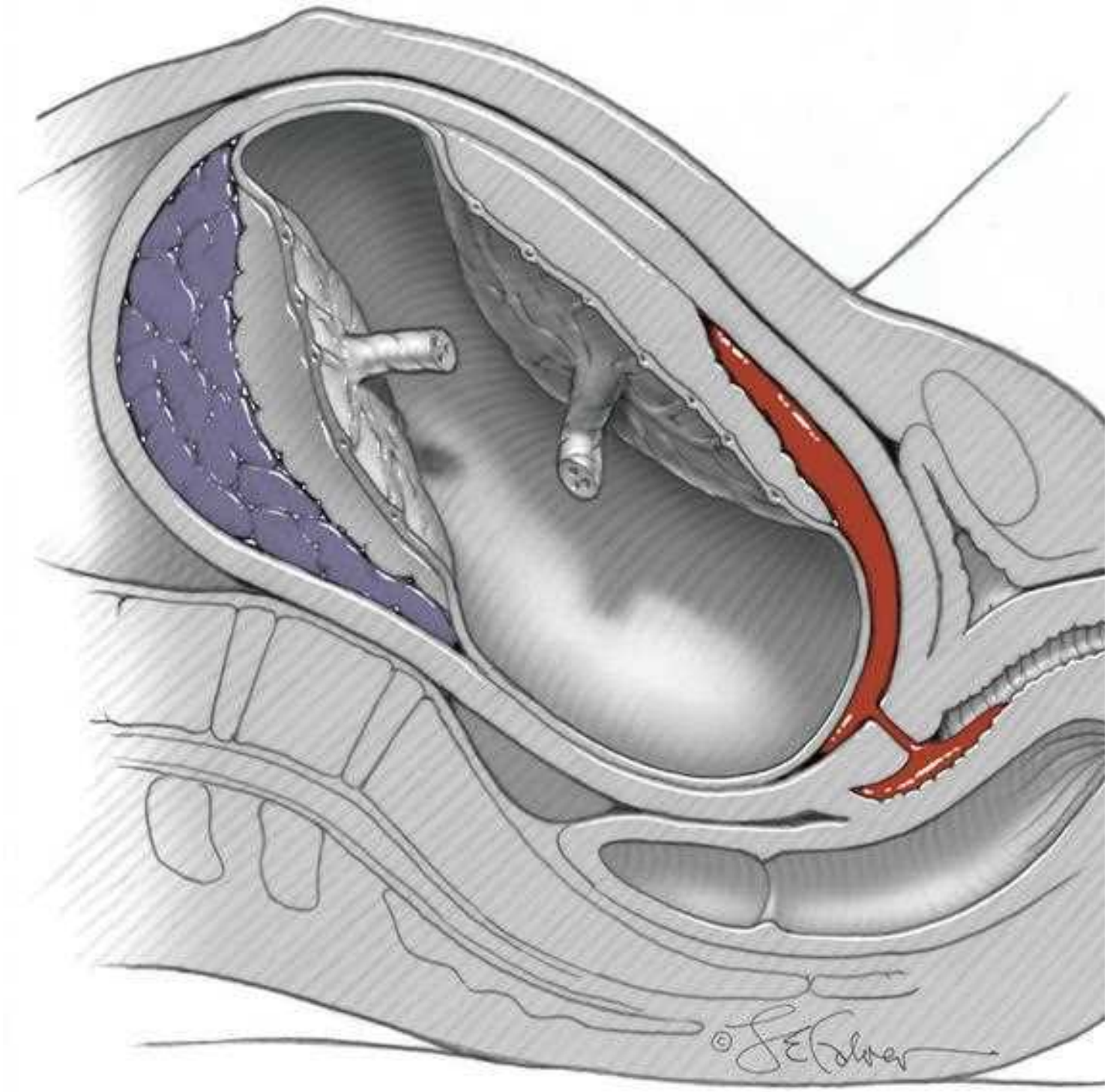
Etiopathogenesis

Separation of the placenta—either partially or totally—from its implantation site before delivery is described by the Latin term *abruptio placentae*. Literally translated, this refers to "rending asunder of the placenta," which denotes a sudden accident that is a clinical characteristic of most cases. In the purest sense, the cumbersome—and thus seldom used—term *premature separation of the normally implanted placenta* is most descriptive because it excludes separation of a placenta previa.

Placental abruption is initiated by hemorrhage into the decidua basalis. The decidua then splits, leaving a thin layer adhered to the myometrium. Consequently, the process begins as a decidual hematoma and expands to cause separation and compression of the adjacent placenta. Inciting causes of many cases have been posited. The phenomenon of impaired trophoblastic invasion with subsequent atherosis is related in some cases of preeclampsia complicated by abruption (Brosens, 2011). Inflammation or infection may be contributory (Mhatre, 2016; Nath, 2007). Histological findings cannot be used to determine timing of the abruption (Chen, 2017).

Abruption likely begins with rupture of a decidual spiral artery and then an expanding retroplacental hematoma. In the early stages of placental abruption, clinical symptoms may be absent. Even with continued bleeding and placental separation, placental abruption can still be either *total* or *partial* (Fig. 41-14). With either, bleeding typically insinuates itself between the membranes and uterus, ultimately escaping through the cervix to cause *external hemorrhage*. Less often, the blood is retained between the detached placenta and the uterus, leading to *concealed hemorrhage* and delayed diagnosis. The delay translates into greater maternal and fetal hazards. Also with concealed hemorrhage, the likelihood of consumptive coagulopathy is elevated. This is because increased pressure within the intervillous space, caused by the expanding retroplacental clot, forces more placental thromboplastin into the maternal circulation (Diagnosis).

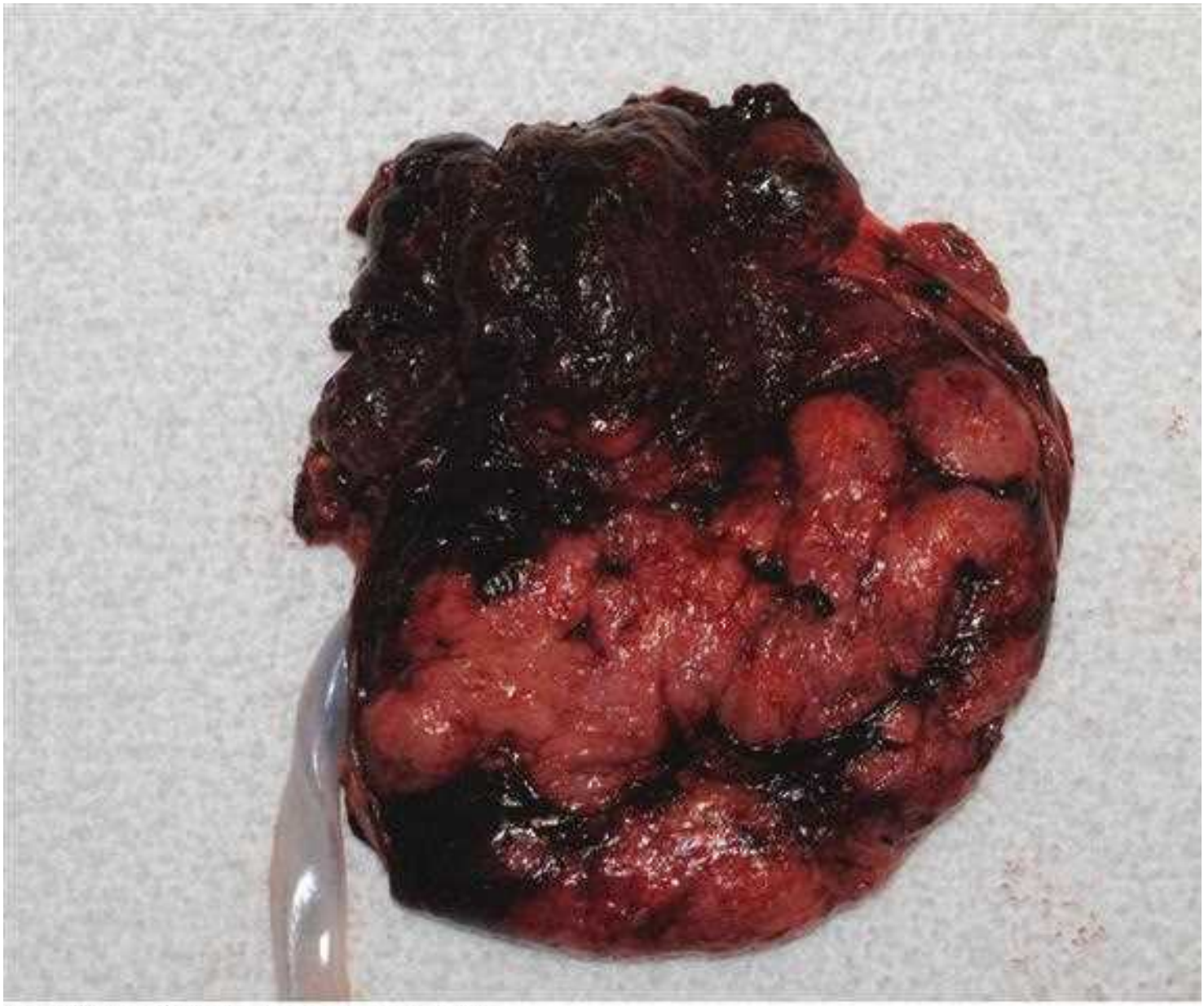
FIGURE 41-14
Schematic of placental abruption. Shown to left is a total placental abruption with concealed hemorrhage. To the right is a partial abruption with blood and clots dissecting between membranes and decidua to the internal cervical os and then externally into the vagina.



Most blood in the retroplacental hematoma in a nontraumatic placental abruption is maternal. This is because hemorrhage derives from separation within the maternal decidua, and placental villi are usually initially intact. In 78 women at Parkland Hospital with a nontraumatic placental abruption, fetal-to-maternal hemorrhage was documented in only 20 percent—and all of these had <10 mL fetal blood loss (Stettler, 1992). Atkinson and colleagues (2015) identified fetal cells in peripheral blood in only 4 percent of 68 women with a placental abruption.

When clinically suspected, an abruption is seen on a freshly delivered placenta as a circumscribed depression on the maternal surface. These usually measure a few centimeters in diameter and are covered by dark, clotted blood. Because several minutes are required for these anatomical changes to materialize, a very recently separated placenta may appear totally normal at delivery. Our experiences are like those of Benirschke and associates (2012) in that the "age" of the retroplacental clot cannot be determined exactly. In the example shown in Figure 41-15, a large dark clot is well formed, it has depressed the placental bulk, and it likely is at least several hours old.

FIGURE 41-15
Partial placental abruption with a dark adherent clot.



Defining severity of placental abruption is problematic. We have considered abruption severe when the fetus dies, however, maternal and fetal complications can be serious even with a liveborn fetus. Ananth and coworkers (2016) have defined *severe abruption* as displaying one or more of the following: (1) maternal sequelae that include disseminated intravascular coagulation, shock, transfusion, hysterectomy, renal failure, or death; (2) fetal complications such as nonreassuring fetal status, growth restriction, or death; or (3) neonatal outcomes that include death, preterm delivery, or growth restriction.

Traumatic Abruption

External trauma—usually from motor vehicle accidents or aggravated assault—can cause placental separation. The frequency of abruption originating from trauma varies. Kettel (1988) and Stafford (1988) and their associates have appropriately stressed that abruption can stem from relatively minor trauma. The clinical presentation and consequences of these abruptions differ somewhat from spontaneous cases. For example, associated fetomaternal hemorrhage, while seldom clinically significant with most spontaneous abruptions, is more common with trauma because of concomitant placental tears or "fractures" (Chap. 47, Placental Injuries). Fetal bleeding that averaged 12 mL was noted in a third of women with a traumatic abruption reported by Pearlman (1990). In eight women cared for at Parkland Hospital, we found fetal-to-maternal hemorrhage of 80 to 100 mL in three of eight cases of traumatic placental abruption (Stettler, 1992). Importantly, in some cases of trauma, a nonreassuring fetal heart rate tracing may not be accompanied by other evidence of placental separation. A sinusoidal tracing is one example. Traumatic abruption is considered in more detail in Chapter 47 (Placental Injuries).

Chronic Abruption

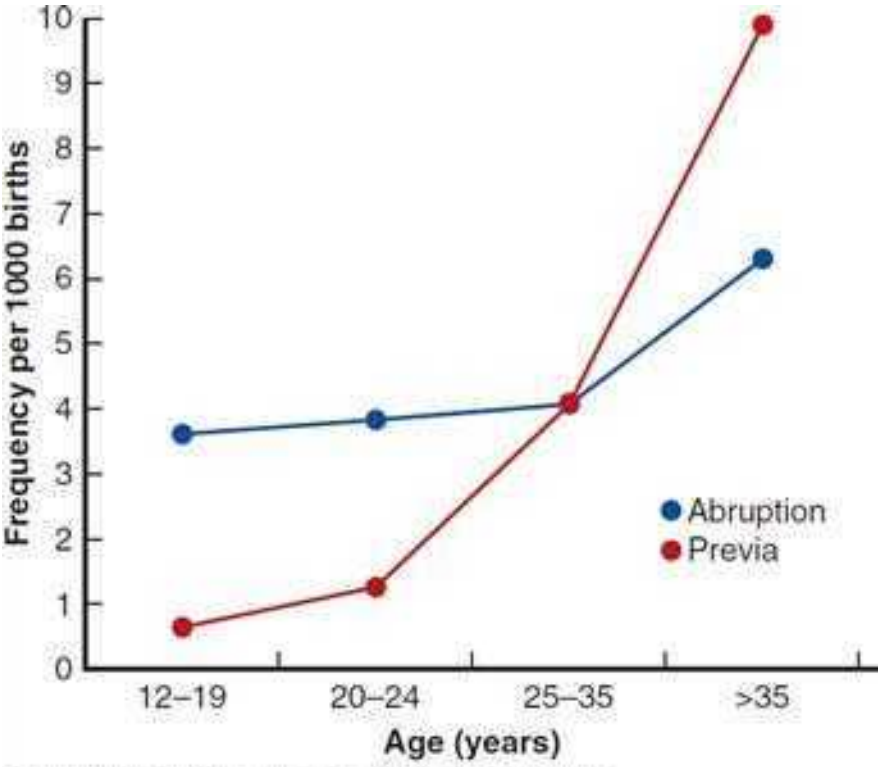
Some cases of chronic placental separation begin early in pregnancy. Dugoff and coworkers (2004) observed an association between some abnormally elevated maternal serum aneuploidy markers and subsequent abruption. Other have correlated first- and second-trimester bleeding with third-trimester placental abruption (Ananth, 2006; Weiss, 2004). In some cases of a chronic abruption, subsequent oligohydramnios develops—*chronic abruption-oligohydramnios sequence—CAOS*

(Elliott, 1998). Even later in pregnancy, hemorrhage with retroplacental hematoma formation is occasionally arrested completely without delivery. These women may have abnormally elevated serum levels of alpha-fetoprotein or placenta-specific RNAs as markers of the event (Miura, 2016; Ngai, 2012).

Frequency

The reported incidence of placental abruption varies because of different criteria used for diagnosis. That said, its frequency averages 0.5 percent or 1 in 200 deliveries. From one database of almost 28 million births from 2006 through 2012, the incidence of placental abruption was nearly 1 percent (Ananth, 2016). From a cohort of more than 1.57 million births in the Netherlands, Ruiter and coworkers (2015) found the frequency was 0.22 percent—1 in 450. In more than 250,000 deliveries at Parkland Hospital from 2000 through 2015, the incidence of placental abruption averaged 0.35 percent or 1 in 290 (Fig. 41-16).

FIGURE 41-16
Frequency of placental abruption and placenta previa by maternal age at Parkland Hospital from 2000 through 2015.

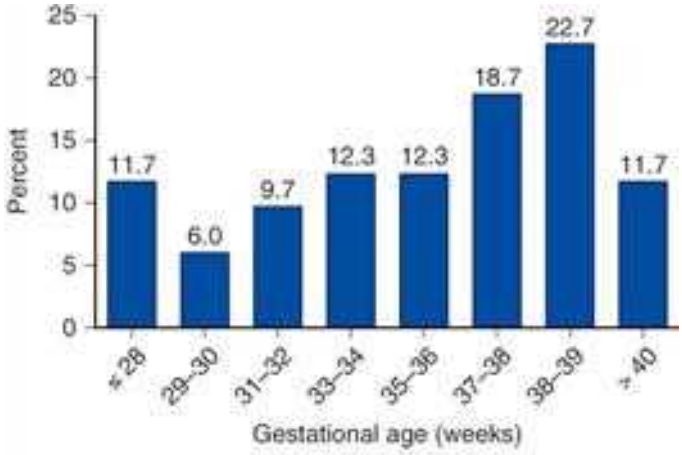


The frequency of placental abruption has *risen* in this country, and most of this increase is in black women (Ananth, 2005, 2016). At Parkland Hospital, however, the frequency of severe abruption has declined. This discrepancy may be explained in part by the variations in management of early-onset preeclampsia (Chap. 40, Preeclampsia). Specifically, with placental abruption *so extensive as to kill the fetus*, the incidence was 0.24 percent or 1 in 420 births from 1956 through 1967 (Pritchard, 1967). As the number of high-parity women giving birth declined along with improved availability of prenatal care and emergency transportation, the frequency of abruption causing fetal death dropped to 0.12 percent through 1989 in our obstetrical population. And, most recently through 2015, it declined to 0.05 percent or 1 in 2060.

Perinatal Morbidity and Mortality

Overall, perinatal outcomes are influenced by gestational age, and the frequency of placental abruption rises across the third trimester. As seen in Figure 41-17, more than half of the placental abruptions at Parkland Hospital developed at gestational ages ≥37 weeks. Perinatal mortality and morbidity, however, are more common with earlier abruptions (Furukawa, 2015a). Of other related factors, major fetal congenital anomalies have greater association with placental abruption (Riihimäki, 2013).

FIGURE 41-17
Frequency of placental abruption by gestational age at Parkland Hospital.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Although the rates of fetal death have declined, the contribution of abruption as a cause of stillbirth remains prominent because other causes have also decreased. For example, since the early 1990s, 10 to 12 percent of all third-trimester stillbirths at Parkland Hospital have been the consequence of placental abruption. Others have documented high perinatal mortality rates caused by placental abruption. Salihu and colleagues (2005) analyzed more than 15 million singleton births between 1995 and 1998. The perinatal mortality rate associated with placental abruption was 119 per 1000 births compared with 8 per 1000 for the general obstetrical population.

Neonatal deaths are common following placental abruption. At Parkland Hospital, 15 percent of liveborn neonates died. Perinatal morbidity—often severe—is also common in surviving newborns (Abdella, 1984). Studies by Matsuda and coworkers (2003, 2013) reported that 20 percent of survivors developed cerebral palsy. These observations are similar to ours from Parkland Hospital. Notably, 20 percent of liveborn neonates of women with an abruption had severe acidemia, defined by a cord arterial blood pH <7.0 or base deficit of ≥12 mmol/L. One review confirmed the associated risk for cerebral palsy (Downes, 2017). Even so, Ananth and coworkers (2017) attribute adverse neurodevelopmental outcomes to be largely attributable to preterm delivery.

Predisposing Factors

Demographic Factors

Several predisposing factors raise the risk for placental abruption, and some are listed in Table 41-4. *Advancing maternal age* is one, although data are conflicting regarding women of *great parity* (Okby, 2017; Pritchard, 1991). *Race* or ethnicity also appears to be important. In almost 366,000 deliveries at Parkland Hospital, abruption severe enough to kill the fetus was most common in black and white women—1 in 200, less so in Asian women—1 in 300, and least common in Latin-American women—1 in 350 (Pritchard, 1991). A *familial association* was found in an analysis of a Norwegian population-based registry (Rasmussen, 2009). If a woman had a severe abruption, the risk for her sister was doubled.

TABLE 41-4

Risk Factors for Placental Abruption

Risk Factor	Relative Risk
Prior abruption	10–188
Increased age and parity	1.3–2.3
Preeclampsia	2.1–4.0
Chronic hypertension	1.8–3.0
Chorioamnionitis	3.0
Preterm ruptured membranes	2.4–4.9
Multifetal gestation	2–8
Low birthweight	14.0
Hydramnios	2–8
Cigarette smoking	1.4–1.9
Single umbilical artery	3.4
Cocaine use	NA
Uterine leiomyoma	NA

NA = not available.

Data from Ananth, 1999a,b, 2004, 2007; Aviram, 2015; Gutvirtz, 2016; Morgan, 2016; Nath, 2007, 2008; Ruiter, 2015.

Pregnancy-Associated Hypertension

Some form of hypertension is the most frequent condition associated with placental abruption. This includes gestational hypertension, preeclampsia, chronic hypertension, or a combination thereof. In a report by Pritchard and colleagues (1991) that described 408 women with placental abruption and fetal demise, hypertension was apparent in half once hypovolemia was corrected. Half of these latter women—a fourth of all 408—had chronic hypertension. Looked at another way, one Maternal–Fetal Medicine Units (MFMU) Network study found that 1.5 percent of pregnant women with chronic hypertension suffered placental abruption (Sibai, 1998). As discussed in Chapter 50 (Adverse Pregnancy Effects), at Parkland Hospital, the frequency of placental abruption in treated chronically hypertensive women was almost 1 percent, which was threefold higher than the 0.3-percent baseline (Morgan, 2016).

Chronic hypertension with superimposed preeclampsia or with fetal-growth restriction confers an even greater risk (Ananth, 2007). Even so, the severity of hypertension does not necessarily correlate with abruption incidence (Morgan, 2016; Zetterstrom, 2005). The long-term effects of these associations are apparent from the significantly elevated cardiovascular mortality risk in women with prior abruption, with or without chronic hypertension (DeRoo, 2016; Pariente, 2013). Observations from the Magpie Trial Collaborative Group suggest that women with preeclampsia, with or without chronic hypertension, given magnesium sulfate may have a reduced risk for abruption (Altman, 2002).

Preterm Prematurely Ruptured Membranes

The abruption risk substantially rises when placental membranes rupture before term (American College of Obstetricians and Gynecologists, 2016a; Hackney, 2016). Major and colleagues (1995) reported that 5 percent of 756 women with ruptured membranes between 20 and 36 weeks' gestation developed an abruption. It was 17 percent with previable prematurely ruptured membranes (Kibel, 2016). The risk for abruption with preterm rupture is further increased with comorbid infection (Ananth, 2004). In these cases, inflammation and infection as well as preterm delivery may be primary causes leading to abruption (Nath, 2007, 2008).

Somewhat related, Aviram and coworkers (2015) found an eightfold higher abruption risk in pregnancies ≥34 weeks if hydramnios was comorbid. Abrupt uterine decompression during membrane rupture may be an inciting factor.

Prior Abruption

Many of the predisposing factors are chronic, and in these cases, placental abruption has a high recurrence rate. Pritchard and associates (1970) identified a recurrence rate of 12 percent—and half of these caused another fetal death. Furuhashi and colleagues (2002) reported a 22-percent recurrence rate—half recurred at a gestational age 1 to 3 weeks earlier than the first abruption. In the Dutch study mentioned previously, Ruiter and coworkers (2015) cited a recurrence risk of 5.8 percent. Looked at a second way, Tikkanen and associates (2006) found that of 114 parous women who experienced an abruption, 9 percent had a prior abruption. A third perspective is provided by a population-based study of 767,000 pregnancies reported by Rasmussen and Irgens (2009). They found a 6.5-fold higher risk for recurrence of a "mild" abruption and 11.5-fold risk for a "severe" abruption. For women who had two severe abruptions, the risk for a third was increased 50-fold.

Management of a pregnancy subsequent to an abruption is difficult because another separation may suddenly occur, even remote from term. In many of these recurrences, fetal well-being is almost always reassuring beforehand. Thus, antepartum fetal testing is usually not predictive. Because term abruptions tend to be recurrent, Ruiter and coworkers (2015) recommend labor induction at 37 weeks. Our practice at Parkland Hospital is to induce labor at 38 weeks if other complications do not develop beforehand.

Other Associations

Cigarette smoking is linked to an elevated risk for abruption (Misra, 1999; Naeye, 1980). Results of a metaanalysis of 1.6 million pregnancies included a twofold risk for abruption in smokers (Ananth, 1999b). This risk was five- to eightfold if smokers had chronic hypertension, severe preeclampsia, or both. Similar findings are reported by others (Hogberg, 2007; Kaminsky, 2007). Antepartum Vitamin C and E were reported to be protective for abruption in smokers (Abramovici, 2015).

Cocaine abuse is linked with an alarming frequency of placental abruption (Addis, 2001; Cressman, 2014). Bingol and colleagues (1987) described 50 women who abused cocaine during pregnancy—eight had a stillbirth caused by placental abruption.

Uterine leiomyomas, especially if located near the mucosal surface behind the placental implantation site, can predispose to placental abruption. This was reviewed recently by Ezzedine and Norwitz (2016).

Isolated single umbilical artery is associated with a 3.4-fold increased risk for placental abruption (Gutvirtz, 2016). Twins resulting from infertility treatments also carry greater risk (Okby, 2017). Subclinical hypothyroidism or high levels of antithyroid antibodies have been associated with a two- to threefold higher risk for abruption (Abbassi-Ghanavati, 2010; Casey, 2014; Maraka, 2016).

Women affected by some of the thrombophilias have higher associated rates of thromboembolic disorders during pregnancy. However, the link with placental abruption is less clear (American College of Obstetricians and Gynecologists, 2017a,b). Lupus anticoagulant is associated with maternal floor infarction of the placenta but is less so with typical abruptions. No convincing evidence supports a role for thrombophilias and placental abruption.

Clinical Findings and Diagnosis

Most women with a placental abruption have sudden-onset abdominal pain, vaginal bleeding, and uterine tenderness. In a prospective study, Hurd and colleagues (1983) reported that 78 percent with placental abruption had vaginal bleeding, 66 percent had uterine tenderness or back pain, and 60 percent had a nonreassuring fetal status. Other findings included frequent contractions and persistent hypertonus. In a fifth of these women, preterm labor was diagnosed, and abruption was not suspected until fetal distress or death followed.

Importantly, the signs and symptoms of placental abruption can vary considerably. In some women, external bleeding can be profuse, yet placental separation may not be so extensive as to compromise the fetus. In others, there may be no external bleeding, but the placenta is sufficiently sheared off that the fetus is dead—a concealed abruption. In one unusual case, a multiparous woman cared for at Parkland Hospital presented with a nosebleed. She had no abdominal or uterine pain, tenderness, or vaginal bleeding. Her fetus was dead, however, and her blood did not clot. The plasma fibrinogen level was 25 mg/dL. Labor was induced, and a total abruption was confirmed at delivery.

Differential Diagnosis

With severe placental abruption, the diagnosis generally is obvious. From the previous discussion, it follows that less severe, more common forms of abruption cannot always be recognized with certainty. Thus, the diagnosis is one of exclusion. Unfortunately, no laboratory tests or other diagnostic methods accurately confirm lesser degrees of placental separation. Sonography has limited use because the placenta and fresh clots may have similar imaging characteristics. Glantz and Purnell (2002) reported only 24-percent sensitivity for sonography in 149 consecutive women with a suspected placental abruption. *Importantly, negative findings with sonographic examination do not exclude placental abruption.* Conversely, magnetic resonance (MR) imaging is highly sensitive for placental abruption and should be considered if the diagnostic information would change management (Masselli, 2011).

With abruption, some degree of intravascular coagulation is almost universal. Thus, elevated serum levels of d-dimers may be suggestive, but this has not been adequately tested. Preliminary data show that serum alpha-fetoprotein levels >280 µg/L have a positive-predictive value of 97 percent (Ngai, 2012).

Thus, in the woman with vaginal bleeding and a live fetus, it is often necessary to exclude placenta previa and other causes of bleeding by clinical and sonographic evaluation. It has long been taught—perhaps with some justification—that *painful* uterine bleeding signifies placental abruption, whereas *painless* uterine bleeding is indicative of placenta previa. The differential diagnosis is usually not this straightforward, and labor accompanying previa may cause pain suggestive of placental abruption. On the other hand, pain from abruption may mimic normal labor, or it may be painless, especially with a posterior placenta. At times, the cause of the vaginal bleeding remains obscure even after delivery.

Hypovolemic Shock

Placental abruption is one of several notable obstetrical entities that may be complicated by massive and sometimes torrential hemorrhage. Hypovolemic shock is caused by maternal blood loss. In an earlier report from Parkland Hospital, Pritchard and Brekken (1967) described 141 women with abruption so severe as to kill the fetus. Blood loss in these women often amounted to at least half of their pregnant blood volume. Importantly, massive blood loss and shock can develop with a concealed abruption. Prompt treatment of hypotension with crystalloid and blood infusion is essential, and resuscitation steps are described later (Hypovolemic Shock).

Consumptive Coagulopathy

Obstetrical events—mainly placental abruption and amnionic fluid embolism—led to the initial recognition of *defibrination syndrome.* This syndrome is currently referred to as *consumptive coagulopathy* or *disseminated intravascular coagulation,* which later is described more broadly in Obstetrical Coagulopathies. The major mechanism causing procoagulant consumption is intravascular activation of clotting. Abruption is the most common cause of clinically profound consumptive coagulopathy in obstetrics—and indeed, probably in all of medicine (Cunningham, 2015).

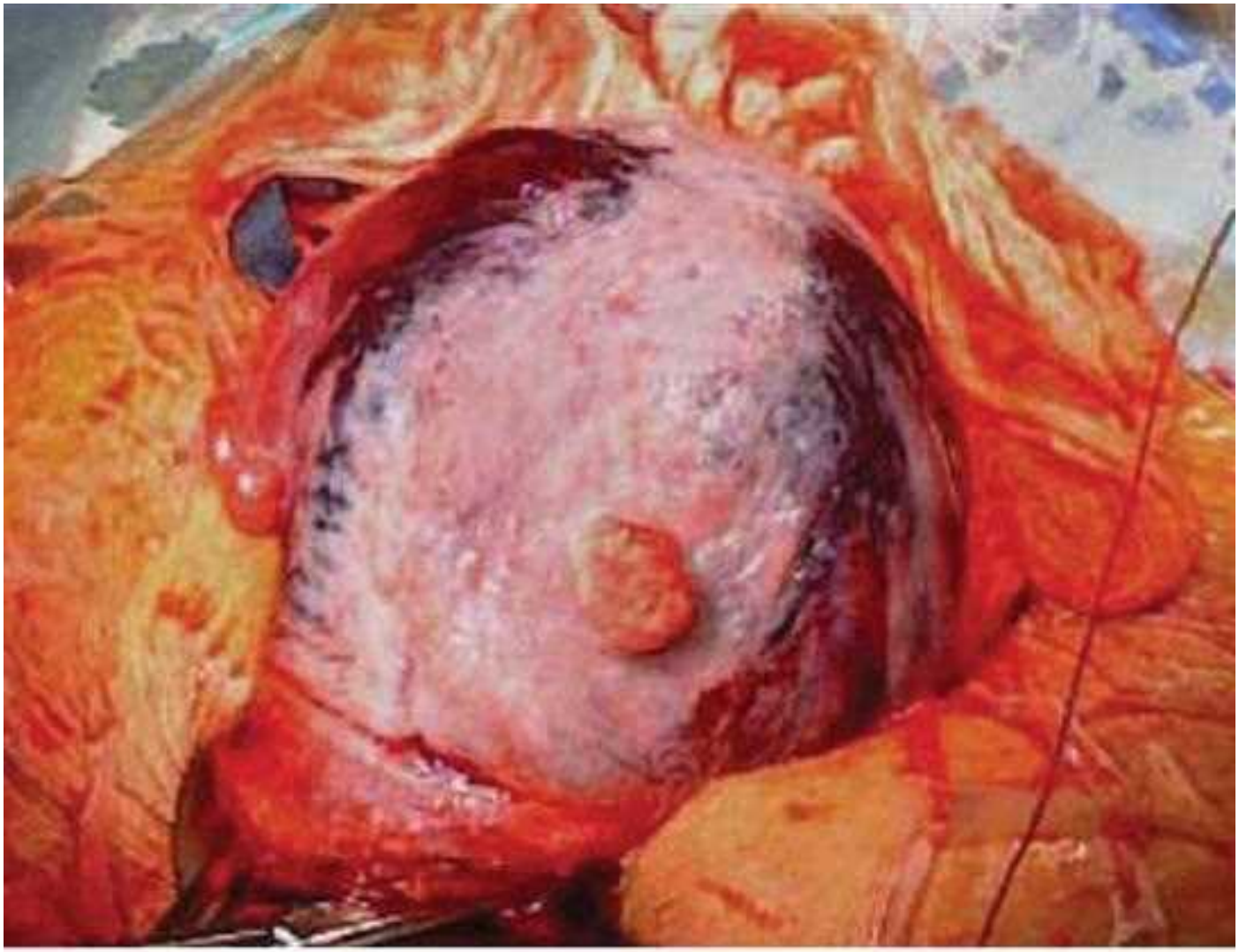
An important consequence of intravascular coagulation is the activation of plasminogen to plasmin, which lyses fibrin microemboli to maintain microcirculatory patency. With placental abruption severe enough to kill the fetus, there are always pathological levels of fibrinogen–fibrin degradation products and D-dimers in maternal serum (Erez, 2015). Their quantification is not clinically useful. In a third of women with an abruption severe enough to kill the fetus, the plasma fibrinogen level will be <150 mg/dL. These levels are dependent on the maternal preabruption fibrinogen level, and thus higher levels are "protective" (Cunningham, 2015; Wang, 2016). Clinically significant low levels may cause troublesome surgical bleeding. Levels of several other coagulation factors are also variably decreased. In addition, thrombocytopenia, sometimes profound, may accompany severe hypofibrinogenemia initially and becomes common after repeated blood transfusions.

Consumptive coagulopathy is more likely with a concealed abruption because intrauterine pressure is higher. This forces more thromboplastin into the large veins draining the implantation site. With a partial abruption and a live fetus, severe coagulation defects are less common. Our experience has been that if serious coagulopathy develops, it is usually evident by the time abruption symptoms appear.

Couvelaire Uterus

At the time of cesarean delivery, it is not uncommon to find widespread extravasation of blood into the uterine musculature and beneath the serosa (Fig. 41-18). It is named after Couvelaire, who in the early 1900s termed it *uteroplacental apoplexy*. These myometrial hemorrhages seldom cause uterine atony, and alone they are not an indication for hysterectomy. Effusions of blood are also seen beneath the tubal serosa, between the leaves of the broad ligaments, in the substance of the ovaries, and free in the peritoneal cavity.

FIGURE 41-18
Couvelaire uterus from total placental abruption after cesarean delivery. Blood markedly infiltrates the myometrium to reach the serosa, especially at the cornua. The small serosal leiomyoma seen on the lower anterior uterine surface is an incidental finding. (Used with permission from Dr. Angela Fields Walker.)



End-Organ Injury

Acute kidney injury (AKI) is a general term describing renal dysfunction from many causes (Chap. 53, Acute Kidney Injury). Delayed or incomplete treatment of hypovolemia with severe placental abruption can be one. However, even with abruption complicated by severe disseminated intravascular coagulation, prompt and vigorous treatment of hemorrhage with blood and crystalloid solution usually prevents clinically significant renal dysfunction. The risk for renal injury with abruption is magnified when preeclampsia coexists (Alexander, 2015; Drakeley, 2002). Most cases of AKI are reversible and not so severe as to require dialysis. Generally, long-term outcomes are good (Arazi, 2015). That said, irreversible *acute cortical necrosis* encountered in pregnancy can be associated with abruption (Gopalakrishnan, 2015).

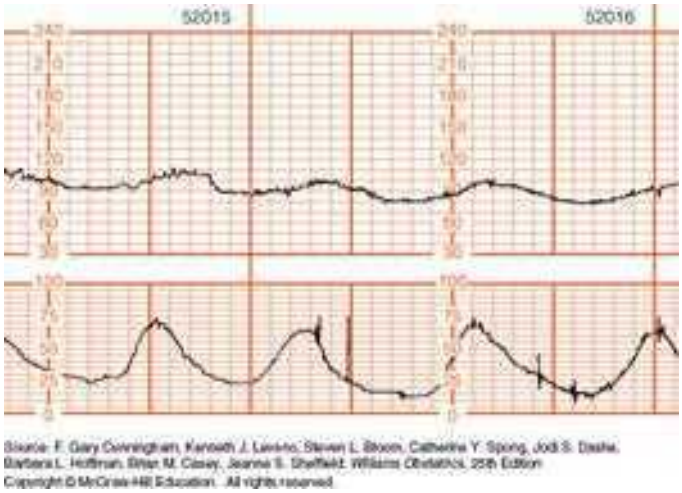
Rarely, pituitary failure—*Sheehan syndrome*—follows severe intrapartum or early postpartum hemorrhage. Described in Chapter 58 (Acromegaly), the exact pathogenesis is not well understood, especially because endocrine abnormalities are infrequent even in women who suffer catastrophic hemorrhage (Matsuwaki, 2014; Robalo, 2012).

Management

Treatment of the woman with a placental abruption varies depending on her clinical condition, gestational age, and the amount of associated hemorrhage. With a living viable-aged fetus, and with vaginal delivery not imminent, emergency cesarean delivery is chosen by most. In some women, fetal compromise will be evident as shown in Figure 41-19. When evaluating fetal status, sonographic confirmation of fetal heart activity may be necessary because sometimes an electrode applied directly to a dead fetus will provide misleading information by recording the maternal heart rate. If the fetus has died or if it is not considered sufficiently mature to live outside the uterus, then vaginal delivery is preferable. In either case, prompt and intensive resuscitation with blood plus crystalloid is begun to replace blood lost from retroplacental and external hemorrhage. These measures are lifesaving for the mother and hopefully for her fetus. If the diagnosis of abruption is uncertain and the fetus is alive and without evidence of compromise, then close observation may be warranted provided that immediate intervention is available. Colón and coworkers (2016) performed a randomized trial and found no benefits to magnesium sulfate tocolysis given to women with a preterm “nonsevere” abruption at 24 to 34 weeks’ gestation.

FIGURE 41-19

Placental abruption with fetal compromise. Lower panel: Uterine hypertonus with a baseline pressure of 20 to 25 mm Hg and frequent contractions peaking at approximately 75 mm Hg. Upper panel: The fetal heart rate demonstrates baseline bradycardia with repetitive late decelerations.



Cesarean Delivery

The compromised fetus is usually best served by cesarean delivery, and the speed of response is an important factor in perinatal outcomes. Kayani and coworkers (2003) studied this relationship in 33 singleton pregnancies with a clinically overt placental abruption and fetal bradycardia. Of the 22 neurologically intact survivors, 15 were delivered within a 20-minute decision-to-delivery interval. However, eight of 11 infants who died or developed cerebral palsy were delivered with intervals >20 minutes.

A major hazard to cesarean delivery is imposed by clinically significant consumptive coagulopathy. Preparations include plans for blood and component replacement and assessment of coagulation—especially fibrinogen levels.

Vaginal Delivery

If the fetus has died, then vaginal delivery is usually preferred. As reviewed earlier, hemostasis at the placental implantation site depends primarily on myometrial contraction and not blood coagulability. Thus, after vaginal delivery, uterotonic agents and uterine massage are used to stimulate myometrial contractions. Uterine muscle fibers compress placental site vessels and prompt hemostasis even if coagulation is defective.

In some instances, vaginal delivery may not be preferable, even with a dead fetus. One example is brisk hemorrhage that cannot be successfully managed by vigorous blood replacement. Others are the myriad obstetrical complications that prohibit vaginal delivery in general. These are listed in Table 30-1.

In some women with extensive placental abruption, labor tends to be rapid because the uterus is usually persistently hypertonic. This can magnify fetal compromise. In some cases, *baseline* intraamnionic pressures reach 50 mm Hg or higher, and with contractions, pressures may attain levels exceeding 100 mm Hg. Overall, however, first-and second-stage labor do not appear to be shortened (Downes, 2016).

Early amniotomy has long been championed in the management of placental abruption. This ostensibly achieves better spiral artery compression to diminish implantation site bleeding and reduce thromboplastin infusion into the maternal vascular system. Although evidence supporting this theory is lacking, membrane rupture may hasten delivery. However, if the fetus is small, the intact sac may be more efficient in promoting cervical dilation. If rhythmic uterine contractions are not superimposed on baseline hypertonus, then oxytocin is given in standard doses. No data indicate that oxytocin augments thromboplastin escape into the maternal circulation to worsen coagulopathy (Clark, 1995; Pritchard, 1967). In light of hypertonus associated with abruption, misoprostol may be a less favored induction agent due to its association with uterine tachysystole.

In the past, some had set arbitrary time limits to permit vaginal delivery. Instead, experiences illustrate that maternal outcome depends on the diligence with which adequate fluid and blood replacement therapy are pursued rather than on the interval to delivery. Observations from Parkland Hospital described by Pritchard and Brekken (1967) are similar to those from the University of Virginia reported by Brame and associates (1968). Specifically, women with severe abruption who were transfused during 18 hours or more before delivery had similar outcomes to those in whom delivery was accomplished sooner.

Expectant Management with a Preterm Fetus

If possible, delaying delivery may benefit an immature fetus. Bond and colleagues (1989) expectantly managed 43 women with placental abruption before 35 weeks' gestation, and 31 of them were given tocolytic therapy. The mean interval-to-delivery for all 43 was approximately 12 days. Cesarean delivery was performed in 75 percent, and there were no stillbirths. As discussed earlier, women with a very early abruption may develop *chronic abruption-oligohydramnios sequence*. In one report, Elliott and coworkers (1998) described four women with an abruption at a mean gestational age of 20 weeks who developed oligohydramnios and delivered at an average gestational age of 28 weeks. In a description of 256 women with an abruption at <28 weeks' gestation, Sabourin and colleagues (2012) reported that a mean of 1.6 weeks was gained. Of the group, 65 percent were delivered <29 weeks, and half of all women underwent emergent cesarean delivery.

Unfortunately, even continuous fetal heart rate monitoring does not guarantee universally good outcomes. For example, a normal tracing may precede sudden further separation with instant fetal compromise. In some of these, if the separation is sufficient, the fetus will die before it can be delivered. Tocolysis is advocated by some for suspected abruption if the fetus does not display compromise. Some investigators have observed that tocolysis improved outcomes in a highly selected cohort of women with preterm pregnancies (Bond, 1989; Combs, 1992; Sholl, 1987). In another study, Towers and coworkers (1999) administered magnesium sulfate, terbutaline, or both to 95 of 131 women with abruption diagnosed before 36 weeks. The perinatal mortality rate was 5 percent in both groups with or without tocolysis. Similar results were reported from a randomized trial (Colón, 2016). We are of the opinion that suspected placental abruption contraindicates use of tocolytic agents.

PLACENTA PREVIA

The Latin *previa* means *going before*—and in this sense, the placenta goes before the fetus into the birth canal. In obstetrics, placenta previa describes a placenta that is implanted somewhere in the lower uterine segment, either over or very near the internal cervical os. Because these anatomical relationships cannot always be precisely defined, and because they frequently change across pregnancy, terminology can sometimes be confusing.

Placental Migration

Beginning with the use of sonography in obstetrics, the term *placental migration* was coined to describe the apparent movement of the placenta away from the internal os (King, 1973). Obviously, the placenta does not move per se, and the mechanism of *apparent* movement is not completely understood. To begin with, *migration* is clearly a misnomer, because decidual invasion anchors chorionic villi at the cervical os.

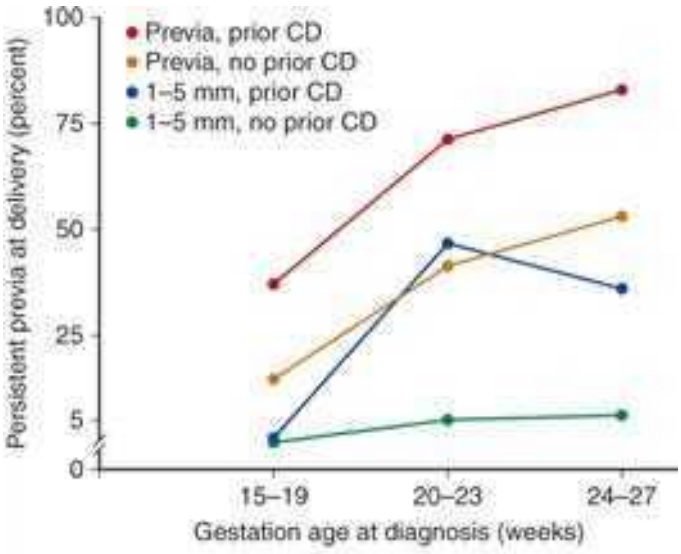
Explanations of placental migration are likely additive. First, apparent movement of the low-lying placenta relative to the internal os is related to the imprecision of two-dimensional sonography. Second, as pregnancy progresses, growth of the lower and upper uterine segments differs. With greater blood flow in the upper uterus, placental growth is more likely directed toward the fundus—*trophotropism*. Many of those placentas that "migrate" most likely never were circumferentially implanted with true villous invasion that reached the internal cervical os. *Importantly, a low-lying placenta or placenta previa is less likely to "migrate" if there is a prior cesarean delivery scar.*

The frequency of placental migration has been quantified. Sanderson and Milton (1991) studied 4300 women at midpregnancy and found that 12 percent had a low-lying placenta. Of placentas not covering the internal os, previa did not persist, and none subsequently had placental hemorrhage. Conversely, approximately 40 percent of placentas that covered the os at midpregnancy continued to do so until delivery. Thus, placentas that lie close to but not over the internal os up to the early third trimester are unlikely to persist as a previa by term (Heller, 2014; Parrott, 2015). However, other evidence from Bohrer and associates (2012) showed that a second-trimester low-lying placenta was associated with antepartum admission for hemorrhage and increased blood loss at delivery.

The likelihood that placenta previa persists after being identified sonographically at given epochs before 28 weeks' gestation is shown in Figure 41-20. For twin pregnancies, similar findings are reported until 23 weeks, after which the previa persistence rate is much higher (Kohari, 2012). Stafford and coworkers (2010), but not Trudell and colleagues (2013), found that a previa and a third-trimester cervical length <30 mm elevated the risks for hemorrhage, uterine activity, and preterm birth. Friszer and associates (2013) showed that women admitted for bleeding had a greater chance of delivery in the subsequent 7 days when the cervical length was <25 mm, although Trudell (2013) again did not confirm this.

FIGURE 41-20

Likelihood of persistence of placenta previa or low-lying placenta 1 to 5 mm from the internal os at delivery. These are shown as a function of sonographic diagnosis at three pregnancy epochs. CD = cesarean delivery. (Data from Oyelese, 2006.)



Classification

Terminology for placenta previa has evolved, and from a Fetal Imaging Workshop sponsored by the National Institutes of Health (NIH), the following classification was recommended:

Placenta previa—the internal os is covered partially or completely by placenta (Figs. 41-21 and 41-22). In the past, these were further classified as either total or partial previa.

Low-lying placenta—implantation in the lower uterine segment is such that the placental edge does not cover the internal os but lies within a 2-cm wide perimeter around the os. A previously used term, *marginal previa,* described a placenta that was at the edge of the internal os but did not overlie it (Reddy, 2014).

FIGURE 41-21
Placenta previa showing that copious hemorrhage could be anticipated with any cervical dilatation.

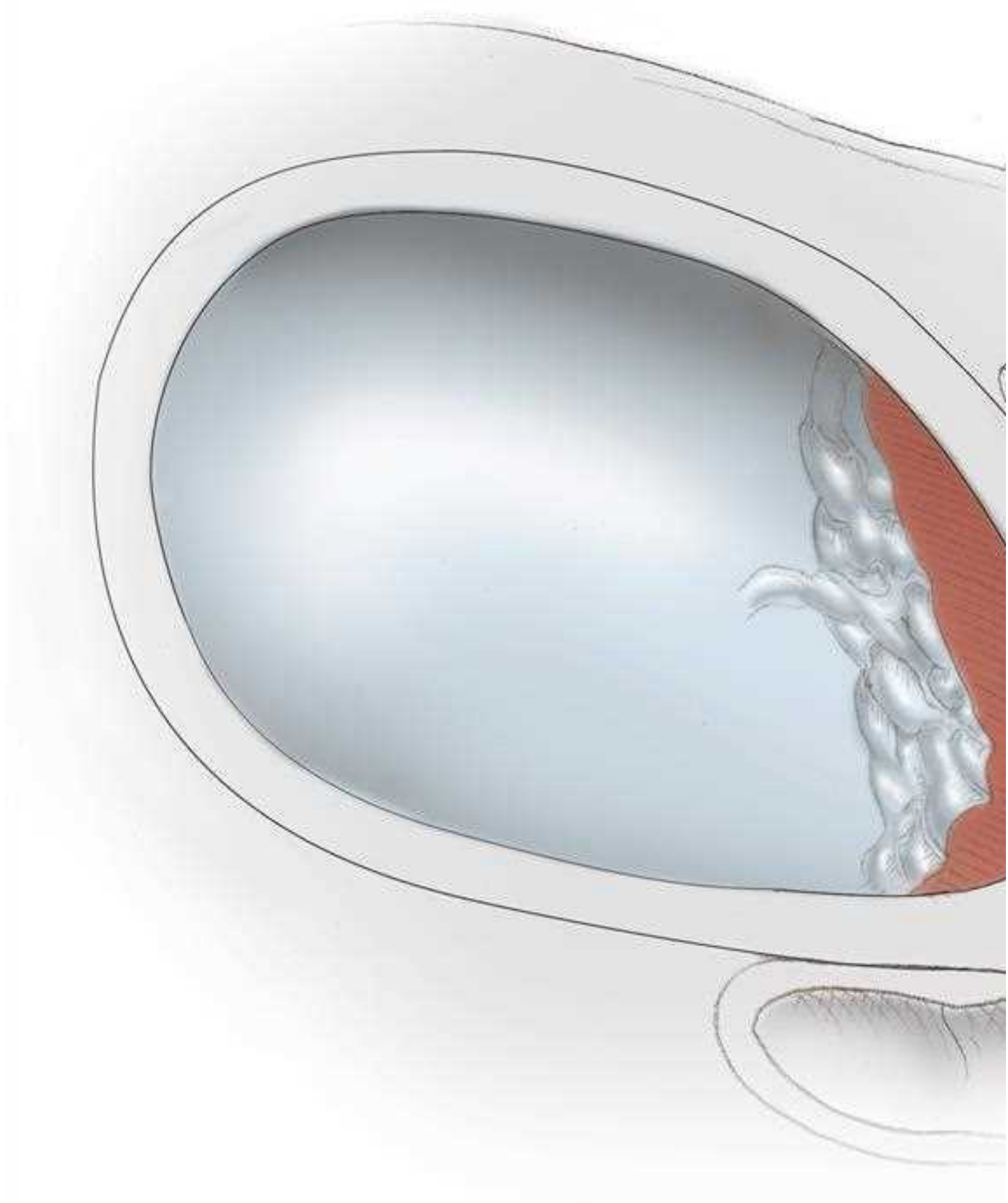
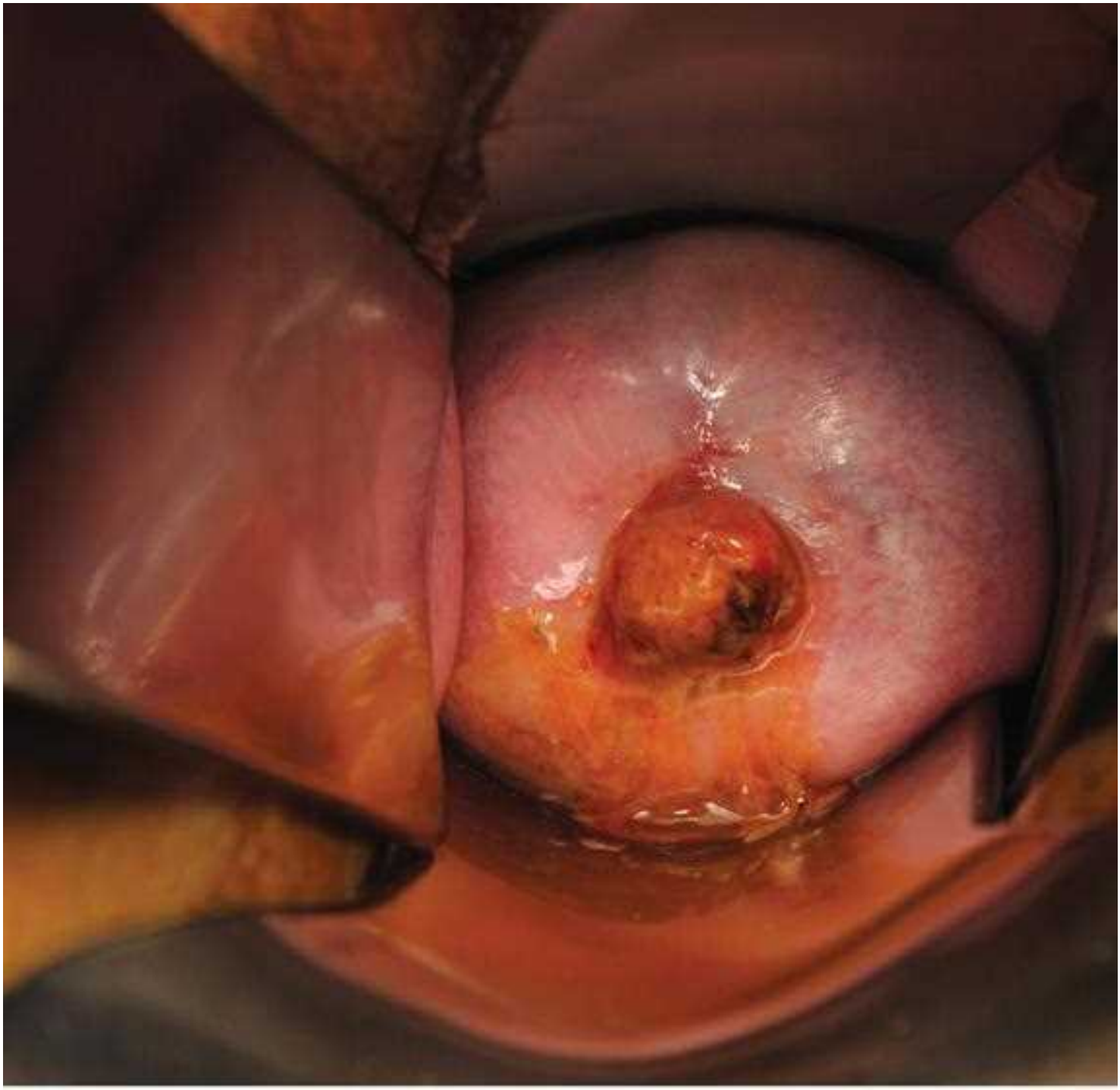


FIGURE 41-22

On speculum examination, placenta is visible protruding through the cervical os. (Used with permission from Dr. Maureen E. Flowers.)



Clearly, the classification of some cases of previa will depend on cervical dilation at the time of assessment (Dashe, 2013; Reddy, 2014). For example, a low-lying placenta at 2-cm dilation may become a partial placenta previa at 4-cm dilation because the cervix has opened to expose the placental edge. Conversely, a placenta previa that appears to be total before cervical dilation may become partial at 4-cm dilation because the cervical opening now extends beyond the edge of the placenta. *Digital palpation in an attempt to ascertain these changing relations between the placental edge and internal os as the cervix dilates usually causes severe hemorrhage!*

With any degree of placenta previa, a certain amount of spontaneous placental separation is inevitable during lower uterine segment remodeling and cervical dilation. Although this frequently causes bleeding, and thus technically constitutes a placental abruption, this term is usually not applied in these instances.

Somewhat but not always related is *vasa previa,* in which fetal vessels course through membranes and present at the cervical os (Catanzarite, 2016). Vasa previa was recently reviewed by the Society for Maternal-Fetal Medicine (2015) and is discussed in Chapter 6 (Remnants and Cysts).

Incidence and Associated Factors

Demographic Factors

The incidence of placenta previa has risen during past 30 years. Reported incidences average 0.3 percent or 1 case per 300 to 400 deliveries. The frequency at Parkland Hospital from 1988 through 2003 for nearly 250,000 births was 2.6 per 1000. For the 2004 to 2015 epoch, it rose to 3.8 per 1000. Similar frequencies have been reported from Austria, Finland, and Israel (Kollmann, 2016; Räisänen, 2014; Rosenberg, 2011).

Several demographic factors may contribute to this higher risk for placenta previa. First, *maternal age* raises the frequency of placenta previa (Biro, 2012; Roberts, 2012). In the First- and Second-Trimester Evaluation of Risk (FASTER) trial, which included more than 36,000 women, the frequency of previa was 0.5 percent for women <35 years compared with 1.1 percent in those ≥35 years (Cleary-Goldman, 2005). At Parkland Hospital, this incidence differed from a low rate of approximately 0.65 per 1000 births for women ≤19 years to almost 10 per 1000 births for women older than 35 (see Fig. 41-16).

Multiparity also elevates the risk for previa (Räisänen, 2014). Obviously, the effects of advancing maternal age and parity are confounding. Still, Babinszki and colleagues (1999) reported that the 2.2-percent incidence in women with parity of five or greater was significantly higher than that of women with lower parity. The interpregnancy interval does not affect this rate (Fox, 2015).

Cigarette smoking increases the relative risk of placenta previa at least twofold (Usta, 2005). It has been postulated that carbon monoxide hypoxemia causes compensatory placental hypertrophy and more surface area. Smoking may also be related to decidual vasculopathy. Last, *uterine leiomyomas* are a risk factor for previa (Jenabi, 2017).

Clinical Factors

Several clinical characteristics also raise previa risks. Foremost, women with one or more *prior cesarean deliveries* are at greater risk for subsequent placental disorders that include placenta previa, abruption, or morbidly adherent placenta (Gibbins, 2018; Klar, 2014). The cumulative risks for placenta previa that accrue with the increasing number of cesarean deliveries are extraordinary. The risk rises even further if there was a prior prelabor cesarean delivery (Downes, 2015). In one MFMU Network study of 30,132 women undergoing cesarean delivery, the incidence was 1.3 percent for those with only one prior cesarean delivery, but it was 3.4 percent if there were six or more prior cesareans (Silver, 2006). In a retrospective cohort of nearly 400,000 women who were delivered of two consecutive singletons, those with a cesarean delivery for the first pregnancy had a 1.6-fold greater risk for previa in the second pregnancy (Gurol-Urganci, 2011). These same investigators reported a 1.5-fold higher risk from six similar population-based cohort studies. The likelihood of previa is increased more than eightfold in women with parity greater than four and who have more than four prior cesarean deliveries (Gesteland, 2004; Gilliam, 2002).

Importantly, women with a prior uterine incision and placenta previa have an elevated likelihood that cesarean hysterectomy will be necessary because of an associated morbidly adherent placenta (Wei, 2014). In one study, 6 percent of women with a primary cesarean delivery for previa required a hysterectomy. This rate was 25 percent for women with a previa undergoing repeat cesarean delivery (Frederiksen, 1999).

Maternal serum alpha-fetoprotein (MSAFP) levels, if abnormally elevated for otherwise unexplained reasons during prenatal screening, raise the risk for previa and a host of other abnormalities. Moreover, women with a previa and comorbid MSAFP level ≥2.0 multiples of the median (MoM) at 16 weeks' gestation were at greater risk for late-pregnancy bleeding and preterm birth (Chap. 14, Maternal Serum AFP Elevation: Neural-Tube Defect Screening).

Last, *assisted reproductive technology (ART)* used for conception elevates previa risks. Some of this association may derive from overlapping effects. For example, older women comprise a significant portion of ART patients (Luke, 2017). In addition, multifetal gestation is a well-known risk of both in vitro fertilization and previa. However, even adjusting for these overlapping elements, ART is still associated with higher previa rates (Romundstad, 2006).

Clinical Features

Painless bleeding is the most characteristic event with placenta previa. Bleeding usually does not develop until near the end of the second trimester or later, but it can begin even before midpregnancy. And undoubtedly, some late abortions are caused by an abnormally located placenta. Bleeding from a previa usually begins without warning and without pain or contractions in a woman who has had an uneventful prenatal course. This so-called *sentinel bleed* is rarely so profuse as to prove fatal. Usually it ceases, only to recur. However, in perhaps 10 percent of women, particularly those with a placenta implanted near but not over the cervical os, there is no bleeding until labor onset. Bleeding at this time varies from slight to profuse, and it may clinically mimic placental abruption.

A specific sequence of events leads to bleeding in cases in which the placenta is located over the internal os. First, the uterine body remodels to form the lower uterine segment. With this, the internal os dilates, and some of the implanted placenta inevitably separates. Bleeding that ensues is augmented by the inherent inability of myometrial fibers in the lower uterine segment to contract and thereby constrict torn vessels. Similarly, bleeding from this lower segment implantation site also frequently continues after placental delivery. Last, there may be lacerations in the friable cervix and lower segment. These may be especially problematic following manual removal of a somewhat adhered placenta.

Morbidly adherent placentas are a frequent and serious complication associated with placenta previa. Described later (Morbidly Adherent Placenta), this abnormally firm placental attachment derives in part from poorly developed decidua that lines the lower uterine segment. Biswas and coworkers (1999) performed placental bed biopsies in 50 women with a previa and in 50 control women. Trophoblastic giant-cell infiltration of spiral arterioles—rather than endovascular trophoblast cells—was found in half of previa specimens. In contrast, only 20 percent of biopsies from normally implanted placentas had these changes. In another study of 514 cases of previa, abnormal placental attachment was identified in 7 percent (Frederiksen, 1999). As discussed, previa overlying a prior cesarean incision conveys a particularly high risk for morbidly adherent placenta.

Coagulation defects are rare complications of placenta previa, even when implantation site separation is extensive (Cunningham, 2015). Placental thromboplastin, which incites the intravascular coagulation seen with placental abruption, is presumed to readily escape through the cervical canal rather than be forced into the maternal circulation. The paucity of large myometrial veins in this area may also be protective.

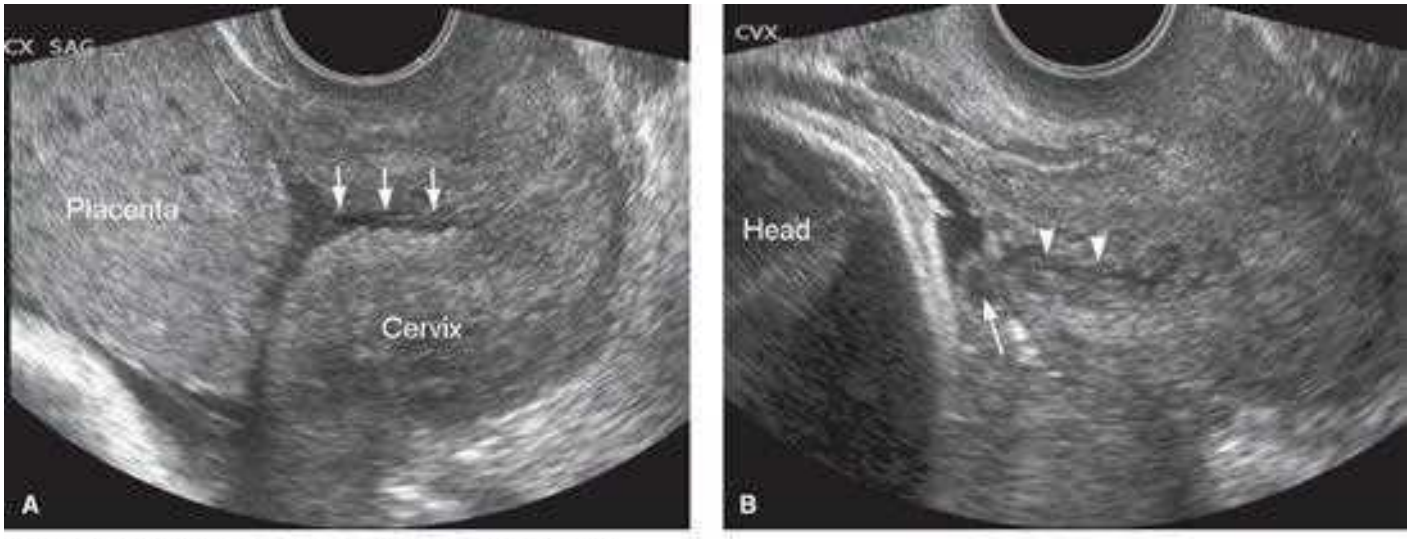
Diagnosis

Whenever there is uterine bleeding after midpregnancy, placenta previa or abruption are always considered. In the Canadian Perinatal Network study discussed earlier (Uterine Atony), placenta previa accounted for 21 percent of women admitted from 22 to 28 weeks' gestation with vaginal bleeding (Sabourin, 2012). Previa should not be excluded until sonographic evaluation has clearly proved its absence. If sonography is not readily available, diagnosis by clinical examination is done using the *double set-up* technique because it requires that a finger be passed through the cervix and the placenta palpated. A digital examination should not be performed unless delivery is planned. *A cervical digital examination is done with the woman in an operating room and with preparations for immediate cesarean delivery. Even the gentlest examination can cause torrential hemorrhage.* Fortunately, double set-up examination is rarely necessary because placental location can almost always be ascertained sonographically.

Quick and accurate localization can be accomplished using standard sonographic techniques (American Institute of Ultrasound in Medicine, 2013). This is usually done with transabdominal sonography. If the placenta clearly overlies the cervix or if it lies away from the lower uterine segment, the examination has excellent sensitivity and negative-predictive value (Olive, 2006; Quant, 2014). Obese women may have limitations of visualization of the lower uterine segment. Also, a full bladder may artificially elongate the cervix and compress the lower uterine segment to give the impression that the placenta overlies the cervix. If placental location remains in question, then transvaginal sonography is the most accurate method of assessment (Fig. 41-23). It is safe, even when there is bleeding.

FIGURE 41-23

Placenta previa. **A.** In this transvaginal image at 34 weeks' gestation, the anterior placenta completely covers the internal cervical os outlined by arrows. **B.** This transvaginal image at 34 weeks' gestation depicts a posterior placenta (*arrow*) that just reaches the level of the internal cervical os. (Reproduced with permission from Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)



Accuracy depends on the sonographic technique used. In a comprehensive study, the internal os was visualized in all cases with transvaginal sonography but in only 30 percent with transabdominal sonography (Farine, 1988). As discussed, according to the Fetal Imaging Workshop, if the placental edge is <2 cm from the internal os, but not covering it, the placenta is considered low lying (Reddy, 2014). In the absence of any other indication, sonography need not be frequently repeated simply to document placental position. At Parkland, women with a placenta previa identified at 18 to 22 weeks' gestation with a prior cesarean delivery are evaluated again at 28 weeks and those without at 32 weeks. Restriction of activity is not necessary unless a previa persists beyond 28 weeks or if clinical findings such as bleeding or contractions develop before this time. At 32 weeks' gestation, if the placental edge is still <2 cm from the os, then transvaginal sonography is repeated at 36 weeks.

Using MR imaging, several investigators have reported excellent results in visualizing placental abnormalities. That said, it is unlikely that this technique will replace sonography for routine evaluation anytime soon. However, MR imaging has proved useful for evaluation of morbidly adherent placenta (Clinical Presentation and Diagnosis).

Management

Women with a placenta previa are managed based on their individual clinical circumstances. Three prominent factors include fetal age and maturity, labor, and bleeding severity. In one study of 214 women with a previa, 43 percent had an emergency delivery, and half of these were preterm (Ruiter, 2015). But, if the fetus is immature and active bleeding subsides, close observation in an obstetrical unit is indicated. Data are sparse regarding tocolytic administration for uterine contractions. Although robust randomized trials are lacking, Bose and colleagues (2011) recommend that if tocolytics are given, they be limited to 48 hours of administration. We categorically recommend against their use in this setting.

After bleeding has ceased for approximately 2 days and the fetus is judged to be healthy, a woman can usually be discharged home with instructions for "pelvic rest." Importantly, the woman and her family must fully appreciate the possibility of recurrent bleeding and be prepared for immediate transport back to the hospital. In other cases, prolonged hospitalization may be ideal.

The frequency of emergency delivery in women with placenta previa ranges from 25 to 40 percent (Gibbins, 2018; Kassir, 2017). But, in properly selected patients, long-term inpatient care does not appear to add benefits compared with outpatient management (Neilson, 2003). In one randomized study of 53 women who had a bleeding previa at 24 to 36 weeks' gestation, maternal or fetal morbidity rates did not differ between management method (Wing, 1996). Of all study women, 60 percent had recurrent bleeding, and half eventually required expeditious cesarean delivery.

For women who are near term and who are not bleeding, plans are made for scheduled cesarean delivery. Timing balances fetal immaturity risks against antepartum hemorrhage. One NIH workshop suggested elective delivery at 36 to 37 completed weeks' gestation (Spong, 2011). The Society for Maternal-Fetal Medicine (2017) recommends delivery between 34 and 37 weeks. At Parkland Hospital, we usually perform elective cesarean delivery at 38 weeks. With a suspected morbidly adherent placenta, delivery is recommended at 34 to 35 completed weeks by the NIH workshop (Management). Our practice is to schedule delivery at 36 completed weeks.

Delivery

Practically all women with placenta previa undergo cesarean delivery. Many surgeons recommend a vertical laparotomy incision to provide rapid entry in cases with torrential bleeding or operating space if hysterectomy is required. As discussed, cesarean delivery is emergently performed in more than half because of hemorrhage, for which about a fourth require blood transfusion (Boyle, 2009; Sabourin, 2012). Although a low transverse hysterotomy is usually possible, this may cause fetal bleeding if the placenta is implanted anteriorly and the placenta is incised. In such cases, fetal delivery should be expeditious (Silver, 2015a). A vertical uterine incision may be preferable in some instances. In either case, even when the incision extends through the placenta, maternal or fetal outcomes are rarely compromised.

Following placental removal, the placenta site may bleed uncontrollably due to poorly contracted smooth muscle, which is characteristic of the lower uterine segment. If hemostasis at the placental implantation site cannot be obtained by adequate uterotonic administration and pressure, it can be oversewn with 0-chromic sutures. Cho and associates (1991) described interrupted 0-chromic sutures at 1-cm intervals to form a circle around the bleeding portion of the lower segment to control hemorrhage. Others have reported success with compression sutures that traversed and compressed the anterior and posterior uterine wall (Kayem, 2011; Penotti, 2012).

Of other methods, Bakri or Foley balloon tamponade used alone or coupled with compression sutures has been described (Albayrak, 2011; Diemert, 2012; Kumru, 2013). Law and coworkers (2010) successfully used a hemostatic gel. Other surgical options are bilateral uterine or internal iliac artery ligation, illustrated later (Adjunctive Surgical Procedures). Finally, pelvic artery embolization has also gained acceptance.

Hysterectomy

If these more conservative methods fail and bleeding is brisk, hysterectomy is necessary. Placenta previa—especially with an abnormally adherent placenta—currently is the most frequent indication for peripartum hysterectomy at Parkland Hospital and other institutions (Jakobsson, 2015; Wong, 2011). When there is no associated accrete syndrome, the reported incidence of hysterectomy is 2 percent (Gibbins, 2018).

Thus, it is not possible to accurately estimate the effect on the hysterectomy rate from previa alone without considering the associated accrete syndromes. *Again, for women whose placenta previa is implanted anteriorly at the site of a prior uterine incision, the likelihood of an associated morbidly adherent placenta and need for hysterectomy is increased.* In a study of 318 peripartum hysterectomies performed in the United Kingdom, 40 percent were done for abnormal placentation (Knight, 2007). Similar results were reported for 211 hysterectomies from the Nordic Obstetric Surveillance Study (Jakobsson, 2015). At Parkland Hospital, 44 percent of cesarean hysterectomies were done for bleeding placenta previa or for a morbidly adherent placenta (Wortman, 2015). The technique for peripartum hysterectomy is described in Chapter 30 (Peripartum Hysterectomy).

Maternal and Perinatal Outcomes

Placenta previa and coexistent accrete syndromes both contribute substantively to maternal morbidity and mortality rates. The maternal mortality ratio is increased approximately threefold for women with a placenta previa (Gibbins, 2018; Oyelese, 2006). In another report of 5367 maternal deaths in the United States from 2006 to 2013, placenta previa alone accounted for nearly 3 percent of deaths from hemorrhage (Creanga, 2015, 2017).

The report from the Consortium on Safe Labor emphasizes the ongoing perinatal morbidity with placenta previa (Lai, 2012). Preterm delivery continues to be a major cause of perinatal death (Nørgaard, 2012). In deliveries with placenta previa in the United States in 1997, the neonatal mortality rate was threefold higher than that in unaffected pregnancies and stemmed primarily from preterm delivery (Salihu, 2003). Ananth and colleagues (2003) reported a comparably elevated risk of neonatal death even for fetuses who delivered at term. This is at least partially related to the fetal anomaly rate, which is two- to threefold higher in pregnancies with placenta previa (Crane, 1999).

The association of fetal-growth restriction with placenta previa is likely minimal after controlling for gestational age. In a population-based cohort of more than 500,000 singleton births, Ananth and associates (2001) found that most low-birthweight newborns associated with placenta previa resulted from preterm birth. Harper and coworkers (2010) reported similar findings from a cohort of nearly 58,000 women. In contrast, at least two studies reported a greater risk for fetal-growth restriction (Räisänen, 2014; Weiner, 2016).

MORBIDLY ADHERENT PLACENTA

Etiopathogenesis

The term *morbidly adherent placenta* describes aberrant placentation characterized by abnormally implanted, invasive, or adhered placenta. We also refer to these disorders collectively as *accrete syndromes* and use these terms interchangeably. Derivation of accrete comes from the Latin *ac-* + *crescere*—to adhere or become attached to (Benirschke, 2012).

In the accrete syndromes, abnormal placental adherence to the myometrium stems in part from partial or total absence of the decidua basalis and imperfect development of the fibrinoid or Nitabuch layer, described in Chapter 5 (Decidual Histology). If the decidual spongy layer is lacking either partially or totally, then the physiological line of cleavage is absent, and some or all cotyledons are densely anchored. Microscopically, placental villi attach to smooth muscle fibers rather than to decidual cells. This decidual deficiency then prevents normal placental separation after delivery. The surface area of the implantation site involved and the depth of trophoblastic tissue ingrowth are variable between women, but all affected placentas can potentially cause significant hemorrhage.

Substantiated data now suggest that accrete syndromes are not solely caused by this anatomical layer deficiency (Duzyj, 2017; Tantbirojn, 2008). Indeed, the cytotrophoblasts may control decidual invasion through factors such as angiogenesis (Duzyj, 2015; Goh, 2016; Wehrum, 2011). Also, accrete syndrome tissue specimens show “hyperinvasiveness” (Pri-Paz, 2012). Myometrial fibers attached to the basal plate in an antecedent pregnancy are predictive markers for a subsequent placenta accreta (Linn, 2015; Miller, 2016). This implies an antecedent “constitutional endometrial defect” in most cases. The greater risk conveyed by previous surgical uterine trauma may be partially explained by an enhanced vulnerability to trophoblast invasion (Garmi, 2012; Gill, 2015; Jauniaux, 2017).

This association with prior trauma is reinforced by the close relationship between *cesarean-scar pregnancy (CSP)* and later development of placenta accreta in the same pregnancy. Indeed, accruing evidence suggests that CSP and accrete syndromes lie on a spectrum and that CSP is a precursor, as both share the same histopathology (Happe, 2018; Timor-Tritsch, 2014). CSP frequency has been reported to approximate 1 in 2000 pregnancies (Berhie, 2015; Rotas, 2006). Described in Chapter 19 (Cesarean Scar Pregnancy), early rupture and hemorrhage are not uncommon with CSP, and women often elect pregnancy-terminating interventions to avoid these (Michaels, 2015; Timor-Tritsch, 2015).

Classification

Variants of the morbidly adherent placenta are classified by the depth of trophoblastic growth (Figs. 41-24 and 41-25). *Placenta accreta* indicates that villi are attached to the myometrium. With *placenta increta*, villi actually invade the myometrium, and *placenta percreta* defines villi that penetrate through the myometrium and to or through the serosa (Bailit, 2015; Silver, 2015a). In clinical practice, these three variants are encountered in an approximate ratio of 80:15:5, respectively (Wong, 2008). In all three varieties, abnormal adherence may involve all lobules—*total placenta accreta*. If all or part of a single lobule is abnormally attached, it is described as a *focal placenta accreta*. Histological diagnosis cannot be made from the placenta alone, and myometrial samples are necessary for confirmation (Benirschke, 2012).

FIGURE 41-24
Morbidly adherent placentas: **A.** Placenta accreta. **B.** Placenta increta. **C.** Placenta percreta.

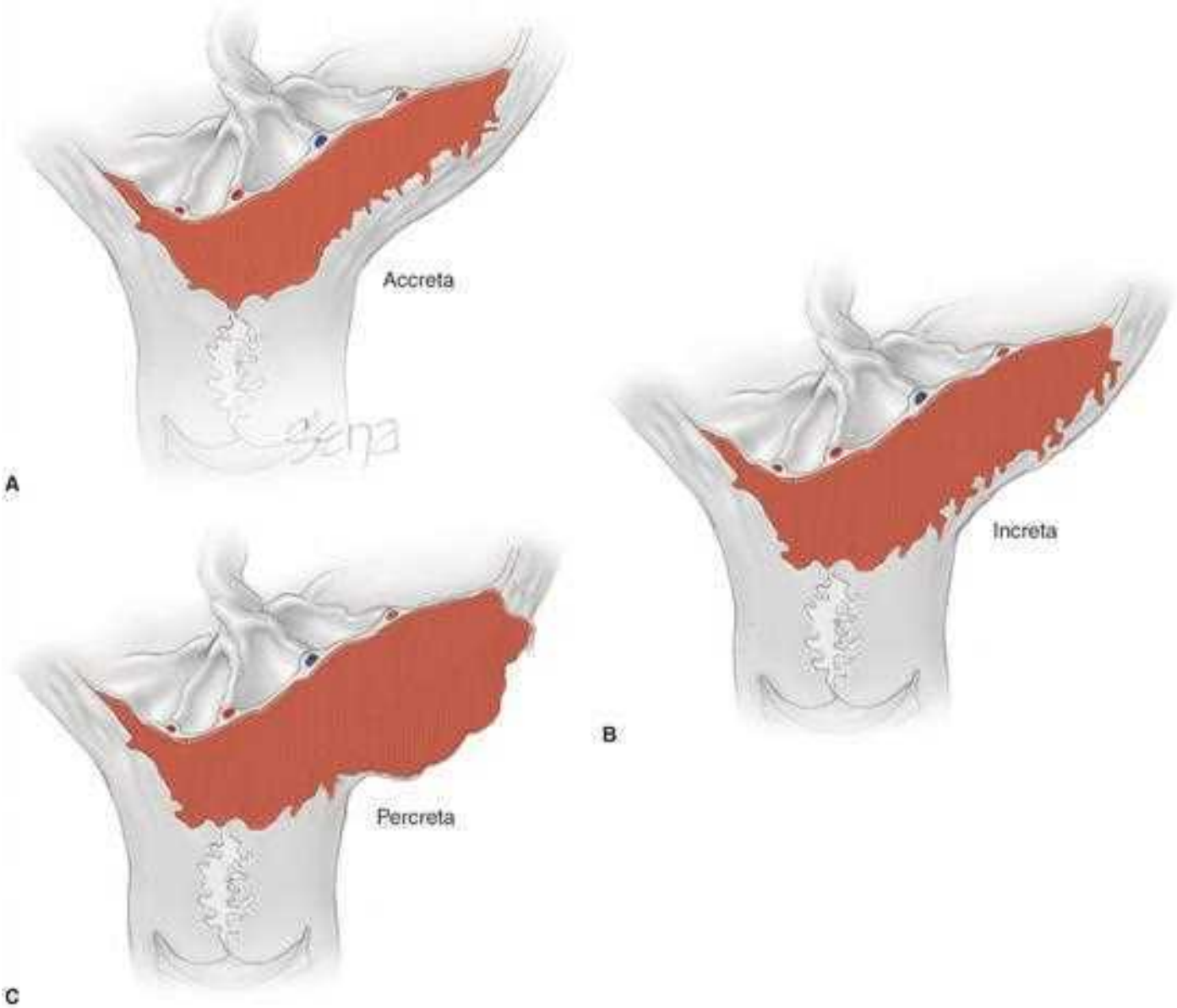
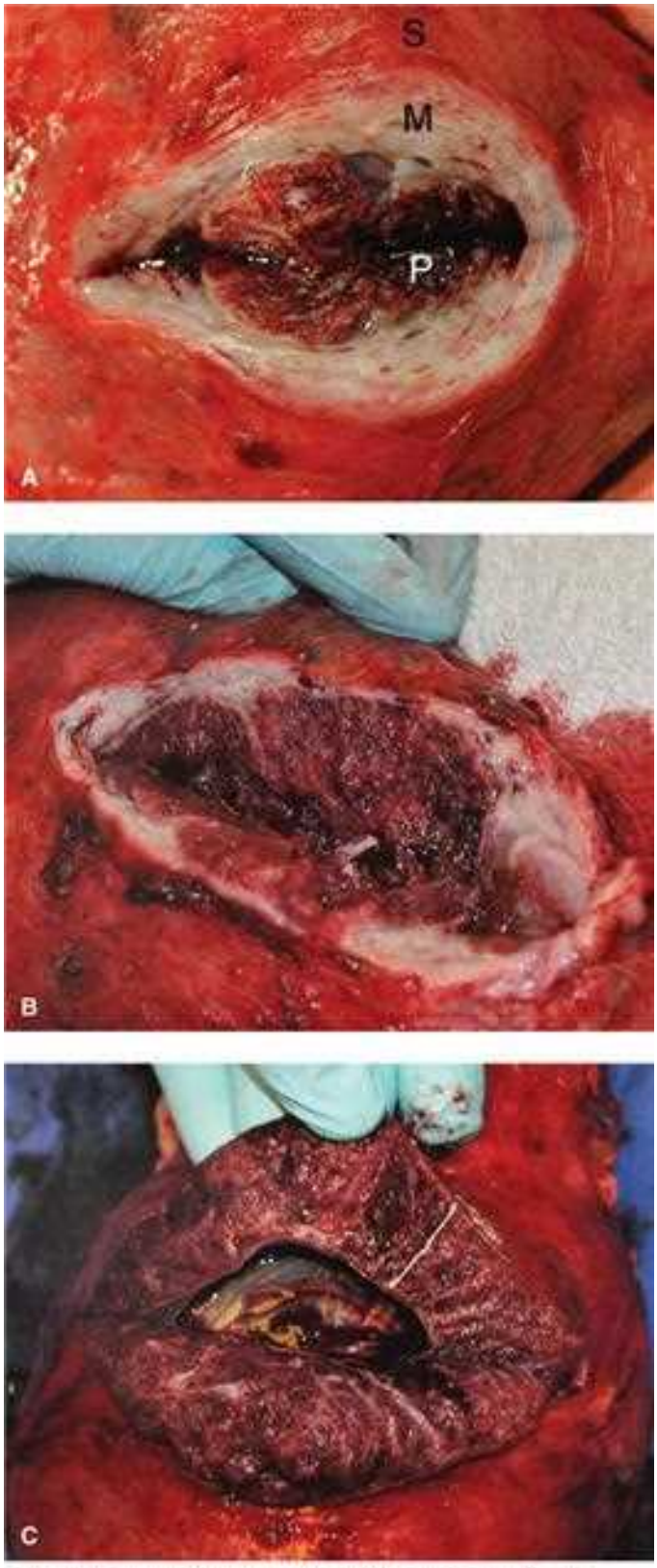


FIGURE 41-25

Varying degrees of myometrial invasion with the accrete syndromes. Incisions begin on the serosal surface and extend through to the placenta. **A.** In this case, the myometrium (*M*) shows minimal invasion by the placenta (*P*). S = uterine serosa. **B.** A greater degree of myometrial invasion is seen here. **C.** In this example, the placenta (*brackets*) extends to the serosal edge, held by the surgeon's hand. No myometrium remains at this site. (Reproduced with permission from Dr. C. Edward Wells in Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)



Incidence

The frequency of accrete syndromes was 1 in 20,000 births almost 100 years ago (McKeogh, 1951). As late as 1971, Hellman and Pritchard in the 14th edition of *Williams Obstetrics* described accreta to be the subject of case reports. Since then, the incidence has grown remarkably in direct relationship to the rising cesarean delivery rate. For example, incidence was 1 in 2500 births in the 1980s, but it was 1 per 731 births in the report from the MFMU Network comprising 115,502 women (Bailit, 2015). And a Canadian study of more than 570,000 births found an incidence of 1 in 700 deliveries (Mehrabadi, 2015). In the Nationwide Inpatient Sample, the prevalence of accreta was 3.7 per 1000 births—1 per 270 (Mogos, 2016).

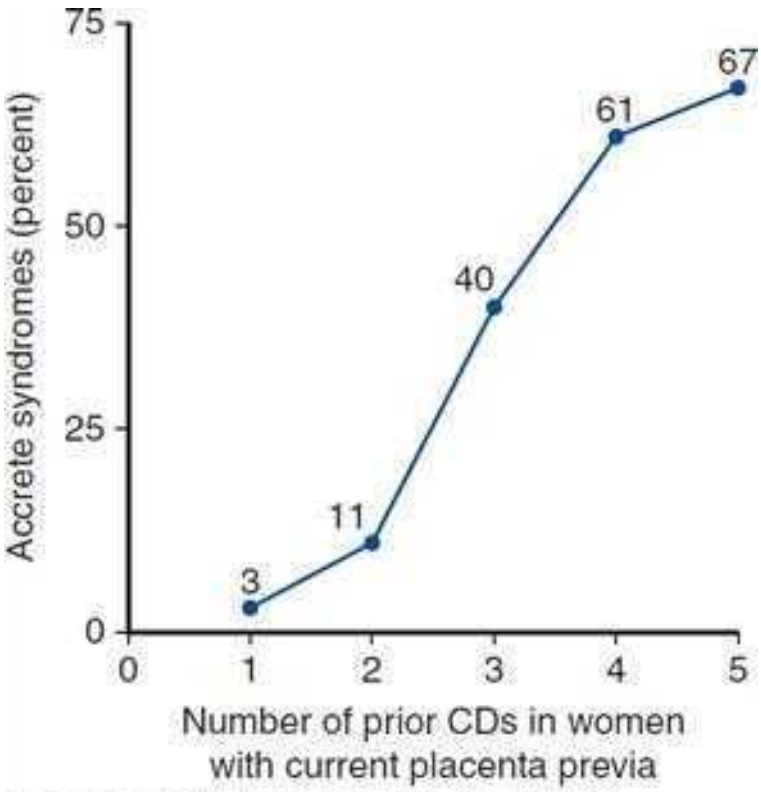
This rising frequency has made accrete syndromes one of the most formidable problems in obstetrics. In one review of 5367 pregnancy-related maternal deaths in the United States from 2006 to 2013, 13 percent were due to hemorrhage caused by accrete syndromes (Creanga, 2015, 2017). In addition, they are a leading cause of hemorrhage and emergency peripartum hysterectomy (Awan, 2011; Eller, 2011; Rossi, 2010). The American College of Obstetricians and Gynecologists (2017c) and the Society for Maternal-Fetal Medicine (2010) have taken the lead to address and optimize management.

In subsequent pregnancies following placenta accreta, recurrence risks are high. Women in whom hysterectomy is avoided have an estimated 20-percent incidence of recurrence (Cunningham, 2016; Roeca, 2017). In addition, some evidence shows that these women have greater risks for previa, uterine rupture, and hysterectomy (Eshkoli, 2013).

Risk Factors

These are similar in many aspects to those for placenta previa (Classification). That said, the two most important risk factors are an associated previa, a prior cesarean delivery, and more likely a combination of the two (Klar, 2014). A classical hysterotomy incision has a higher risk for a subsequent accrete placenta (Gyamfi-Bannerman, 2012). In fact, almost half of women with a prior cesarean delivery had myometrial fibers seen microscopically adhered to the placenta (Hardardottir, 1996; Miller, 2016). An associated previa confers an even higher risk. This is shown in Figure 41-26, and the astonishing increase in frequency of associated accrete syndromes is apparent with a concomitant previa.

FIGURE 41-26
Frequency of morbidly adherent placenta in women with 1 to 5 prior cesarean deliveries (CDs) now with a previa. (Data from Silver, 2006.)



Dysfunctional decidual formation also may follow any other type of myometrial trauma such as curettage or endometrial ablation (Benirschke, 2012; Gill, 2015). Even without a prior hysterotomy, coexisting placenta previa is additive to frequency, and in one study, 10 percent of such women with a previa had an associated accrete syndrome. A shorter cervical length with placenta accrete syndromes did not confer a greater risk for preterm delivery (Rac, 2017).

Another risk marker became apparent with widespread use of MSAFP and human chorionic gonadotropin (hCG) screening for neural-tube defects and aneuploidies. In one study of more than 9300 women screened at 14 to 22 weeks' gestation, the risk for accrete syndromes was eightfold higher with MSAFP levels >2.5 MoM, and it was increased fourfold with maternal serum free β-hCG levels >2.5 MoM (Hung, 1999).

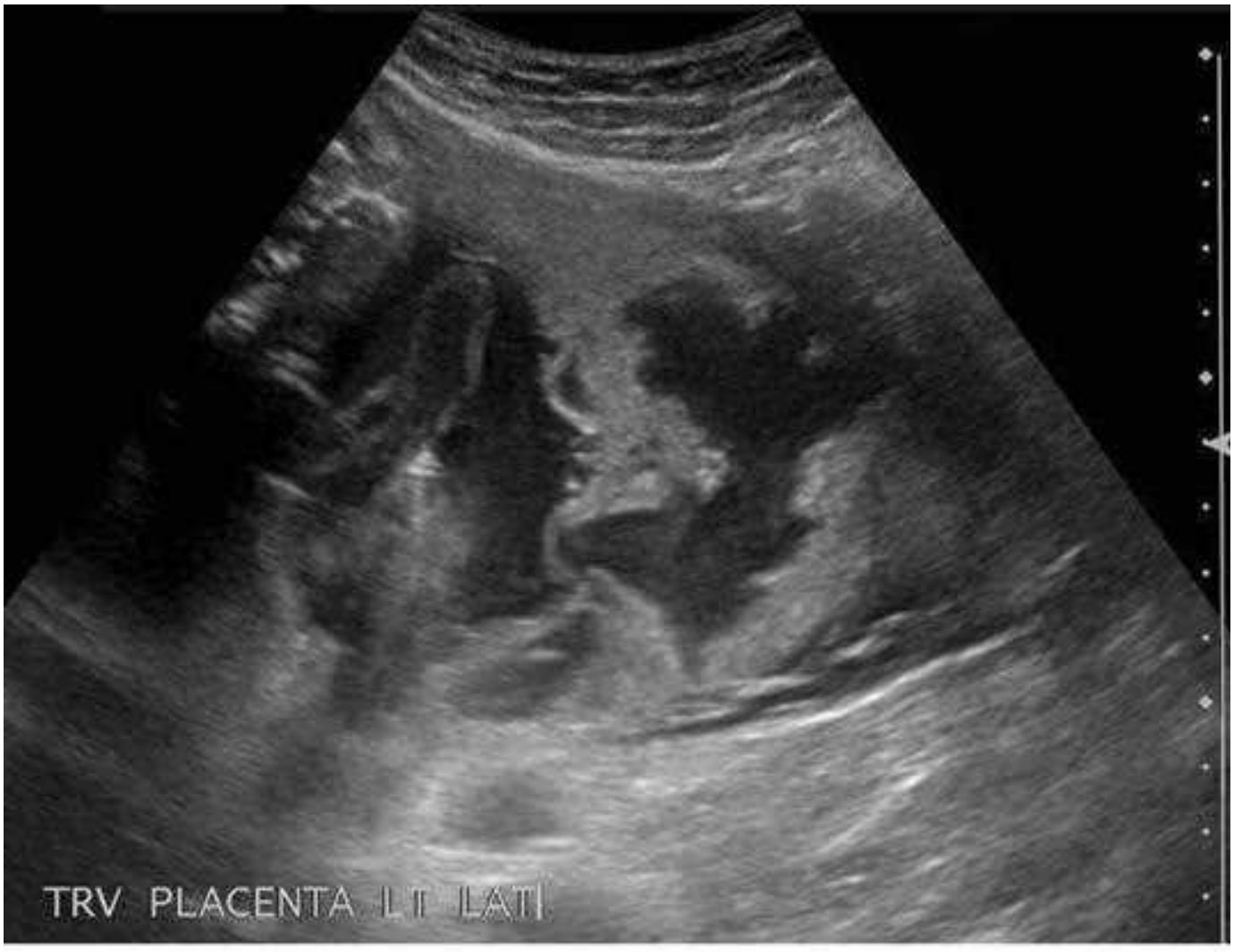
Clinical Presentation and Diagnosis

In cases of first- and second-trimester accrete syndromes, there is usually hemorrhage that is the consequence of coexisting placenta previa. Such bleeding will typically prompt evaluation and management. In some women who do not have an associated previa, accreta may not be identified until third-stage labor when an adhered placenta is encountered. Unfortunately, imaging modalities are less than perfect to identify all of these placentas early.

Ideally, sonography is used for antepartum identification of abnormal placental ingrowth (Chantraine, 2013; Jauniaux, 2016; Reddy, 2014; Tam Tam, 2012). Happe and colleagues (2018) found that first-trimester measurement of the smallest myometrial thickness can be used to predict the necessity for peripartum hysterectomy with an accrete syndrome. Other findings include loss of the normal hypoechoic retroplacental zone between the placenta and uterus, placental vascular lacunae,

and placental bulging into the posterior bladder wall (Fig. 41-27). Using these criteria, Warshak and associates (2006) calculated the following values: sensitivity of 77 percent; specificity of 96 percent; positive-predictive value of 98 percent. Similar values are cited by the American College of Obstetricians and Gynecologists (2017c) and others (Chalubinski, 2013; Elhawary, 2013; Maher, 2013).

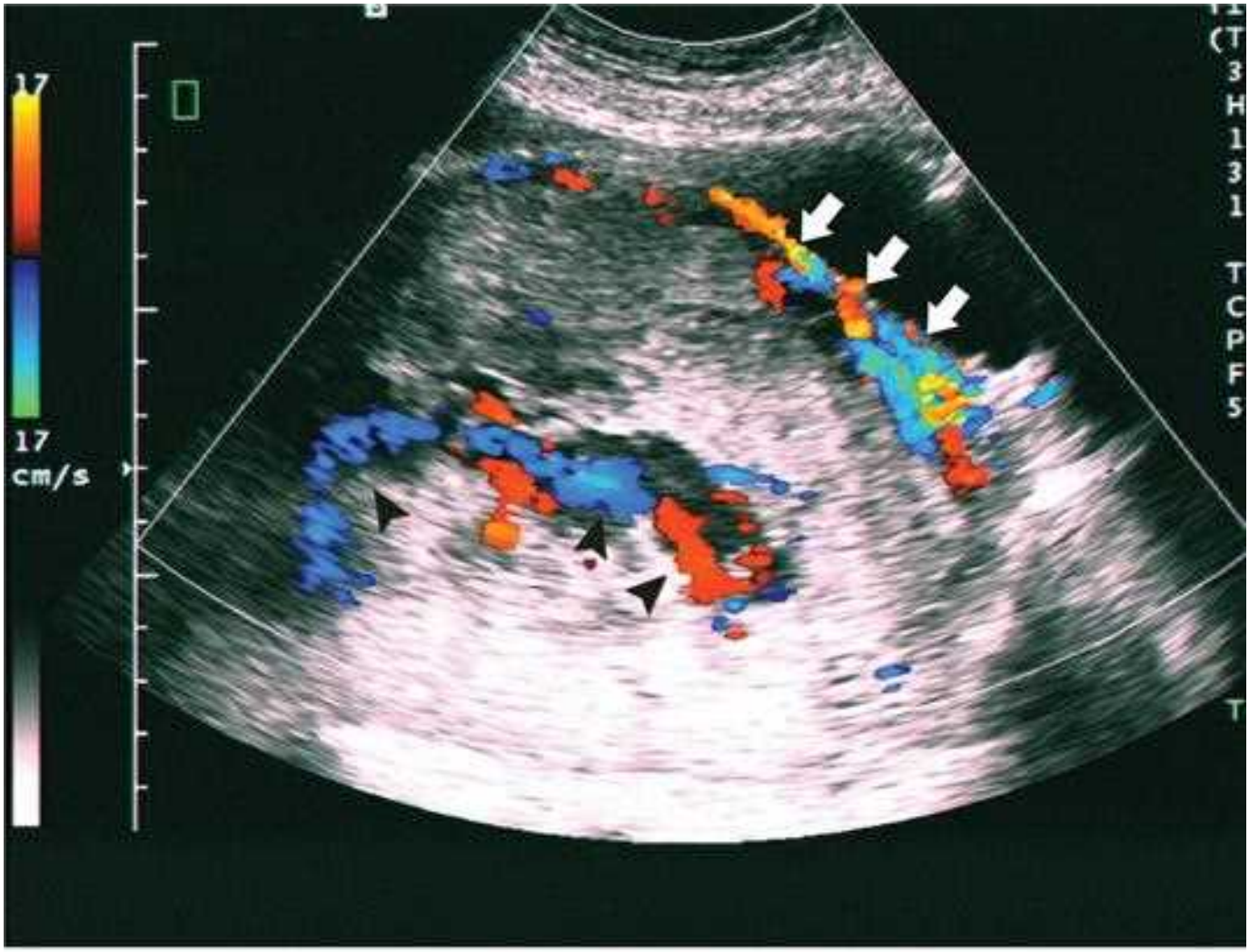
FIGURE 41-27
Transabdominal sonogram of placental percreta shows multiple and massive placental "lakes" or "lacunae". (Reproduced with permission from Dr. Martha Rac in Cunningham FG: Placenta previa and morbidly adherent placenta. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics, 3rd edition. New York, McGraw-Hill Education, 2017b.)



Despite these findings, some investigators report less spectacular results with sonography (Jauniaux, 2016; Primo, 2014). Bowman and colleagues (2014) described the sensitivity of sonography to be 54 percent; specificity, 88 percent; positive-predictive value, 82 percent; negative-predictive value, 65 percent; and accuracy, 65 percent. Location affects sonographic accuracy. In one study, the detection rate was 90 percent for anterior placenta accreta compared with 50 percent for posterior wall ones (Pilloni, 2016). Nageotte (2014) concluded that identification of the morbidly adherent placenta with sonography should be interpreted along with clinical and operative findings.

Better results have been reported by some using three-dimensional (3-D) sonography and power Doppler (Collins, 2015; Doyle, 2015). We too have found that the addition of Doppler color flow mapping is highly predictive of myometrial invasion (Fig. 41-28). This is suspected if the distance between the uterine serosa–bladder wall interface and the retroplacental vessels measures <1 mm and if there are large intraplacental lacunae (Rac, 2015a; Twickler, 2000). Similarly, Cali and associates (2013) reported that hypervascularity of the uterine serosa–bladder wall interface had the highest positive- and negative-predictive values for placenta percreta.

FIGURE 41-28
Transvaginal sonogram of placental invasion with a morbidly adherent placenta. Retroplacental vessels (*white arrows*) invade the myometrium and obscure the bladder–serosal interface. Abnormal intraplacental venous lakes (*black arrowheads*) are commonly seen in this setting.



MR imaging can be added to outline anatomy and to identify invasion of adjacent structures, including possible ureteral involvement (Chalubinski, 2013; Reddy, 2014). Although gadolinium is usually not added during pregnancy, this contrast may enhance images (Millischer, 2017). Lax and coworkers (2007) described three MR imaging findings that suggest accreta: uterine bulging, heterogeneous signal intensity within the placenta indicative of lacunae, and dark intraplacental bands on T2-weighted imaging. Some recommend use of MR imaging if sonography results are inconclusive or there is a posterior previa (American College of Obstetricians and Gynecologists, 2017c; Silver, 2015a).

Management

Preoperative assessment ideally begins once a possible accrete syndrome is recognized antenatally (Fitzpatrick, 2014; Sentilhes, 2013). *A major decision concerns the timing of and the ideal facility for delivery.* Considerations include appropriate surgical, anesthesia, intensive care, and blood banking capabilities. An obstetrical surgeon or gynecological oncologist and surgical, urological, and interventional radiological consultants should be available (Brennan, 2015; Shamshirsaz, 2015). The American College of Obstetricians and Gynecologists (2017c) and the Society for Maternal-Fetal Medicine (2010) recommend planned delivery in a tertiary-care facility. In some of these, specially designed teams have been assembled and are on call (Al-Khan, 2014; Erfani, 2017a; Smulian, 2017; Walker, 2013).

Silver and colleagues (2015b) have provided criteria for accreta centers of excellence. Shown in Table 41-5 are some criteria to consider transfer to a higher level-of-care facility. Women who refuse blood or its derivatives pose especially difficult management dilemmas (Barth, 2011). If possible, delivery is best scheduled for peak availability of all resources and team members. Even so, a third of cases require unscheduled delivery, and contingency plans should be ready (Pettit, 2017).

TABLE 41-5

Criteria for Consideration of Delivery in an Accrete Center of Excellence

Suspicion for morbidly adherent placenta on sonogram
Placenta previa with abnormal ultrasound appearance
Placenta previa with ≥3 prior cesarean deliveries
Prior classical cesarean delivery and anterior placentation
Prior endometrial ablation or pelvic irradiation
Inability to adequately evaluate or exclude placenta accreta
Any other reason to suspect morbidly adherent placenta

Reproduced with permission from Silver, 2015b.

Timing of Delivery

Timing balances fetal immaturity risks against serious adverse maternal consequences of emergency cesarean delivery (Stephenson, 2016). The American College of Obstetricians and Gynecologists (2017c) recommends individualization of delivery timing. It cites a decision-analysis study that justifies elective delivery without fetal lung maturity testing after 34 completed weeks (Robinson, 2010). The Society for Maternal-Fetal Medicine (2017) recommends delivery between 34 and 37 weeks. Two recent surveys found that most practitioners do not deliver these women until 36 weeks or later (Esakoff, 2012; Wright, 2013). At Parkland Hospital, we generally schedule these procedures after 36 completed weeks but are prepared also to manage them in nonelective situations (Rac, 2015b). Perlman and colleagues (2017) recommend individualization based on specific risk criteria.

In some cases, placenta accrete syndrome is not recognized until laparotomy. If there are inadequate resources to surgically manage the percreta, and if the woman is stable and not bleeding, then the fetus is not delivered, the abdominal incision is closed, and she is transferred to a tertiary-care facility.

Preoperative Prophylactic Catheterization

In cases that may involve one or both ureters, catheterization may aid in dissection or identification and repair of injury. Some, but not all, advocate preoperative ureteral catheterization (Eller, 2011; Society for Maternal-Fetal Medicine, 2010; Tam Tam, 2012).

Balloon-tipped intraarterial catheters to mitigate blood loss and thereby enhance surgical visibility have also gained supporters. Catheters are advanced preoperatively into the internal iliac arteries, and then after delivery, they are inflated to occlude pelvic blood flow (Ballas, 2012; Desai, 2012). Alternatively, the catheters can be used to deliver occluding emboli to bleeding arterial sites. Others have concluded that these procedures offer borderline efficacy and have serious risks (Salim, 2015; Sentilhes, 2009). Complications have included thromboses of the common and left iliac arteries (Bishop, 2011). At this time, the American College of Obstetricians and Gynecologists (2017c) concludes that a firm recommendation cannot be made for or against intraarterial catheter use. Similarly, there are no obvious benefits to internal artery ligation (Eller, 2011; Po, 2012).

Cesarean Delivery and Hysterectomy

Before commencing with delivery, the risk of hysterectomy to prevent exsanguination should be estimated. Some of these abnormal placentations, especially if partial, may be amenable to placental delivery with hemostatic suture placement. Confirmation of a percreta or increta almost always mandates hysterectomy. Because the scope of invasion may not be apparent before delivery of the fetus, we complete many dissection steps early. This also minimizes blood loss during potentially tedious dissection after hysterotomy. Thus, we usually attempt to create a wide bladder flap *before* making the hysterotomy incision (Cunningham, 2017b). The round ligaments are divided, and the lateral edges of the peritoneal reflection are dissected downward. If possible, these incisions are extended to encircle the entire placental implantation site that visibly occupies the prevesical space and posterior bladder wall. Following this, a classical hysterotomy or transverse fundal incision is made to avoid the placenta (Kotsuji, 2013).

After fetal delivery, the extent of placental invasion is assessed without attempts at manual placental removal. In a report from the United Kingdom, attempts for partial or total placental removal prior to hysterectomy were associated with twice as much blood loss (Fitzpatrick, 2014). Generally speaking, with obvious percreta or increta, hysterectomy is usually the best course, and the placenta is left in situ (Eller, 2011). With more extensive placental ingrowth, there may be little or no bleeding until manual placental removal is attempted. Unless there is spontaneous separation with bleeding that mandates emergency hysterectomy, the operation begins after full assessment is made. With bleeding, successful treatment depends on immediate blood replacement therapy and other measures that can include uterine or internal iliac artery ligation, balloon occlusion, or embolization.

The group at Baylor College of Medicine has described a modified radical hysterectomy for surgical management of the morbidly adherent placenta (Shamshirsaz, 2015). For a description of this technique, refer to *Cunningham and Gilstrap's Operative Obstetrics* (Yeomans, 2017). At Parkland Hospital, we have had cases in which

a traditional radical hysterectomy was necessary to excise all abnormally implanted placenta.

Conservative Management

Occasionally, it may be possible to trim the umbilical cord, repair the hysterotomy incision, leave the placenta in situ, and not pursue hysterectomy. This option may be used for women in whom abnormal placentation was not suspected before cesarean delivery and in whom uterine closure stops bleeding. After this, she can be transferred to a higher-level facility for definitive management. Another consideration is the woman with a strong desire for fertility and who has received extensive counseling.

Conservative management was reviewed by Perez-Delboy (2014) and Fox (2015) and their colleagues. In some of these cases, the placenta spontaneously resorbed between 1 and 12 months with a mean of 6 months. Numerous complications can occur and include sepsis, disseminated intravascular coagulation, pulmonary embolism, and arteriovenous malformation (Fox, 2015; Judy, 2015; Roach, 2015).

In some of these women, a subsequent hysterectomy—either planned or prompted by bleeding or infection—is performed days to weeks postpartum when blood loss might be lessened (Al-Khan, 2014; Sentilhes, 2009). In one study, only 21 percent of such women ultimately required hysterectomy (Bretelle, 2007). In other reports, however, up to 60 percent eventually required emergency hysterectomy (Clausen, 2013; Pather, 2014). Evidence that treatment with methotrexate aids resorption is lacking. Last, for women in whom the placenta is left in situ, serial serum β-hCG measurements are not informative, and serial sonographic or MR imaging is recommended (Timmermans, 2007; Worley, 2008).

At this time, we agree with the American College of Obstetricians and Gynecologists (2017c) that leaving the placenta in situ is seldom indicated. Exceptions are for temporization to permit transfer to a higher level of care.

Pregnancy Outcomes

In sum, these syndromes can have disastrous outcomes for both mother and fetus. Although the depth of placental invasion does not correspond with perinatal outcome, it is of paramount maternal significance (Seet, 2012). Shown in Table 41-6 are outcomes from reports of women from tertiary-care hospitals and in whom the diagnosis of morbidly adherent placenta was made preoperatively. Despite these advantages, a litany of complications included hemorrhage, urinary tract injury, intensive care unit admission, and secondary surgical procedures. Some of these reports chronicle outcomes in a second cohort of women in whom care was not given at a tertiary-care facility or in whom the diagnosis of percreta was not made until delivery, or both. In these cohorts, morbidity was higher, and there was one maternal death.

TABLE 41-6

Selected Maternal Outcomes in Women with a Morbidly Adherent Placenta Identified Prenatally and Delivered in Tertiary-Care Units

Outcome[a]	San Diego[b] n = 62	Utah[c] n = 60	Toronto[d] n = 33	New Jersey[e] n = 42	Houston[f] n = 107
Gestational age (wk)	33.9 ± 1.1	34 (17–41)	~32 (19–39)	~34.6 (25–40)	~33 (29–35)
Operating time (min)	194 ±1.6	NS	107 (68–334)	NS	287 (74–608)
Transfusions	~75%	70%	NS	NS	~65%
RBC (units)	4.7 ± 2.2	≥4 (30%)	3.5 (0–20)	0–11	3 (0–6)
FFP (units)	4.1 ± 2.3	NS	NS	0–6	1 (0–2.5)
Surgical outcomes					
Bladder injury	23%	37%	30%	17%	35%
Ureteral injury	8%	7%	0	NS	2%
Postoperative					
ICU admission	72%	30%	15%	21%	100%
LOS (days)	7.4 ± 1.8	3–13	2–13	4–13	2–12

[a]Outcomes shown as mean ± 1 SD; median (range).

[b]Data from Warshak, 2010.

[c]Data from Eller, 2011.

[d]Data from Walker, 2013.

[e]Data from Al-Khan, 2014.

[f]Data from Erfani, 2017b; Shamshirsaz, 2015.

FFP = fresh-frozen plasma; ICU = intensive care unit; LOS = length of stay; NS = not stated; RBC = red blood cells.

OBSTETRICAL COAGULOPATHIES

The terms *consumptive coagulopathy, defibrination syndrome,* or *disseminated intravascular coagulation (DIC)* are often used interchangeably, but there is an important distinction in these terms. An event related to actual consumption of procoagulants within the intravascular tree results in a *consumptive* coagulopathy. In contrast, massive loss of procoagulants from hemorrhage results in a *dilutional* coagulopathy. Semantics aside, the clinicopathological coagulation disturbances with consumptive coagulopathy culminate in a systemic intravascular activation that completely disrupts natural hemostasis. As a result, an ineffective balance of natural anticoagulant mechanisms leads to widespread fibrin deposition that can cause multiorgan failure (Levi, 2013).

Disseminated Intravascular Coagulation in Pregnancy

Because of the many definitions and variable severity, citing an accurate incidence for consumptive coagulopathy in pregnant women is problematic, but it ranges from 0.03 to 0.35 percent (Erez, 2014; Rattray, 2012). For example, some degree of significant coagulopathy is found in virtually all cases of placental abruption and amnionic fluid embolism. Other instances in which frequently occurring but less recognized degrees of coagulation activation can be found include sepsis, thrombotic microangiopathies, acute kidney injury, acute fatty liver, severe preeclampsia, and hemolysis, elevated liver enzyme levels, low platelet count (HELLP) syndrome (Cunningham, 2015). The overall contribution of each of these obstetrical disorders also varies depending on the population studied (Erez, 2015).

When consumptive coagulopathy is severe, the likelihood of maternal and perinatal morbidity and mortality is increased. In one study of 49 cases, antecedent causes included those listed above, and 59 percent received blood transfusions, 18 percent underwent hysterectomy, 6 percent were dialyzed, and three mothers died (Rattray, 2012). The perinatal mortality rate was 30 percent. Callaghan and associates (2012) reviewed data from the Nationwide Inpatient Sample and found a rising prevalence of DIC from 1998 to 2009. And, from 2010 to 2011, DIC was the second most common severe maternal morbidity indicator (Creanga, 2014). Notably, DIC

was associated with nearly a fourth of maternal deaths during this study period. Despite these statistics, consumptive coagulopathy as the sole cause of maternal death is relatively uncommon and accounts for only 0.2 percent of pregnancy-related deaths in the United States (Creanga, 2015).

Pregnancy-Induced Coagulation Changes

During normal pregnancy, extensive changes in coagulation and fibrinolysis develop to create a procoagulant state. Some of these include appreciable increases in the plasma concentrations of factors I (fibrinogen), VII, VIII, IX, and X. A partial list of these normal values is found in the Appendix (Serum and Blood Constituents). At the same time, plasminogen levels rise considerably, but levels of plasminogen activator inhibitor-1 and 2 (PAI-1 and PAI-2) also grow. Thus, *plasmin activity* usually declines until after delivery (Hale, 2012; Hui, 2012). The mean platelet count drops by 10 percent during pregnancy, and platelet activation is enhanced (Kenny, 2015).

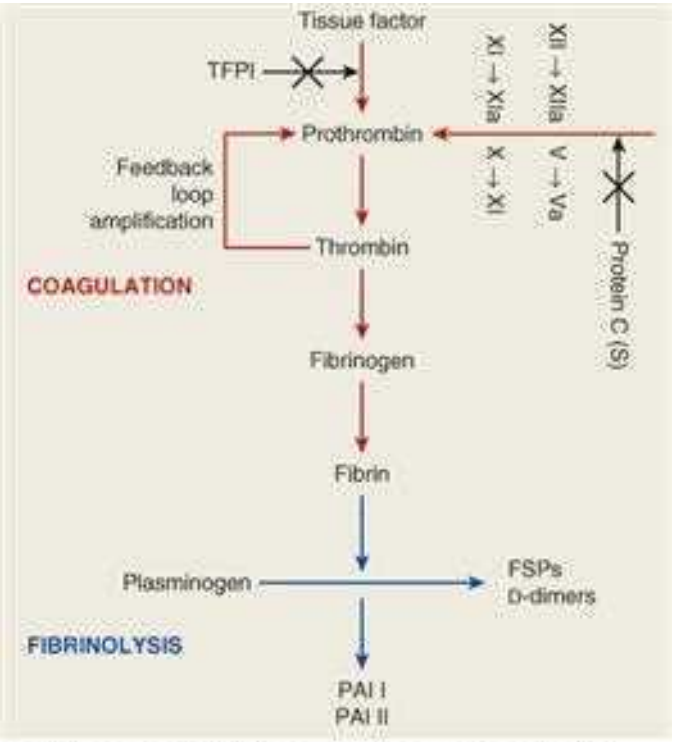
The net results of these changes include greater levels of fibrinopeptide A, β-thromboglobulin, platelet factor 4, and fibrinogen-fibrin degradation products, which includes d-dimers. Along with lower concentrations of anticoagulant protein S, hypercoagulability, and decreased fibrinolysis, there is augmented—yet compensated—intravascular coagulation that may function to maintain the uteroplacental interface.

Activation of Normal Coagulation

Instead of the "waterfall" sequential activation of clotting, a current theory proposes that tissue factor—an integral membrane glycoprotein—serves as the principal initiator of coagulation (Levi, 2010b). Coagulation then moves forward but incorporates a feedback loop. To begin, tissue factor forms complexes with factor VII/VIIa to activate factors IX and X. Tissue factor is found in highly vascularized organs such as the brain, lungs, and placenta; in amnionic fluid; and in certain other cell types (Kuczyński, 2002; Østerud, 2006; Uszyński, 2001).

Tissue factor-factor VIIa complexes ultimately generate activated factor X (Xa) to initiate clotting. Subsequently, the previously labeled "intrinsic" pathway amplifies this process. Specifically, the initial thrombin produced directly activates factor XI by providing a feedback amplification loop. This primary role of tissue factor–factor VIIa complex in coagulation and consequent amplification loop of thrombin is depicted in Figure 41-29 (Rapaport, 1995). The end result of this amplified coagulation process is fibrin formation. This is then counterbalanced by the fibrinolytic system, in which plasminogen is activated. As shown in Figure 41-29, even this process is tied initially to tissue factor. The final result is production of fibrinogen/fibrin degradation products, which include d-dimers.

FIGURE 41-29
Schematic of coagulation pathway. FSP = fibrin split products; PAI = plasminogen activator inhibitor; TFPI = tissue factor pathway inhibitor.



Activation of Pathological Coagulation

The initiation of DIC begins with the release of tissue factor by pathological entities. Tissue factor is released by subendothelial tissue and stimulated monocytes, which in turn provoke release of cytokines from the endothelium. With generalized endothelial activation, diffuse activation of coagulation follows. This pathological cycle of coagulation and fibrinolysis becomes clinically important when coagulation factors and platelets are sufficiently depleted to create consumptive coagulopathy.

Several obstetrical syndromes can trigger consumptive coagulopathy. The best known and most common is placental abruption with its significant release of thromboplastin. Another is embolization of amnionic fluid and debris into the maternal circulation. This causes activation of factor X by abundant mucin found in fetal squames. Other causes include endotoxins from gram-negative bacteria and exotoxins from gram-positive bacteria.

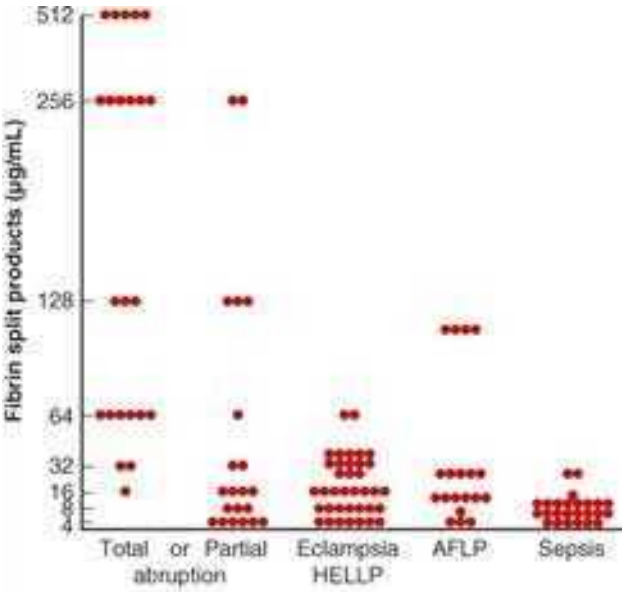
Diagnosis

Bioassay is an excellent method to detect or suspect clinically significant coagulopathy. Excessive bleeding at sites of modest trauma characterizes defective hemostasis. Examples include persistent bleeding from venipuncture sites, nicks from shaving the perineum or abdomen, trauma from bladder catheterization, and spontaneous bleeding from the gums, nose, or gastrointestinal tract. Purpura or petechiae at pressure sites such as sphygmomanometer cuffs or tourniquets suggest significant thrombocytopenia. Any surgical procedure provides the ultimate bioassay and elicits generalized oozing from abdominal wall layers, the retroperitoneal space, the episiotomy, or incisions and dissections for cesarean delivery or hysterectomy.

Of laboratory tests, fibrinogen, fibrin, and degradation product levels can be informative. In late pregnancy, plasma fibrinogen levels typically have risen to 300 to 600 mg/dL. Even with severe consumptive coagulopathy, levels may sometimes be sufficiently high to protect against clinically significant hypofibrinogenemia. For example, defibrination caused by a placental abruption might lower an initial fibrinogen level of 600 mg/dL to 250 mg/dL. Although this would indicate massive fibrinogen consumption, levels are still adequate to promote clinical coagulation—usually about 150 mg/dL. If serious *hypofibrinogenemia*—less than 50 mg/dL—is present, the clot formed from whole blood in a glass tube may initially be soft but not necessarily remarkably reduced in volume. Then, over the next half hour or so, as platelet-induced clot retraction develops, the clot becomes quite small. When many of the erythrocytes are extruded, the volume of liquid in the tube clearly exceeds that of clot.

As depicted in Figure 41-29, fibrinolysis cleaves fibrin and fibrinogen into various fibrin degradation products that are detected by several sensitive assays. There are many fragment types, and monoclonal antibodies in assay kits usually measure d-dimers specific for that assay. These values are always abnormally high with clinically significant consumptive coagulopathy. At least in obstetrical disorders, quantification has not been correlated with outcomes. Examples of the magnitude of fibrin split product elevations in various obstetrical coagulopathies is shown in Figure 41-30.

FIGURE 41-30
Quantification of fibrin-split products in various obstetrical syndromes that cause disseminated intravascular coagulation. AFLP = Acute fatty liver of pregnancy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count. (Reproduced with permission from Cunningham FG, Nelson DB: Disseminated intravascular coagulation syndromes in obstetrics. Obstet Gynecol. 2015 Nov;126(5):999–1011.)



Thrombocytopenia is likely if petechiae are abundant or if clotted blood fails to retract within an hour or so. Confirmation is provided by a low platelet count. If severe preeclampsia syndrome is comorbid, there may also be *qualitative platelet dysfunction* (Chap. 40, Maternal Thrombocytopenia).

Prothrombin time (PT) and partial thromboplastin time (PTT) are standard coagulation tests. Prolongation may stem from very low fibrinogen concentrations, from appreciably reduced levels of the procoagulants needed to generate thrombin, or from large amounts of circulating fibrinogen-fibrin degradation products.

Thromboelastometry and thromboelastography are point-of-care tests used as adjuncts to conventional laboratory studies (Abdul-Kadir, 2014). Their current role may serve to guide blood product replacement, discussed later (Viscoelastic Assays).

Using many of these tests, several organizations have attempted to establish a more uniform definition of DIC. One is the International Society on Thrombosis and Haemostasis (ISTH) scoring system. The score is used *only after* a condition known to cause intravascular coagulation is identified and is calculated using a combination of laboratory tests. Composite ISTH-DIC scores <5 suggest nonovert DIC, whereas scores ≥5 are compatible with overt DIC. Other than one report of acute fatty liver of pregnancy, this scoring system has not been applied widely in obstetrics (Nelson, 2014).

General Management

To halt ongoing defibrination, prompt identification and removal of the inciting source of the coagulopathy is a priority. With surgical incisions or extensive lacerations accompanied by severe hemorrhage, rapid replacement of procoagulants is usually indicated. Vigorous restoration and maintenance of the circulation to treat hypovolemia cannot be overemphasized. Adequate perfusion restores hepatic and endothelial synthesis of procoagulants and permits prompt removal of activated coagulation factors, fibrin, and fibrin degradation products by the reticuloendothelial system.

Aside from these fundamental steps, few other agents have proven soundly effective. Although seemingly counterintuitive, unfractionated heparin had been recommended but has now been abandoned. Other examples include use of antifibrinolytic agents—either tranexamic acid or epsilon-aminocaproic acid (Amicar) (American College of Obstetricians and Gynecologists, 2017d; Pacheco, 2017). Currently, use of these two agents is not recommended because the fibrinolytic system is necessary for dissolution of widespread fibrin thromboses caused by generalized intravascular coagulation (Hunt, 2014). Discussed later (Packed Red Blood Cells), recombinant factor VIIa (rFVIIa) has been used to help control severe obstetrical hemorrhage from other causes. However, current clinical evidence is insufficient to make firm recommendations on its administration for obstetrical coagulopathies.

Specific Comorbid Conditions

Placental abruption is the most common cause of severe consumptive coagulopathy in obstetrics and is discussed more fully in Placental Abruption. Typical quantified levels of fibrin-split products with abruption are shown in Figure 41-30. With *preeclampsia, eclampsia,* and *HELLP syndrome,* endothelial activation is a hallmark and is discussed in Chapter 40 (Pathogenesis). In general, the clinical severity of preeclampsia is directly correlated with thrombocytopenia and fibrinogen-fibrin degradation products (Kenny, 2015; Levi, 2010b). As shown in Figure 41-30, intravascular coagulation is seldom severe enough to be clinically worrisome (Pritchard, 1976).

Fetal Death and Delayed Delivery

Consumptive coagulopathy associated with prolonged retention of a dead fetus is unusual today because fetal death can be easily confirmed and there are highly effective methods for labor induction. With singleton pregnancies, if the dead fetus is undelivered, most women enter spontaneous labor within 2 weeks. Gross disruption of maternal coagulation rarely develops before 4 weeks (Pritchard, 1959, 1973). After 1 month, however, almost a fourth will develop consumptive coagulopathy.

Obvious coagulation derangement occasionally develops in a multifetal pregnancy in which one fetus dies while the other survives (Chescheir, 1988; Landy, 1989). This situation is uncommon, and in one study of 22 such pregnancies, none developed a coagulopathy (Petersen, 1999). Most cases are seen in monochorionic twins with shared circulations, which are described in Chapter 45 (Monochorionic Twins and Vascular Anastomoses).

Amnionic Fluid Embolism

The classic triad of abrupt hemodynamic and respiratory compromise along with DIC underpins its diagnosis (Clark, 2016). Most reports describe a frequency of 1 in 40,000 to 1 in 50,000 (Clark, 2014; Knight, 2010; Kramer, 2012). The case-fatality rate in all of these studies ranges from 11 to 43 percent. From another perspective, amnionic fluid embolism was the cause of 5 to 15 percent of all pregnancy-related deaths in the United States and Canada (Berg, 2003, 2010; Creanga, 2015; Kramer, 2012).

Predisposing conditions are rapid labor, meconium-stained fluid, and tears into uterine and other large pelvic veins that permit an exchange of fluids between the maternal and fetal compartment (Society for Maternal-Fetal Medicine, 2016). Other commonly cited risks include older maternal age; postterm pregnancy; labor induction or augmentation; eclampsia; cesarean, forceps, or vacuum delivery; placental abruption or previa; and hydramnios (Knight, 2010, 2012; Kramer, 2012). The association of uterine hypertonus appears to be the *effect* rather than the *cause* because uterine blood flow ceases when intrauterine pressures exceed 35 to 40 mm Hg. Thus, a hypertonic contraction would be the *least* likely circumstance for amnionic fluid and other debris to enter uterine veins (Clark, 1985). For this reason, hypertonus from oxytocin is not implicated.

Diagnosis

Proposed criteria for diagnosis of amnionic fluid embolism are shown in Table 41-7. The classic example is dramatic, and a woman in the late stages of labor or immediately postpartum begins gasping for air. Seizures or cardiorespiratory arrest rapidly follows accompanied by massive hemorrhage from consumptive coagulopathy. Clinical manifestations are variable. For example, we and others have managed several women in whom otherwise uncomplicated vaginal or cesarean delivery was followed by severe acute consumptive coagulopathy without overt cardiorespiratory difficulties. In those women, consumptive coagulopathy appears to be the *forme fruste* of amnionic fluid embolism (Kramer, 2012; Porter, 1996).

TABLE 41-7

Diagnostic Criteria for Amnionic Fluid Embolism

Abrupt onset of cardiorespiratory arrest, or both hypotension and respiratory compromise.
Documentation of overt disseminated intravascular coagulation. Coagulopathy must be detected prior to loss of sufficient blood to cause dilutional or shock-related consumptive coagulopathy.
Clinical onset during labor or within 30 minutes of placental delivery.
No fever ≥38°C.

Adapted from Clark, 2016.

Because of this clinical variability, other sources of acute cardiac or respiratory failure should be considered. These include myocardial infarction, pulmonary or air embolism, high spinal blockade, eclampsia, and anaphylactic shock. In some cases, the temporal relationship of events aids diagnosis. *Unfortunately, no specific diagnostic laboratory test confirms or refutes the diagnosis of amnionic fluid embolism, and it remains a clinical diagnosis.* Importantly, women suffering from excessive blood loss and resulting coagulopathy may be misdiagnosed with amnionic fluid embolism, when the true culprit is unrecognized or underappreciated hemorrhage (Clark, 2016). In either event, a woman with cardiopulmonary compromise should receive immediate resuscitation (Society for Maternal-Fetal Medicine, 2016).

Pathophysiology

The mechanism of injury from amnionic fluid embolism has evolved. Early theories proposed that amnionic fluid and debris entered maternal circulation and obstructed pulmonary artery flow, which led to hypoxia, right heart failure, and death. However, during normal delivery, amnionic fluid commonly enters the maternal circulation through venous channels at the placental implantation site or from small lacerations. Accordingly, squames, fetal cells, and trophoblasts can often be identified in maternal peripheral blood at delivery (Clark, 1986; Lee, 1986). And, infused amnionic fluid is generally innocuous, even in large amounts (Adamsons, 1971; Stolte, 1967).

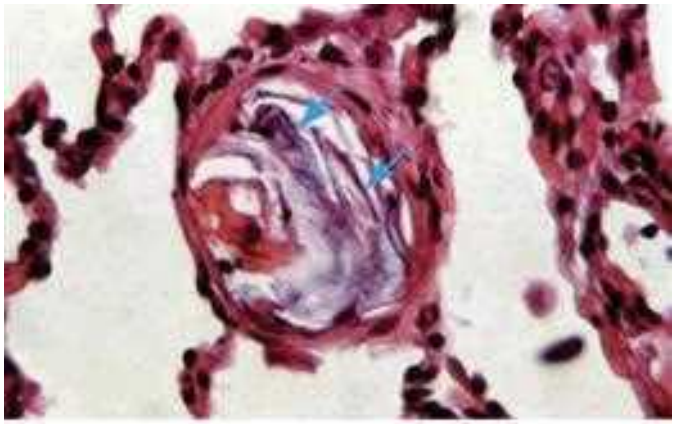
Current explanations describe disruption of the maternal-fetal interface, which allows material from the fetal compartment to enter maternal circulation. This leads to abnormal activation of proinflammatory mediator systems, similar to the systemic inflammatory response syndrome (SIRS), and causes initial, transient pulmonary vasoconstriction and hypertension. Acute right ventricular failure is then followed by hemodynamic collapse from right ventricular infarction coupled with interventricular septum displacement to the left and ultimately decreased left-sided cardiac output. This right and now left ventricular dysfunction is followed by cardiogenic pulmonary edema and systemic hypotension. Concurrently in this process, acute respiratory failure with severe hypoxemia from shunting develops. Notably, the resulting multiorgan dysfunction is an interrelated process, with both the cardiac and pulmonary systems affecting each other.

Women who survive beyond these first phases invariably have the third component of the classic triad—a consumptive coagulopathy. Similar to the coagulation process described earlier, the material from the fetal compartment containing tissue factor activates factor VII. This leads to the development of DIC (see Fig. 41-29).

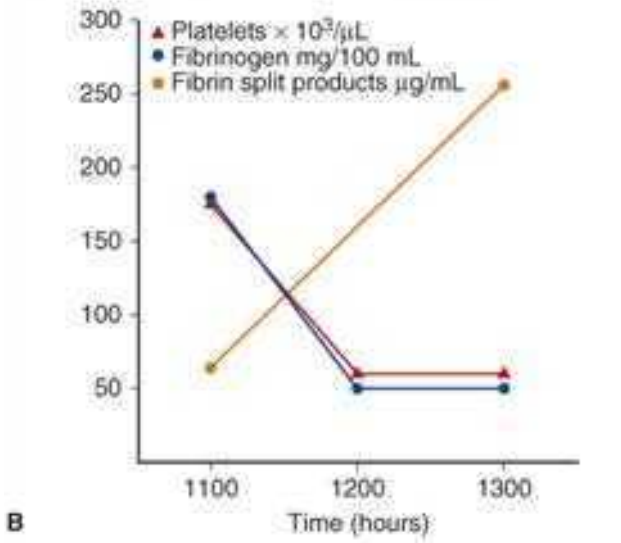
In those who succumb, postmortem histopathological findings may be obvious (Fig. 41-31). However, detection of such material may require special stains, and even then, debris may not be seen. In one study, fetal elements were detected in 75 percent of autopsies and in 50 percent of specimens prepared from concentrated buffy coat aspirates taken antemortem from a pulmonary artery catheter (Clark, 1995).

FIGURE 41-31

Fatal amnionic fluid embolism. **A.** Autopsy findings of fetal squames (*arrows*) packed into a small pulmonary artery. **B.** Results of coagulation studies from the same woman with abruptly decreased fibrinogen levels and platelets and simultaneously increased fibrin split products.



A



B

Management

The initial period of systemic and pulmonary hypertension with amnionic fluid embolism is transient. Thus, immediate high-quality cardiopulmonary resuscitation and advanced cardiac life support must be initiated without delay (Society for Maternal-Fetal Medicine, 2016). These are discussed in detail in Chapter 47 (Cardiopulmonary Resuscitation).

If resuscitation is successful, hemodynamic instability is common in survivors. Both fever and hyperoxia will worsen ischemia–reperfusion injury to the brain, and thus both are avoided. A suitable goal for temperature is 36°C and for mean arterial pressure is 65 mm Hg (Society for Maternal-Fetal Medicine, 2016). Additional supportive care measures such as intubation are usually necessary. During the phase of right ventricular failure, inotropic agents such as dobutamine may improve right heart output, and later systemic hypotension should be treated with vasopressors such as norepinephrine. Excess fluid administration is discouraged due to risks of worsening dilation of an already engorged right ventricle, which may cause right-sided myocardial infarction and displacement of the interventricular septum.

Beginning either immediately after cardiopulmonary collapse or during the ensuing phases of injury, a coagulopathy develops in most cases from activation of factor VII and X. This may be exacerbated by ongoing hemorrhage. A common source of obstetrical bleeding is uterine atony. Therefore, immediate evaluation of coagulation parameters is prudent with concurrent clinical management of bleeding.

Clinical Outcomes

Most reports describe dismal outcomes with amnionic fluid embolism. This is likely influenced by underdiagnosis and reporting biases that favor the most severe cases with the highest mortality rates. Several reports are illustrative. From a California database of 1.1 million deliveries, the mortality rate with amnionic fluid embolism was 60 percent (Gilbert, 1999). In a report of 34 mothers from China, 90 percent died (Weiwen, 2000). Death can be amazingly rapid, and 12 of the 34 died within 30 minutes. The mortality rate was somewhat better in the largest study from Canada. Of 120 women with an amnionic fluid embolism, only a fourth died. Survivors commonly have profound neurological impairment. Clark (1995) observed that only 8 percent of women who lived despite cardiac arrest survived neurologically intact. Overall, prognosis appears to be more associated with disease severity and the attendant cardiac arrest than with any specific treatment modality (Clark, 2014).

As perhaps expected, perinatal outcomes are also poor and are inversely related to the maternal cardiac arrest-to-delivery interval. Even so, neonatal survival rate is 70 percent, but unfortunately, up to half of survivors suffer residual neurological impairment. In the Canadian study, 28 percent of infants were considered to be asphyxiated at birth (Kramer, 2012).

Sepsis Syndrome

Various infections that are accompanied by endo- or exotoxin release can lead to sepsis syndrome. Although a feature of this syndrome includes activation of coagulation, seldom does sepsis alone cause massive procoagulant consumption. *Escherichia coli* bacteremia is frequently seen with antepartum pyelonephritis and puerperal infections, however, accompanying consumptive coagulopathy is usually not severe. Some notable exceptions are septicemia associated with puerperal infection or septic abortion caused by exotoxins released from infecting organisms such as group A *Streptococcus pyogenes, Staphylococcus aureus*, or *Clostridium perfringens, C sordellii*, or *C novyi* (Herrera, 2016). Treatment of sepsis syndrome and septic shock is discussed in Chapter 47 (Sepsis Syndrome).

Purpura Fulminans

This severe—often lethal—form of consumptive coagulopathy is caused by microthrombi in small blood vessels leading to skin necrosis and sometimes vasculitis. Debridement of large areas of skin over the extremities and buttocks frequently requires treatment in a burn unit. Purpura fulminans usually complicates sepsis in women with heterozygous protein C deficiencies and low protein C serum levels (Levi, 2010b). Note that homozygous protein C or S deficiency results in fatal *neonatal purpura fulminans* (Chap. 52, Protein S Deficiency).

Abortion

Septic abortion—especially associated with the organisms just discussed—can incite coagulation and worsen hemorrhage, especially with midtrimester abortions. Indeed, sepsis syndrome accompanied by intravascular coagulation accounts for 25 percent of abortion-related deaths (Saraiya, 1999). In the past, especially with illegal abortions, infections with *C perfringens* were a frequent cause of intense intravascular hemolysis at Parkland Hospital (Pritchard, 1971). More recently, however, septic abortions from infection with *C sordellii* have emerged as important causes (Chap. 18, Inevitable Abortion).

Second-trimester induced abortions can stimulate intravascular coagulation even in the absence of sepsis. Ben-Ami and associates (2012) described a 1.6-percent incidence in 1249 late second-trimester pregnancies terminated by dilation and evacuation. Two thirds were done for fetal demise, which may have been contributory to coagulopathy. Another source of intense coagulation is from instillation of hypertonic solutions to effect midtrimester abortions. These are not commonly used currently for pregnancy terminations. The mechanism is thought to initiate coagulation by thromboplastin release into maternal circulation from the placenta, fetus, and decidua by the necrobiotic effect of hypertonic solutions (Burkman, 1977).

MANAGEMENT OF HEMORRHAGE

Recognition of obstetrical hemorrhage severity is crucial to its management. Visual estimation of blood loss, especially when excessive, is notoriously inaccurate, and true blood loss is often two to three times the clinical estimate. Consider also that in obstetrics, part and sometimes even all of the lost blood may be concealed. Estimation is further complicated in that peripartum hemorrhage also includes the pregnancy-induced augmented blood volume. After pregnancy hypervolemia is lost at delivery, blood loss can be estimated by calculating 500 mL loss for each 3 volume percent drop in hematocrit. The hematocrit nadir depends on the speed of resuscitation with intravenous crystalloids. *With acute blood loss, the real-time hematocrit is at its maximum whenever measured in the delivery, operating, or recovery room.*

A prudent rule is that any time blood loss is considered more than average, then the hematocrit is determined and plans are made for close observation for potential physiological deterioration. Urine output measured hourly is one of the most important "vital signs." *Unless diuretic agents are given—and these are seldom indicated with active bleeding—accurately measured urine flow reflects renal perfusion, which in turn reflects perfusion of other vital organs.* Urine flow of at least 30 mL, and preferably ≥50 mL per hour, should be maintained.

Hypovolemic Shock

Shock from hemorrhage evolves through several stages. Early in the course of massive bleeding, mean arterial pressure, stroke volume, cardiac output, central venous pressure, and pulmonary capillary wedge pressure decline. Increases in arteriovenous oxygen content difference reflect a relative rise in tissue oxygen extraction, although overall oxygen consumption falls.

Blood flow to capillary beds in various organs is controlled by arterioles. These are resistance vessels that are partially controlled by the central nervous system. However, approximately 70 percent of total blood volume is contained in venules, which are passive resistance vessels controlled by humoral factors. Catecholamine release during hemorrhage prompts greater venular tone, which provides an autotransfusion from this capacitance reservoir (Barber, 1999). This is accompanied by compensatory rises in heart rate, systemic and pulmonary vascular resistance, and myocardial contractility. In addition, cardiac output and blood volume are redistributed from the effect of selective, centrally mediated arteriolar constriction or relaxation—*autoregulation*. Thus, although perfusion to the kidneys, splanchnic beds, muscles, skin, and uterus is diminished, relatively more blood flow is diverted to the heart, brain, and adrenal glands.

When the blood volume deficit exceeds approximately 25 percent, compensatory mechanisms usually are inadequate to maintain cardiac output and blood pressure. Importantly, additional small losses of blood will now cause rapid clinical deterioration. Following an initial augmented *total oxygen extraction* by maternal tissue, maldistribution of blood flow results in *local* tissue hypoxia and metabolic acidosis. This creates a vicious cycle of vasoconstriction, organ ischemia, and cellular death.

Another important clinical effect of hemorrhage is activation of lymphocytes and monocytes, which in turn causes endothelial cell activation and platelet aggregation. These promote release of vasoactive mediators that occlude small vessels and further impair microcirculatory perfusion. Other common obstetrical syndromes—preeclampsia and sepsis—also lead to loss of capillary endothelial integrity, additional loss of intravascular volume into the extracellular space, and platelet aggregation. These then can incite DIC.

The pathophysiological events just described create important but often overlooked extracellular fluid and electrolyte shifts involved in both the genesis and successful treatment of hypovolemic shock. These include changes in the cellular transport of various ions such as sodium and water into skeletal muscle as well as potassium loss. Replacement of extracellular fluid and intravascular volume are both necessary. *Survival is enhanced in acute hemorrhagic shock if blood plus crystalloid solution is given compared with blood transfusions alone.*

Fluid Resuscitation

Whenever excessive blood loss is suspected in a pregnant woman, steps are simultaneously taken to identify the bleeding source and to begin resuscitation. If she is undelivered, restoration of blood volume is beneficial to mother and fetus, and it also prepares for emergent delivery. If she is postpartum, it is essential to immediately identify uterine atony, retained placental fragments, or genital tract lacerations. At least one and preferably more large-bore intravenous infusion systems are established promptly with rapid administration of crystalloid solutions, while blood is made available. An operating room is readied, and a surgical and anesthesia team are assembled immediately. Specific management of hemorrhage is further dependent on its etiology.

It cannot be overemphasized that treatment of serious hemorrhage demands prompt and adequate refilling of the intravascular compartment with crystalloid solutions. These rapidly equilibrate into the extravascular space, and only 20 percent of crystalloid remains intravascularly in critically ill patients after 1 hour (Zuckerbraun, 2010). *Because of this, initial fluid is infused in a volume two to three times the estimated blood loss.*

Resuscitation of hypovolemic shock with colloid versus crystalloid solutions has been debated. In a Cochrane review of resuscitation of nonpregnant critically ill patients, Perel and coworkers (2013) found equivalent benefits but concluded that colloid solutions were more expensive. Similar results were found in the Saline versus Albumin Fluid Evaluation (SAFE) randomized trial of almost 7000 nonpregnant patients (Finfer, 2004). We concur with Zuckerbraun and colleagues (2010) that acute volume resuscitation is preferably done with crystalloid and blood.

Blood Replacement

The hematocrit level or hemoglobin concentration that mandates blood transfusion is controversial. Cardiac output does not substantively drop until the hemoglobin concentration falls to approximately 7 g/dL or hematocrit of 20 volume percent. At this level, several organizations recommend consideration for red cell transfusions (Carson, 2017). Also, Military Combat Trauma Units in Iraq used a target hematocrit of 21 volume percent (Barbieri, 2007). In general, with *ongoing* obstetrical hemorrhage, we recommend rapid blood infusion when the hematocrit is <25 volume percent. This decision is dependent on whether the fetus has been delivered; surgery is imminent or ongoing operative blood loss is expected; or acute hypoxia, vascular collapse, or other factors are present.

Scant clinical data elucidate these issues. In a study from the Canadian Critical Care Trials Group, nonpregnant patients were randomly assigned to restrictive red cell transfusions to maintain hemoglobin concentration >7 g/dL or to liberal transfusions to maintain the hemoglobin level at 10 to 12 g/dL. The 30-day mortality rate was similar—19 versus 23 percent in the restrictive versus liberal groups, respectively (Hébert, 1999). Transfusion therapy in nonpregnant patients with septic shock had similar mortality rates when 7 g/dL was compared with 9 g/dL as targets for transfusions (Holst, 2014). *The number of units transfused in a given woman to reach a target hematocrit depends on her body mass and on expectations of additional blood loss.*

Blood Component Products

Contents and effects of transfusion of various blood components are shown in Table 41-8. *Compatible whole blood is ideal for treatment of hypovolemia from catastrophic hemorrhage.* It has a shelf life of 40 days, and 70 percent of the transfused red cells function for at least 24 hours following transfusion. One unit raises the hematocrit by 3 to 4 volume percent. Important for obstetrical hemorrhage, whole blood replaces many coagulation factors in obstetrics—especially fibrinogen—and its plasma treats hypovolemia. A collateral derivative is that women with severe hemorrhage are resuscitated with fewer blood donor exposures than with packed red cells and components (Shaz, 2009).

TABLE 41-8

Blood Products Commonly Transfused in Obstetrical Hemorrhage

Product	Volume per Unit	Contents per Unit	Effect on Hemorrhage
Whole blood	About 500 mL; Hct ~40 percent	RBCs, plasma, 600–700 mg fibrinogen, no platelets	Restores blood volume and fibrinogen, increases Hct 3–4 volume percent per unit
Packed RBCs	250–300 mL; Hct ~55–80 percent	RBCs, minimal fibrinogen, no platelets	Increases Hct 3–4 volume percent per unit
Fresh-frozen plasma (FFP)	About 250 mL; 30-minute thaw	Colloid, 600–700 mg fibrinogen, no platelets	Restores circulating volume and fibrinogen
Cryoprecipitate	About 15 mL, frozen	One unit ~200 mg fibrinogen, other clotting factors, no platelets	15–20 units or 3–4 g will increase baseline fibrinogen ~150 mg/dL
Platelets	About 50 mL, stored at room temperature	One unit raises platelet count about 5000/µL; single-donor apheresis bag preferable	6–10 units transfused: single-donor bag preferable to raise platelets ~30,000/µL

Hct = hematocrit; RBCs = red blood cells.

Evidence supports the preferable use of whole blood for massive hemorrhage, including our experiences at Parkland Hospital (Alexander, 2009; Hernandez, 2012). Of more than 66,000 deliveries, women with obstetrical hemorrhage treated with whole blood had significantly lower incidences of renal failure, acute respiratory distress syndrome, pulmonary edema, hypofibrinogenemia, intensive care unit admissions, and maternal death compared with those given packed red cells and component therapy. Freshly donated whole blood has also been used successfully for life-threatening massive hemorrhage at combat support hospitals (Murdock, 2014; Stubbs, 2016).

In most institutions today, however, whole blood is rarely available. Thus, most women with obstetrical hemorrhage and ongoing massive blood loss are given packed red cells and crystalloid. In these instances, no data support a 1:1 plasma: red cell transfusion ratio. As subsequently discussed, many institutions use *massive transfusion protocols* designed to anticipate all facets of massive obstetrical hemorrhage. These “recipes” commonly contain a combination of red cells, plasma, cryoprecipitate, and platelets (Cunningham, 2015; Pacheco, 2011; Shields, 2011).

Several studies have assessed plasma:red cell ratio with massive transfusion protocols used in civilian trauma units and military combat hospitals (Borgman, 2007; Gonzalez, 2007; Hardin, 2014; Johansson, 2007). Patients undergoing massive transfusion—defined as 10 or more units of blood—had much higher survival rates as the ratio of plasma to red cell units neared 1:1.4, that is, one unit of plasma given for each 1.4 units of packed red cells. By way of contrast, the highest mortality group had a ratio of 1:8. *Most of these studies found that component replacement is rarely necessary with acute replacement of 5 to 10 units of packed red cells.*

From the foregoing, when red cell replacement exceeds five units or so, evaluation of platelet count, clotting studies, and plasma fibrinogen concentration is reasonable. In the woman with obstetrical hemorrhage, the platelet count should be maintained >50,000/µL by the infusion of platelet concentrates. A fibrinogen level <150 mg/dL or a sufficiently prolonged PT or PTT in a woman with surgical bleeding is an indication for replacement. Fresh-frozen plasma is administered in doses of 10 to 15 mL/kg, or alternatively, cryoprecipitate is infused (see Table 41-8).

Dilutional Coagulopathy

A major drawback of treatment for massive hemorrhage with crystalloid solutions and packed red blood cells is depletion of platelets and clotting factors. This can lead to a *dilutional coagulopathy* that is clinically indistinguishable from DIC (Hossain, 2013).

Thrombocytopenia is the most frequent coagulation defect found with blood loss and multiple transfusions (Counts, 1979). In addition, packed red cells have only very small amounts of soluble clotting factors, and stored whole blood is deficient in platelets and in factors V, VIII, and XI. As discussed, massive replacement with red cells only and without factor replacement can also cause *hypofibrinogenemia* and prolongation of the PT and PTT. Because many causes of obstetrical hemorrhage also cause consumptive coagulopathy, the distinction between dilutional and consumptive coagulopathy can be confusing. Fortunately, treatment for both is similar.

Type and Screen versus Crossmatch

A blood type and antibody screen should be performed for any woman at significant risk for hemorrhage. Screening involves mixing maternal serum with standard reagent red cells that carry antigens to which most of the common clinically significant antibodies react. Crossmatching involves the use of actual donor erythrocytes rather than the standardized red cells. This process is efficient, and only 0.03 to 0.07 percent of patients identified as having no antibodies are subsequently found to have antibodies (Boral, 1979). *Importantly, administration of screened blood rarely results in adverse clinical sequelae.*

Packed Red Blood Cells

One unit of packed erythrocytes is derived from one unit of whole blood to have a hematocrit of 55 to 80 volume percent. One unit will increase the hematocrit by 3 to 4 volume percent.

Platelets

With surgical delivery or with lacerations, platelet transfusions are considered with ongoing obstetrical hemorrhage when the platelet count falls below 50,000/μL (Kenny, 2015). In the *nonsurgical patient*, bleeding is rarely encountered if the platelet count is 10,000/μL or higher (Murphy, 2010). The preferable source of platelets is one "bag" obtained by single-donor apheresis. This contains the equivalent of six units from six individual donors. Depending on maternal size, each single-donor apheresis six-unit bag raises the platelet count by approximately 20,000/μL (Schlicter, 2010). If these bags are not available, then individual-donor platelet units are used, and six to eight such units are generally transfused one at a time.

Importantly, the donor plasma in platelet units must be compatible with recipient erythrocytes. Further, because some red blood cells are invariably transfused along with the platelets, only units from D-negative donors should be given to D-negative recipients. If it is necessary to give these, however, adverse sequelae are unlikely (Lin, 2002).

Fresh-Frozen Plasma

This component is prepared by separating plasma from whole blood and then freezing it. Approximately 30 minutes are required for frozen plasma to thaw. It is a source of all stable and labile clotting factors, including fibrinogen. Thus, it is often used for treatment of women with consumptive or dilutional coagulopathy. *Plasma is not appropriate for use as a volume expander in the absence of specific clotting factor deficiencies.* It should be considered in a bleeding woman with a fibrinogen level <150 mg/dL or with an abnormal PT or PTT.

An alternative to frozen plasma is *liquid plasma (LQP).* This never-frozen plasma is stored at 1 to 6°C for up to 26 days, and in vitro, it appears to be superior to thawed plasma (Matijevic, 2013).

Cryoprecipitate and Fibrinogen Concentrate

Each unit of cryoprecipitate is prepared from one unit of fresh-frozen plasma. Each 10- to 15-mL unit contains at least 200 mg of fibrinogen along with factor VIII:C, factor VIII:von Willebrand factor, factor XIII, and fibronectin (American Association of Blood Banks, 2014). It is usually given as a "pool" or "bag" using an aliquot of fibrinogen concentrate taken from 8 to 120 donors. Cryoprecipitate is an ideal source of fibrinogen when levels are dangerously low and there is oozing from surgical incisions. Another alternative is virus-inactivated fibrinogen concentrate. Each gram of this raises the plasma fibrinogen level approximately 40 mg/dL (Ahmed, 2012; Kikuchi, 2013).

Recombinant Activated Factor VII

This synthetic vitamin K-dependent protein is available as *NovoSeven.* It binds to exposed tissue factor at the site of injury to generate thrombin that activates platelets and the coagulation cascade. Since its introduction, rFVIIa has been used to help control hemorrhage from surgery, trauma, and obstetrical causes (Goodnough, 2016; Murakami, 2015). Most Level I trauma centers include it in their massive transfusion protocols, and it is included in the one used at Parkland Hospital. Importantly, rFVIIa will not be effective if the plasma fibrinogen level is <50 mg/dL or the platelet count is <30,000/μL.

One major concern with rFVIIa use is arterial—and to a lesser degree venous—thrombosis. In a review of 35 randomized trials with nearly 4500 subjects, arterial thromboembolism developed in 55 percent (Levi, 2010a). A second concern is that it was found to be only marginally effective (Pacheco, 2011).

Tranexamic Acid

This antifibrinolytic drug has been used for traumatic and obstetrical hemorrhage. Tranexamic acid inhibits clot lysis to help forestall bleeding by preventing plasmin from degrading fibrin. Its use has been associated with a higher incidence of renal cortical necrosis (Frimat, 2016). The evidence supporting its use as an adjunct in obstetrical hemorrhage is limited, and its routine use for prophylaxis is not recommended American College of Obstetricians and Gynecologists, 2017d; Pacheco, 2017).

Massive Transfusion Protocols

These function to speed blood product delivery to the bedside or operating room, which permits product infusion early in the resuscitation process. The rationale is to prevent adverse effects of aggressive resuscitation solely with crystalloid and packed red blood cells. That said, it is not necessary to activate massive transfusions until at least four to five units of red cells have been given within 2 hours or so. Once activated, red cells, plasma, platelets, and fibrinogen are given by protocol in amounts shown in Table 41-9. Some protocols include rFVIIa and others include tranexamic acid.

TABLE 41-9

Parkland Hospital Obstetrical Massive Transfusion Protocol

Round No.	PRBC 5 Units	FFP 3 Units	Plts 6-pack	Cryo 1 Unit	rVIIa 2 mg
1	X	X			
2	X	X	X		X
3	X	X		X	
4	X	X	X		X
5	X	X			
6	X	X	X	X	X
7	X	X			
8	X	X	X		X

Cryo = cryoprecipitate; FFP = fresh frozen plasma; Plts = Platelets; PRBC = packet red blood cells; rVIIa = recombinant activated factor VII (NovoSeven).

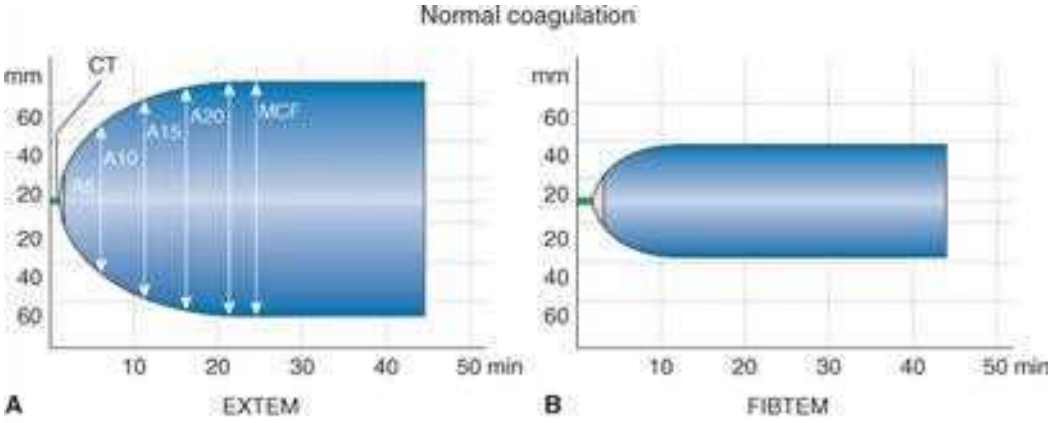
As expected, studies attesting to the superiority for survival with massive transfusion protocols are limited. Most reports describe nonpregnant trauma victims, but some observational studies address obstetrical hemorrhage (Green, 2016; Pacheco, 2016). More data with use of these protocols is needed.

Viscoelastic Assays

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point-of-care tests that assess coagulation in whole blood during massive transfusions. These tests work by analyzing both clot formation and breakdown in a whole blood sample from a given patient. Testing produces a profile of coagulation dynamics, and displayed values indicate the speed and quality of clot formation (Fig. 41-32). These assays provide information regarding time to clot formation, clot strength, and fibrinolysis. Currently, they guide blood product replacement in trauma, liver transplant, and cardiac surgery patients. Studies of TEG and ROTEM techniques in pregnant women have confirmed the hypercoagulable state of pregnancy and provide reference ranges for use in this population (Butwick, 2015; de Lange, 2014; Solomon, 2012).

FIGURE 41-32

TEG/ROTEM based viscoelastic assays of coagulation profiles in a pregnant woman. **A.** EXTEM clot profile: CT = clotting time; A5–20 = clot amplified at 5, 10, 15, 20 min; MCF = maximum clot firmness. **B.** FIBTEM clot profile showing excellent fibrin-based clot quality. (Reproduced with permission from Solomon C, Collis RE, Collins PW: Haemostatic monitoring during postpartum haemorrhage and implications for management, Br J Anaesth. 2012 Dec;109(6):851–863.)



Although these point-of-care tests appear promising, they also have several limitations. For example, they cannot be used to detect disorders of primary hemostasis (Solomon, 2012). Additionally, these tests cannot diagnose coagulopathies stemming from platelet dysfunction or antiplatelet drugs. A major drawback is the risk of misinterpretation when tests are used by inadequately trained personnel. Further study is necessary before these tests are widely applied for treatment of obstetrical hemorrhage.

Topical Hemostatic Agents

Several agents can be used to control persistent surgical oozing. These were recently reviewed by Miller and colleagues (2015). Other than for cesarean hysterectomy, these are seldom used in obstetrical hemorrhage.

Cell Salvage and Autologous Transfusion

Preoperative patient phlebotomy and autologous blood storage for transfusion has been disappointing. Exceptions are women with a rare blood type or with unusual antibodies. Most have concluded that autologous transfusions are not cost effective (Etchason, 1995; Pacheco, 2011, 2013).

Intraoperative blood salvage with reinfusion is considered to be a safe intervention in obstetrical patients. As discussed in Chapter 30 (Patient Preparation), this practice may be helpful for women declining transfusion. Prior concern centered on amnionic fluid contamination and embolism (Dhariwal, 2014; Goucher, 2015; Pacheco, 2011). A recent randomized trial involving 3028 women compared routine cell salvage use against routine care, in which salvage was employed only for bleeding indications. The rate of nonautologous donor blood transfusion was reduced in the cell salvage group—2.5 versus 3.5 percent, but this was not a significant difference (Khan, 2017). Similar to prior reports, no cases of amnionic fluid embolism were reported.

Transfusion Complications

Of serious known risks, *transfusion of an incompatible blood component* may result in acute hemolysis. If severe, this can cause DIC, acute kidney injury, and death. Preventable errors responsible for most of such reactions frequently include mislabeling of a specimen or incorrectly transfusing a patient not slated for those products. The rate of such errors in the United States is estimated to be 1 in 14,000 units, but these events are likely underreported (Lerner, 2010). A transfusion reaction is characterized by fever, hypotension, tachycardia, dyspnea, chest or back pain, flushing, severe anxiety, and hemoglobinuria. Immediate supportive measures include stopping the transfusion, treating hypotension and hyperkalemia, provoking diuresis, and alkalinizing the urine.

Transfusion-related acute lung injury (TRALI) is the most common cause of transfusion-related mortality. The syndrome is characterized by severe dyspnea, hypoxia, and noncardiogenic pulmonary edema that develop within 6 hours of transfusion (Peters, 2015). TRALI is estimated to complicate at least 1 in 12,000 transfusions (Carson, 2017). Although the pathogenesis is incompletely understood, injury to the pulmonary capillaries may arise from anti-human leukocyte antigen (HLA) and neutrophil (HNA) antibodies in donor plasma (Lerner, 2010). A delayed form of TRALI has been reported to begin 6 to 72 hours following transfusion (Marik, 2008). Management is supportive and may include mechanical ventilation (Chap. 47, Clinical Course).

Bacterial infection from transfusion of a contaminated blood component is unusual because organism growth is discouraged by refrigeration. The most often implicated contaminants of red cells include *Yersinia, Pseudomonas, Serratia, Acinetobacter,* and *Escherichia* species. The more important risk is from bacterial contamination of platelets, which are stored at room temperature. Current estimates are that 1 in 1000 to 2000 platelet units are contaminated. Death from transfusion-related sepsis is 1 per 17,000 for single-donor platelets and 1 per 61,000 for apheresis-donor packs (Lerner, 2010).

Viral infection risks from transfusion have been curtailed. The risk of HIV or hepatitis C virus infection in screened blood is estimated to be 1 case per 1 to 2 million units transfused (Carson, 2017; Stramer, 2004). The risk for HIV-2 infection is less. Other viral infections include hepatitis B transmission, which is estimated to be <1 per 100,000 transfused units (Jackson, 2003). Because of its high prevalence, cytomegalovirus-infected leukocytes are often transfused. Thus, precautions are taken for immunosuppressed recipients, keeping in mind that this includes the fetus.

Also, risks for transmitting West Nile virus, human T-lymphotropic virus type I, parvovirus B19, and toxoplasmosis are slight (American Association of Blood Banks, 2013; Foroutan-Rad, 2016). Finally, Zika virus has emerged as another relevant transfusion-transmitted infection (Motta, 2016). The Food and Drug Administration (2016) revised recommendations for collection of all whole blood components to include testing for Zika virus. This practice has been affirmed by the Centers for Disease Control and Prevention (2016).

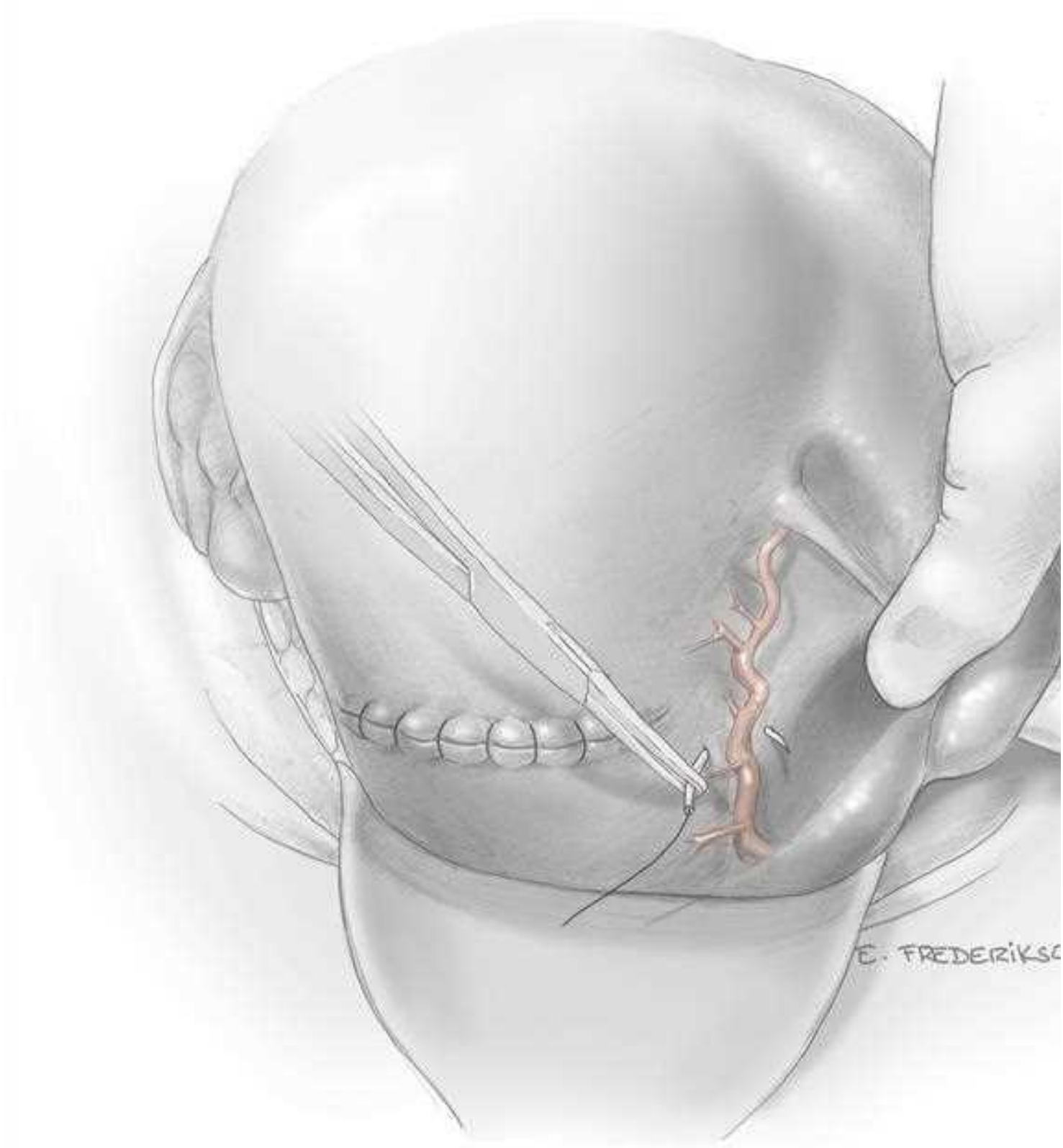
Adjunctive Surgical Procedures

Several invasive procedures can help arrest postpartum hemorrhage. A report from the Agency for Healthcare Research and Quality concluded that most studies addressing these methods are of poor quality (Likis, 2015). In one study of 6660 women with postpartum hemorrhage, 4.4 percent underwent an invasive procedure, and 1.1 percent had a hysterectomy (Kayem, 2016). The failure rate of conservative measures was 15 percent in surgical and embolization procedures.

Uterine Artery Ligation

The technique for unilateral or bilateral uterine artery ligation is used primarily for lacerations at the lateral part of a hysterotomy incision (Fig. 41-33). In our experiences, this procedure is less helpful for hemorrhage from uterine atony.

FIGURE 41-33
Uterine artery ligation. The suture goes through the lateral uterine wall anteriorly, curves around posteriorly, then re-enters anteriorly. When tied, it encompasses the uterine artery.

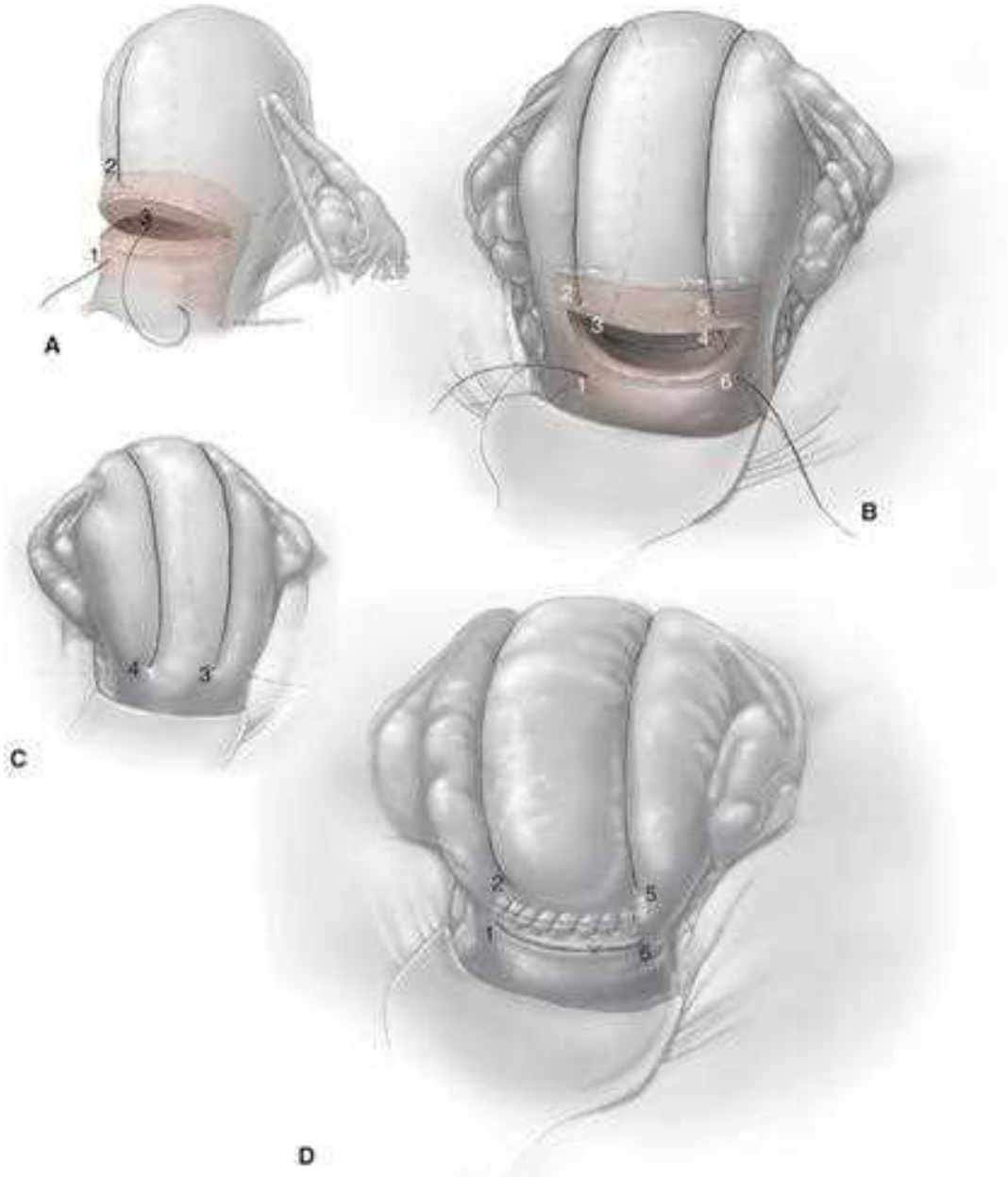


Uterine Compression Sutures

This surgical technique uses a no. 2 chromic suture to compress the anterior and posterior uterine walls together (B-Lynch, 1997). Because they give the appearance of suspenders, they are also called *braces* (Fig. 41-34). Several modifications of the B-Lynch technique have been described (Cho, 2000; Hayman, 2002; Matsubara, 2013; Nelson, 2007). Indications vary for its application, and this will affect the success rate. For example, B-Lynch (2005) cited 948 cases with only seven failures. Conversely, Kayem and associates (2011) described 211 women who had an overall failure rate of 25 percent, which did not differ between B-Lynch sutures and their modifications. In another series, the failure rate was 20 percent (Kaya, 2016). From their review, Sathe and coworkers (2016) reached similar conclusions.

FIGURE 41-34

Uterine compression suture or “brace.” The B-Lynch suture technique is illustrated from an anterior view of the uterus in Figures **A**, **B**, and **D** and a posterior view in Figure **C**. The numbers denote the sequential path of the suture and are shown in more than one figure. **Step 1.** Beginning below the incision, the needle pierces the lower uterine segment to enter the uterine cavity. **Step 2.** The needle exits the cavity above the incision. The suture then loops up and around the fundus to the posterior uterine surface. **Step 3.** The needle pierces the posterior uterine wall to reenter the uterine cavity. The suture then traverses to the opposite side within the cavity. **Step 4.** The needle exits the uterine cavity through the posterior uterine wall. From the back of the uterus, the suture loops up and around the fundus to the front of the uterus. **Step 5.** The needle pierces the myometrium above the incision to reenter the uterine cavity. **Step 6.** The needle exits below the incision and the sutures at points 1 and 6 are tied below the incision. The hysterotomy incision is then closed in the usual fashion.



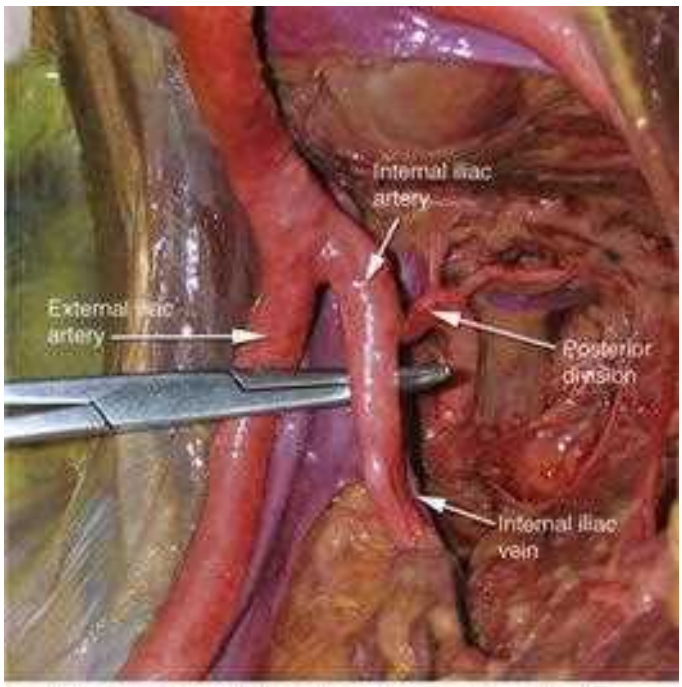
Some unique complications can rarely follow compression sutures (Matsubara, 2013). Most involve variations of uterine ischemic necrosis with peritonitis (Gottlieb, 2008; Joshi, 2004; Ochoa, 2002; Treloar, 2006). In one case, total uterine necrosis followed B-Lynch sutures that were placed in combination with bilateral ligation of uterine, uteroovarian, and round ligament arteries (Friederich, 2007). In most cases, subsequent pregnancies are uneventful if compression sutures are used (An, 2013). A few women, however, with B-Lynch or Cho sutures developed uterine wall defects (Akoury, 2008). Another long-term complication is uterine cavity synechiae (Alouini, 2011; Ibrahim, 2013; Poujade, 2011).

Internal Iliac Artery Ligation

For years, ligation of one or both internal iliac arteries has been used to reduce pelvic hemorrhage. Drawbacks are that the procedure may be technically difficult and is only successful half of the time (American College of Obstetricians and Gynecologists, 2017d). It is not particularly helpful for abating hemorrhage with postpartum atony (Clark, 1985).

For ligation, adequate exposure is obtained by opening the peritoneum over the common iliac artery and dissecting down to the bifurcation of the external and internal iliac arteries (Fig. 41-35). Branches distal to the external iliac arteries are palpated to verify pulsations at or below the inguinal area. Ligation of the internal iliac artery 5 cm distal to the common iliac bifurcation will usually avoid the posterior division branches (Bleich, 2007). The areolar sheath of the artery is incised longitudinally, and a right-angle clamp is carefully passed just beneath the artery from lateral to medial. Care must be taken not to perforate contiguous large veins, especially the internal iliac vein. Suture—usually nonabsorbable—is passed under the artery with a clamp, and the vessel is then securely ligated.

FIGURE 41-35
Ligation of the right internal iliac artery. Unembalmed cadaveric dissection shows the right-angle clamp passing underneath the anterior division of the internal iliac artery just distal to its posterior division. (Used with permission from Dr. Marlene Corton.)



The most important mechanism of action with internal iliac artery ligation is an 85-percent reduction in pulse pressure in those arteries distal to the ligation (Burchell, 1968). This converts an arterial pressure system into one with pressures approaching those in the venous circulation. This creates vessels more amenable to hemostasis via pressure and clot formation.

Even bilateral internal iliac artery ligation does not appear to interfere with subsequent reproduction. Nizard and colleagues (2003) reported follow-up in 17 women who had bilateral artery ligation. From a total of 21 pregnancies, 13 were normal, three ended with miscarriage, three were terminated, and two were ectopic.

Angiographic Embolization

This modality is now used for many causes of intractable hemorrhage when surgical access is difficult. In more than 500 women reported, embolization was 90-percent effective (Grönvall, 2014; Lee, 2012; Poujade, 2012; Zhang, 2015). After his review, Rouse (2013) concluded that embolization can be used to arrest refractory postpartum hemorrhage. Other reports have been less enthusiastic. Fertility is not impaired, and many subsequent successful pregnancies have been reported (Chauleur, 2008; Fiori, 2009; Kolomeyevskaya, 2009). *An important caveat for these procedures is that women with hemodynamic instability related to active bleeding should not be removed from the operating room.*

Complications of embolization are relatively uncommon but can be severe. Case reports detail instances of iatrogenic iliac artery rupture, uterine ischemic necrosis, and uterine infection (Grönvall, 2014; Katakam, 2009; Nakash, 2012). Finally, Al-Thunyan and coworkers (2012) described a woman with massive buttock necrosis and paraplegia following bilateral internal iliac artery embolization.

In a few instances, massive blood loss and difficult surgical dissection is anticipated. The use of balloon-tipped catheters preoperatively inserted into the iliac or uterine arteries was described earlier in management of placenta accrete syndromes (Management).

Pelvic Packing

For significant bleeding refractory to suture or topical hemostats, pelvic packing with gauze and termination of the operation may be considered. Rolls of gauze are packed to provide constant local pressure. This may serve as a temporizing step prior to interventional embolization. In other cases, packing alone may be left for 24 to 48 hours. If the patient is stable and bleeding appears to have stopped, packing is removed.

The *umbrella* or *parachute pack* uses a similar concept (Logothetopulos, 1926). Although seldom used today, it can be lifesaving if all other measures have failed, especially in low-resource areas (Dildy, 2006; Howard, 2002). The pack is constructed of a sturdy sterile plastic bag that is filled with gauze rolls that are unwound and

knotted together. Sufficient rolls are used to provide enough volume to fill the pelvis. The pack is introduced transabdominally with the stalk exiting the vagina. Mild traction is applied by tying the stalk to a 1-liter fluid bag, which is hung over the foot of the bed. The umbrella pack is removed vaginally after 24 hours.

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CHAPTER 42: Preterm Birth

It is generally admitted that there exists in the medulla a centre for uterine contractions, which can be stimulated by an excess of carbon dioxide in the blood, by anaemia and the presence of various toxic substances; and it seems highly probable that the frequency of premature labour in cases of renal insufficiency and eclampsia may be due to the action of metabolic poisons upon the centre.

—J. Whitridge Williams (1903)

INTRODUCTION

In this textbook's first edition, very little was mentioned regarding preterm birth. Indeed, preterm birth was not incorporated as a stand-alone topic until the 13th edition in 1966. And, this content totaled only three sentences that cited use of isoxsuprine as a tocolytic agent. In contrast, present-day research now produces more than 3000 articles published annually. Data derive from study of animal models, translational research, clinical trials, and genetic investigations. Despite efforts, elucidating the biology of human parturition and the subsequent efforts to prevent preterm birth remain elusive (Martin, 2017).

DEFINITION OF PRETERM BIRTH

Low birthweight defines neonates who are born too small. *Preterm* or *premature birth* describes neonates who are born too early. With respect to gestational age, a newborn may be preterm, term, or postterm. With respect to size, a newborn may be normally grown and *appropriate for gestational age*; undersized, thus, *small for gestational age*; or overgrown and consequently, *large for gestational age*. Small for gestational age categorizes newborns whose birthweight is <10th percentile for gestational age. Other frequently used terms have included *fetal-growth restriction* or *intrauterine growth restriction*. The term large for gestational age describes newborns whose birthweight is >90th percentile for gestational age. The term *appropriate for gestational age* designates newborns whose weight is between the 10th and 90th percentiles.

Thus, neonates born before term can be small or large for gestational age, but still preterm by definition. *Low birthweight* refers to neonates weighing 1500 to 2500 g; *very low birthweight* are those between 1000 and 1500 g; and *extremely low birthweight* refers to those between 500 and 1000 g.

Before the 15th edition of this textbook, a *preterm* or *premature newborn* was defined by a birthweight <2500 g. With that edition, preterm neonates were considered to be those delivered before 37 completed weeks, that is, $<36^{6/7}$ weeks (Pritchard, 1976). This definition, which has now been in use for more than 40 years, was first promulgated in 1976 by the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO). The definition derived from a statistical analysis of gestational age distribution at birth (Steer, 2005). Importantly, the denotation lacks a specific functional basis and should be clearly distinguished from the concept of *prematurity*. Prematurity represents incomplete development of various organ systems at birth. For example, the lungs are particularly affected, leading to the respiratory distress syndrome (RDS) (Chap. 34, Respiratory Distress Syndrome).

In 2013 in the United States, 23,446 infants died in their first year of life, and a third of infants died from preterm-related causes (Matthews, 2015). Gestational age at delivery and the risk of neonatal morbidity and mortality are inversely related (Frey, 2016). Namely, neonates born in the early-preterm period make up the smallest proportion of births, but these infants experience disproportionately higher rates of prematurity-related complications (Table 42-1).

TABLE 42-1

Infant Mortality Rates in the United States in 2013

	Live Births No. (%)	Infant Deaths (per 1000 births)
Total infants	3,932,181 (100)	23,446 (6)
Gestational age:		
<34 weeks	133,503 (3)	13,284 (100)
34–36 weeks	313,858 (8)	2268 (7)
<37 weeks	447,361 (11)	15,552 (35)
37–38 weeks	974,162 (25)	2933 (3)
39–41 weeks	2,291,468 (58)	4218 (2)
≥42 weeks	215,510 (5)	515 (2)

Data from Matthews, 2015.

Beginning in 2005, in recognition that neonates born between $34^{0/7}$ weeks and $36^{6/7}$ weeks experience morbidities and mortality characteristic of premature newborns, preterm births were subdivided. Those before $33^{6/7}$ weeks are labeled *early preterm,* and those occurring between 34 and 36 completed weeks are *late preterm*. Indeed, compared with births at $39^{0/7}$ weeks through $40^{6/7}$ weeks, these late-preterm infants experience morbidities that are also associated with prematurity (Spong, 2013). Recently, this concept has expanded to births $37^{0/7}$ weeks through $38^{6/7}$ weeks, which are now defined as *early term,* and those $39^{0/7}$ weeks through $40^{6/7}$ weeks, which are defined as *term*.

This revised terminology has led some to redefine a short gestation as those $<39^{0/7}$ weeks. By doing so, more than a third of live births in the United States in 2015 would be defined as having a shortened period of gestation (Martin, 2017). One implication is that only 65 percent of births in the United States occurred during the optimal 39 to 41 weeks' gestation. This emphasizes the realization that fetal maturation in humans is a continuum that is completed later in human pregnancy than previously appreciated. As a result, adverse neonatal sequelae from neonatal immaturity with elective delivery before 39 completed weeks are appreciable (Reddy, 2009; Tita, 2009).

This knowledge resulted in the development and application of the "39-week rule" to deter nonmedically indicated deliveries before 39 weeks (Spong, 2011). An unintended consequence of this health-care strategy has been a rise in stillbirth rates in the United States. One concern is that the rule may be misapplied to gestations with true medical indications for early delivery (Hill, 2017; Nicholson, 2016). Spong (2016) has emphasized the need to perform necessary obstetrical interventions when indicated.

PRETERM BIRTH RATE TRENDS

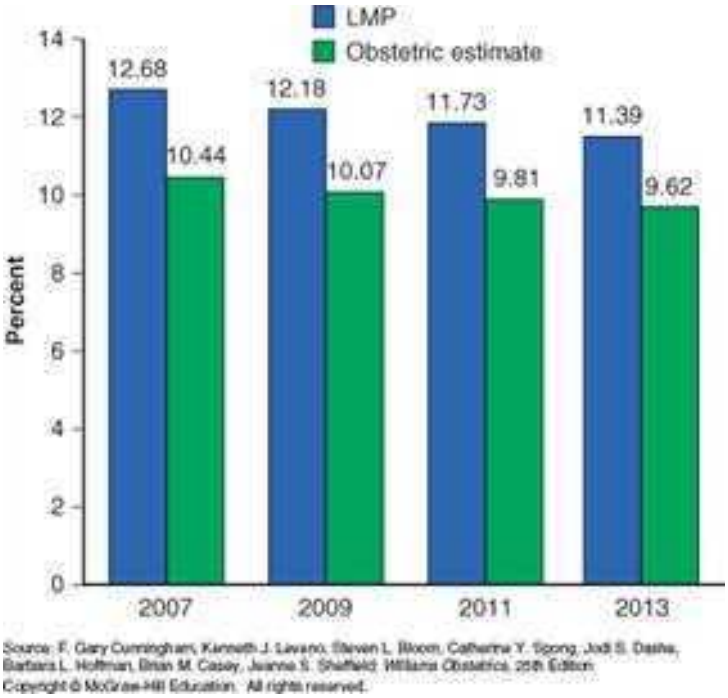
Methodology

In the United States, the preterm birth rate rose slightly from 9.57 percent in 2014 to 9.63 percent for 2015 (Martin, 2017). This marks the first rise in this percentage since 2007. Although concerning, some argue that the drop in preterm birth rates from 2007 to 2014 reflected systematic bias associated with changes in obstetrical dating (Frey, 2016).

Specifically, beginning with the 2014 data year, the National Vital Statistics Reports from the National Center for Health Statistics transitioned to a new standard for estimating newborn gestational age for birth certificate completion (Martin, 2015). The new measure—obstetrical estimate of gestational age at delivery—replaced calculations based on the date of the last normal menses (Chap. 44, Fetal Growth versus Birthweight). As shown in Figure 42-1, these measures differ and do not provide equivalent absolute numerical comparisons of preterm birth rates. For example, the 2015 obstetrical estimate-based preterm birth rate was 9.6 percent compared with the last menstrual period-based rate of 11.3 percent (Martin, 2017). *Thus, current national data are now not directly comparable to previously reported rates of preterm birth due to differing gestational age calculation methodologies.* The national data are now reported starting with year 2007, which coincides with the year that this information became available.

FIGURE 42-1

Percentage of preterm births in the United States according to method of assessment of gestational age. LMP = date of last normal menses. (Adapted with permission from Martin JA, Osterman MJ, Kirmeyer SE, et al: Measuring gestational age in vital statistics data: transitioning to the obstetric estimate. Natl Vital Stat Rep. 2015 Jun 1;64(5):1–20.)



Trend Factors

Ferré and colleagues (2016) using National Vital Statistics System data showed that the overall reduction of preterm birth before 2014 was in part due to the changes in maternal age distribution. Specifically, teen birth rates declined. This translated into a drop in preterm birth rates over the same epoch and could explain the lower infant mortality rates (Callaghan, 2017).

One disturbing aspect of preterm birth rate trends in the United States is persistent racial and ethnic disparities. Rates of preterm birth among black women are markedly elevated above those for white and Hispanic women in every year recorded (Martin, 2017). Moreover, rates of births before 32 completed weeks in black women are higher than those in white and Hispanic women combined. Some investigators attribute this disparity to socioeconomic circumstances (Collins, 2007; Leveno, 2009).

Internationally, the rates of preterm birth in the United States are also higher compared with those in other industrialized countries (Ananth, 2009; Delnord, 2017; Martin, 2017).

PRETERM NEWBORN MORBIDITY

Newborns born before 37 weeks suffer various morbidities, largely due to organ system immaturity (Table 42-2). That said, remarkable strides have been made in neonatal survival for those born preterm. This is especially true for neonates born after 28 weeks. In a study of more than 18,000 newborns weighing between 400 and 1500 g or aged between 22 and 32 weeks' gestation, survival rates were analyzed as a function of both birthweight *and* gestational age (Fanaroff, 2007). After achieving a birthweight of ≥1000 g or a gestational age of 28 weeks for females, or 30 weeks for males, survival rates reach 95 percent.

TABLE 42-2

Major Short- and Long-Term Problems in Very-Low-Birthweight Infants

Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure	Failure to thrive, short-bowel syndrome, cholestasis
Immunological	Hospital-acquired infection, immune deficiency, perinatal infection	Respiratory syncytial virus infection, bronchiolitis
Central nervous system	Intraventricular hemorrhage, periventricular leukomalacia, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss
Ophthalmological	Retinopathy of prematurity	Blindness, retinal detachment, myopia, strabismus
Cardiovascular	Hypotension, patent ductus arteriosus, pulmonary hypertension	Pulmonary hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid-base disturbances	Hypertension in adulthood
Hematological	Iatrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrinological	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

Data from Eichenwald, 2008.

Threshold of Viability

Births once considered to be “abortuses” because the fetus weighed <500 g are now classified as live births. In the United States in 2014, 5863 live births <500 g were recorded (Martin, 2017). For those newborns delivered before 33 weeks’ gestation, perinatal and neonatal care has advanced tremendously. As a result, the *threshold of viability,* which is the lower limit of fetal maturation compatible with extrauterine survival, has been reassessed. Currently, the threshold of viability lies between 20 and 26 weeks’ gestation.

Neonates born in this *periviable period* have been described as fragile and vulnerable because of their immature organ systems. Many of these are described in Chapter 34 (Retinopathy of Prematurity) and include brain injury from hypoxic-ischemic injury and sepsis. In this setting, hypoxia and sepsis start a cascade of events that lead to brain hemorrhage, to white-matter injury that causes periventricular leukomalacia, and to poor subsequent brain growth eventuating in neurodevelopmental impairment. Associated morbidities include intellectual disability, cerebral palsy, blindness, seizures, and spastic quadriparesis that can result in the need for a lifetime of medical care (Annas, 2004). Because active brain development normally occurs throughout the second and third trimesters, those born <25 weeks are believed to be especially vulnerable to brain injury.

To clarify obstetrical care of these fetuses, the Society for Maternal-Fetal Medicine, the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists convened a joint workshop in 2013 (Raju, 2014). The executive summary statement from this meeting served as the underpinnings for an Obstetric Care Consensus document from the American College of Obstetricians and Gynecologists (2017e).

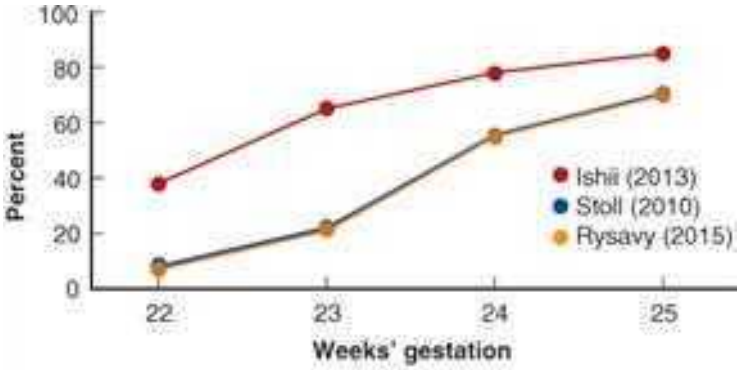
Periviable Neonatal Survival

The Obstetric Care Consensus summary provides a review of outcomes for those born in the periviable period. Delivery before 23 weeks typically results in death, and survival rates approximate only 5 percent (Fig. 42-2). Among those that live, morbidity is nearly universal. Notably, the authors highlight the wide variation in practices regarding active resuscitation and suggest that these variations may explain the differing perinatal outcomes

among different institutions. An important caveat, however, is ascertainment bias. For example, the mean survival rate is 45 percent if the denominator is all live births compared with 72 percent if the denominator is only newborns admitted to neonatal intensive care (Guillen, 2011). Another source of bias is use of multicenter datasets with considerable differences in obstetrical and early neonatal interventions, particularly at 22 and 23 weeks' gestation (Stoll, 2010).

FIGURE 42-2

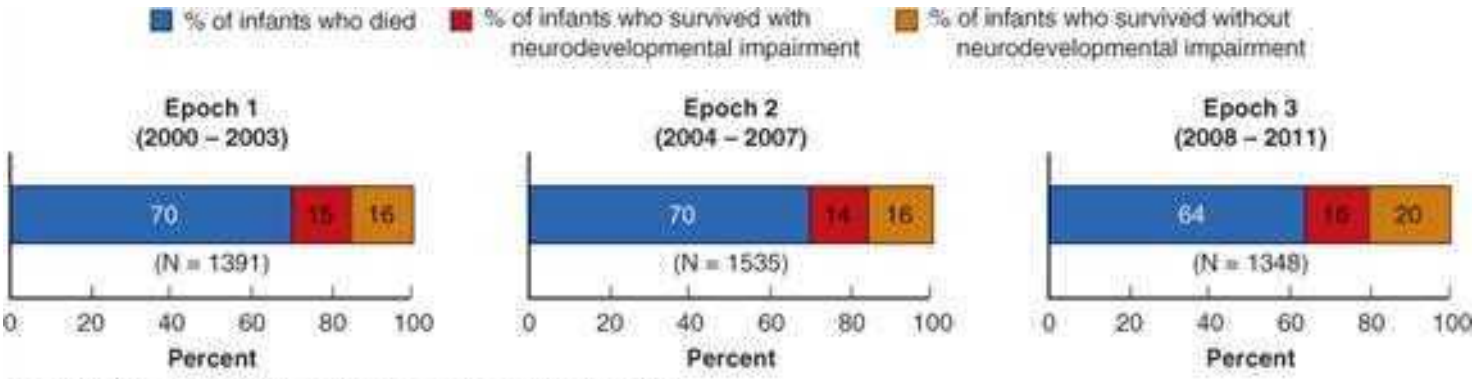
Neonatal survival rates according to condition at birth and gestational age. Ishii (2013) data curve reflects liveborn survival rates; Stoll (2010) curve reflects liveborn survival rates; Rysavy (2015) curve reflects overall survival rates.



To evaluate contemporaneous outcomes of neonates born at 22 to 24 weeks, the NICHD Neonatal Research Network reported both survival and neurodevelopmental outcomes assessed across consecutive birth-year epochs of 2000 to 2003, 2004 to 2007, and 2008 to 2011 in infants aged 18 to 22 months (Younge, 2017). The percentage of infants who survived rose significantly from 30 percent in 2000 to 2003 to 36 percent in 2008 to 2011. The percentage of infants who survived without neurodevelopmental impairment also significantly grew from 16 percent to 20 percent during the same time period (Fig. 42-3). Although rates of survival without neurodevelopmental impairment increased over time among infants born at 23 and 24 weeks, only 1 percent of infants born at 22 weeks survived without neurodevelopmental impairment (Younge, 2017).

FIGURE 42-3

Mortality and neurodevelopmental outcomes at 18 to 22 months of corrected age by birth epoch in neonates born at 22 to 24 weeks. (Data from Younge N, Goldstein RF, Bann CM, et al: Survival and neurodevelopmental outcomes among periviable infants, N Engl J Med. 2017 Feb 16;376(7):617–628.)



Somewhat similar results were published from Sweden (Serenius, 2013). This report details a national population-based prospective study of all neonates born before 27 weeks. Shown in Table 42-3 are the survival and disability rates for 707 Swedish infants born alive from 22 to 26 weeks' gestation between 2004 and 2007 in Sweden. Compared with rates in the United States, rates of survival without neurodevelopmental impairment were higher in the Swedish cohort for infants born at 24 weeks during 2004 to 2007.

TABLE 42-3

Outcomes at 2½ Years Corrected Age by Gestational Age at Birth in Sweden, 2004–2007

	Gestational Age (wk)					
Outcome	**22**	**23**	**24**	**25**	**26**	**Total**
Liveborn infants (no.)	51	101	144	205	206	707
Survived to 1 year (%)	10	53	67	82	85	70
Percent disabled[a]						
No disability	0	30	34	44	49	42
Mild	40	19	33	29	34	31
Moderate	20	30	21	17	10	16
Severe	40	21	13	10	7	11

[a]Percentage with disability at 2½ years corrected age. The overall rate of disabilities includes performance on the Bayley III assessments, mental development delay, cerebral palsy, and visual and hearing disabilities.

Data from Serenius F, Källén K, Blennow M, et al: Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden, JAMA 2013 May 1;309(17):1810–1820.

Clinical Management

The Obstetric Care Consensus document also addresses management options based on the clinical characteristics of a given pregnancy. Nonmodifiable factors are fetal gender, weight, and plurality. Potentially modifiable antepartum and intrapartum factors include the location of delivery, intent to intervene by cesarean delivery or labor induction, and administration of antenatal corticosteroids and magnesium sulfate. Postnatal management addresses the initiation or withdrawal of intensive care after birth. Areas of general guidance were then reviewed for each week of gestation (Table 42-4).

TABLE 42-4

General Guidelines for Obstetrical Interventions for Threatened and Imminent Periviable Delivery

	<22 Weeks	22 Weeks	23 Weeks	24 Weeks+
Neonatal assessment for resuscitation	Not recommended	Consider	Consider	Recommended
Corticosteroid therapy	Not recommended	Not recommended	Consider	Recommended
Magnesium sulfate neuroprotection	Not recommended	Not recommended	Consider	Recommended
Tocolysis	Not recommended	Not recommended	Consider	Recommended
Antimicrobial therapy for PPROM	Consider	Consider	Consider	Recommended
Continuous EFM	Not recommended	Not recommended	Consider	Recommended
GBS prophylaxis	Not recommended	Not recommended	Consider	Recommended
Cesarean delivery for fetal indication	Not recommended	Not recommended	Consider	Recommended
Aggressive resuscitation	Comfort care only	Not recommended unless considered potentially viable	Consider	Recommended

EFM = electronic fetal monitoring; GBS = group B streptococcus; PPROM = preterm premature rupture of membranes.

Data from the American College of Obstetricians and Gynecologists, 2017e; Raju, 2014.

Mode of delivery represents another dilemma because cesarean delivery at the threshold of viability is controversial. For example, if the fetus-neonate is perceived to be too immature for aggressive support, then cesarean delivery for common indications such as breech presentation or nonreassuring fetal heart rate patterns might be preempted. Moreover, observational studies have failed to document a benefit of cesarean delivery for the sole indication of periviability (Alfirevic, 2013).

In a study of 2906 singletons between $24^{0/7}$ and $31^{6/7}$ weeks eligible for attempted vaginal birth, 84 percent of cephalic presenting fetuses were delivered vaginally (Reddy, 2012). Neonatal mortality rates did not differ compared with those associated with planned cesarean delivery. For *breech* presentations, however, relative risk for mortality was threefold higher with attempted vaginal delivery. In another study, Werner and colleagues (2013) analyzed 20,231 newborns delivered at 24 to 34 weeks. Cesarean delivery did not protect against poor outcomes such as neonatal death, intraventricular hemorrhage, seizures, respiratory distress, and subdural hemorrhage. From these findings, the Obstetric Care Consensus proposes that cesarean delivery be *considered* for fetal indications at $23^{0/7}$ to $24^{6/7}$ weeks. However, before 22 weeks, this route is reserved only for maternal indications.

It is difficult to summarize the current practices of obstetrical care in the management of the periviable pregnancy given its rapid evolution. For example, since January 2016, the American College of Obstetricians and Gynecologists has penned three iterations of its Practice Bulletin "Management of Preterm Labor," and three versions of the "Obstetric Care Consensus" document have been published since November 2015. In this uncertain environment, individualized, patient-centered care with a multidisciplinary team remain as bedrock for the clinician.

While we do not have the answers, we describe our strategies from Parkland Hospital as one approach to management. Our policies were developed in conjunction with the Division of Neonatal Medicine. Importantly, the decision not to perform cesarean delivery does not necessarily imply that care for the fetus is discounted. Neonatologists are consulted before delivery, and a trilateral discussion of survival and morbidity rates ensues with the woman and her family. A neonatologist attends each delivery and determines subsequent management.

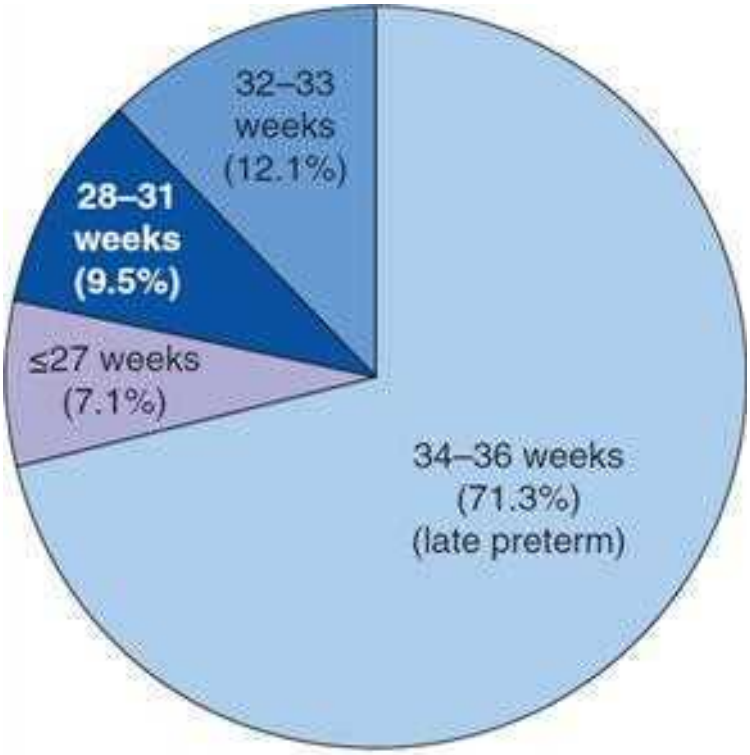
In our institution, traditional fetal indications for cesarean delivery are practiced in women at $25^{0/7}$ weeks or beyond. Cesarean delivery is not offered for fetal indications before $24^{0/7}$ weeks. At $24^{0/7}$ weeks, cesarean delivery is not offered unless fetal weight is estimated at 750 g or greater. Aggressive obstetrical management is practiced in cases of growth restriction, wherein gestational age is used to guide management rather than fetal size.

Late-Preterm Birth

Neonates born between 34 and 36 weeks account for more than 70 percent of all preterm births (Fig. 42-4). This group has been the fastest rising proportion of singleton preterm births in the United States (Raju, 2006). Nationally, the late-preterm birth rate rose from 6.82 percent to 6.87 percent from 2014 to 2015 (Martin, 2017).

FIGURE 42-4

Distribution of preterm births by gestational age in the United States in 2015. (Data from Martin JA, Hamilton BE, Osterman MJ: Births: final data for 2015. Natl Vital Stat Rep 66(1):1, 2017.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield, Williams Obstetrics, 25th Edition

To estimate the risks associated with late-preterm births, investigators analyzed neonatal mortality and morbidity rates at 34, 35, and 36 weeks compared with those of births at term between 1988 and 2005 at Parkland Hospital (McIntire, 2008). Approximately 3 percent of all births during the study period were between 24 and 32 weeks, and 9 percent were during the late-preterm weeks. Thus, and similar to the national rates, late-preterm births accounted for three fourths of all preterm births. Approximately 80 percent of these resulted from idiopathic spontaneous preterm labor or prematurely ruptured membranes (Fig. 42-5). Other obstetrical complications were implicated in the remaining 20 percent of cases. Rates of morbidity and mortality were greater in these late-preterm newborns compared with rates in term ones (Table 42-5 and Fig. 42-6). Similarly, Tomashek (2017) also reported higher neonatal mortality rates for late-preterm newborns. Rates of adverse neurodevelopment outcomes are also increased in these late-preterm infants (Petrini, 2009).

TABLE 42-5

Neonatal Morbidity Rates at Parkland Hospital in Live Births Delivered Late Preterm Compared with 39 Weeks

	Preterm Births			Term Births
Morbidity[a]	**34 Weeks n = 3498**	**35 Weeks n = 6571**	**36 Weeks n = 11,702**	**39 Weeks n = 84,747**
Respiratory distress				
Ventilator	116 (3.3)[b]	109 (1.7)[b]	89 (0.8)[b]	275 (0.3)
Transient tachypnea	85 (2.4)[b]	103 (1.6)[b]	130 (1.1)[b]	34 (0.4)
Intraventricular hemorrhage				
Grades 1, 2	16 (0.5)[b]	13 (0.2)[b]	7 (0.06)[c]	13 (0.01)
Grades 3, 4	0	1 (0.02)	1 (0.01)	3 (0.004)
Sepsis				
Evaluation	1073 (31)[b]	1443 (22)[b]	1792 (15)[b]	10,588 (12)
Culture proven	18 (0.5)[b]	23 (0.4)[b]	26 (0.2)[c]	97 (0.1)
Phototherapy	13 (6.1)[b]	227 (3.5)[b]	36 (2.0)[b]	857 (1)
Necrotizing enterocolitis	3 (0.09)[b]	1 (0.02)[c]	1 (0.001)	1 (0.001)
Apgar ≤3 at 5 min	5 (0.1)	12 (0.2)[b]	10 (0.9)	54 (0.06)
Intubation in delivery room	49 (1.4)[b]	55 (0.8)[c]	36 (0.6)	477 (0.6)
One or more of the above	1175 (34)[b]	1565 (24)[b]	1993 (17)[b]	11,513 (14)

[a]Data presented as n (%).

[b]$p < .001$ compared with 39 weeks referent.

[c]$p < .05$ compared with 39 weeks referent.

Reproduced with permission from McIntire DD, Leveno KJ: Neonatal mortality and morbidity rates in later preterm births compared with births at term, Obstet Gynecol. 2008 Jan;111(1):35–41.

FIGURE 42-5

Obstetrical complications associated with 21,771 late-preterm births at Parkland Hospital. (Data from McIntire DD, Leveno KJ: Neonatal mortality and morbidity rates in later preterm births compared with births at term, Obstet Gynecol. 2008 Jan;111(1):35–41.)

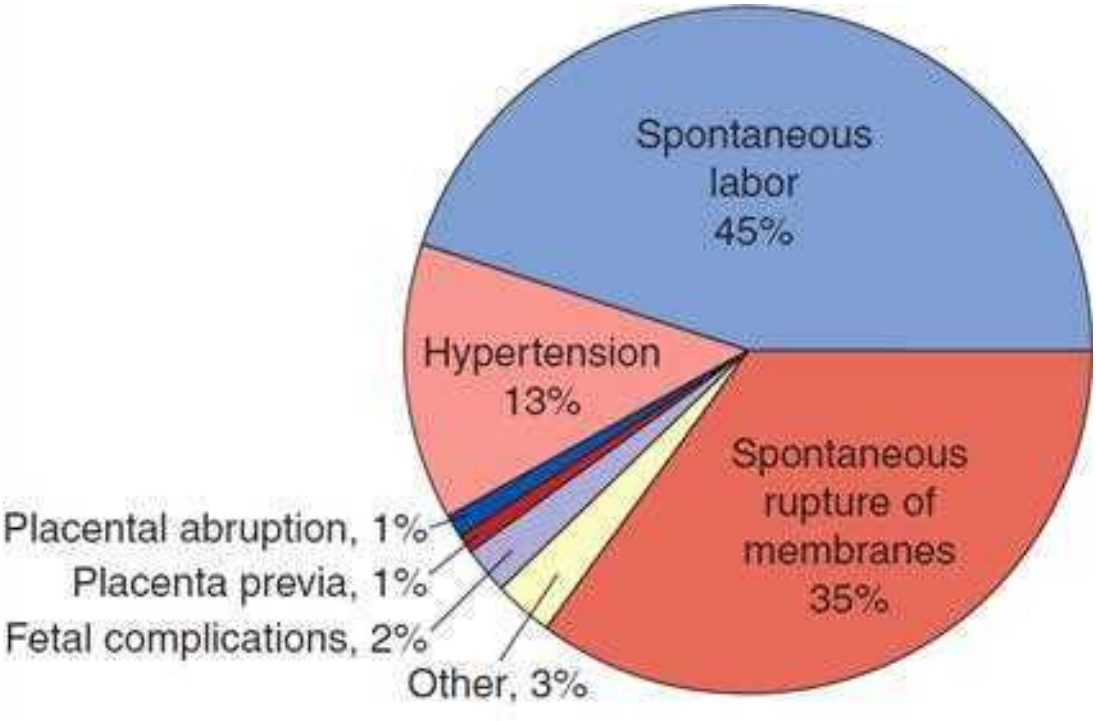
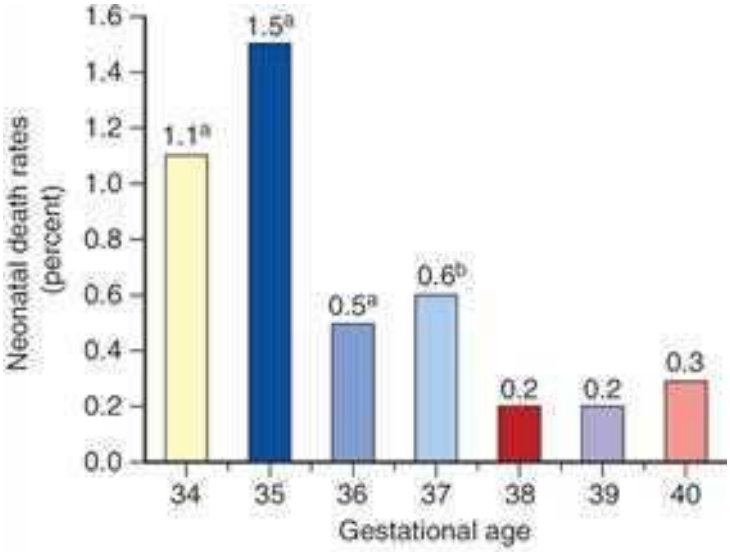


FIGURE 42-6

Neonatal death rates at Parkland Hospital from 34 to 40 weeks' gestation in singleton infants without malformations. [a] p <0.001 compared with 39 weeks as the referent. [b] p = 0.02 compared with 39 weeks as the referent. (Reproduced with permission from McIntire DD, Leveno KJ: Neonatal mortality and morbidity rates in later preterm births compared with births at term, Obstet Gynecol. 2008 Jan;111(1):35–41.)



Taken together, these findings suggest that a health-care focus on prematurity should include these late-preterm births. Moreover, approximately 80 percent of affected women begin labor spontaneously—similar to births before 34 weeks—and attempts to interrupt preterm labor have been insufficient (Institute of Medicine, 2007). Because of this, a national strategy aimed at prevention of late-preterm births is unlikely to provide discernible benefit without new developments in the prevention and management of preterm labor. In the meantime, the American College of Obstetricians and Gynecologists (2017c) emphasizes that *intentional* late-preterm delivery should occur only if an accepted maternal or fetal indication for delivery exists.

CAUSES OF PRETERM BIRTH

Four direct causes for preterm births in the United States include: (1) spontaneous unexplained preterm labor with intact membranes, (2) idiopathic preterm premature rupture of membranes (PPROM), (3) delivery for maternal or fetal indications, and (4) twins and higher-order multifetal births. Of

all preterm births, 30 to 35 percent are indicated, 40 to 45 percent are due to spontaneous preterm labor, and 30 to 35 percent follow preterm membrane rupture (Goldenberg, 2008). Indeed, much of the increase in the singleton preterm birth rate in the United States is explained by rising numbers of indicated preterm births (Ananth, 2005). Last, more than one of every two twins and more than nine of every ten triplets are born preterm or with low birthweight in the United States (Chap. 45, Unique Fetal Complications) (Martin, 2017).

Reasons for preterm birth have multiple, often interacting, antecedents and contributing factors (Esplin, 2016). This is particularly true for PPROM and spontaneous preterm labor.

Analogous to other complex disease processes, multiple coexistent genetic alterations and environmental factors may lead to preterm birth (Esplin, 2005; Velez, 2008; Ward, 2008). For example, inherited mutations in genes regulating collagen assembly may predispose to cervical insufficiency or prematurely ruptured membranes (Anum, 2009; Wang, 2006; Warren, 2007). And, whole blood gene expression and proteonomic biomarkers are now being used to help identify predictors of preterm birth (Cantonwine, 2016; Heng, 2016).

Spontaneous Preterm Labor

For both clinical and research purposes, pregnancies with spontaneous preterm labor yet intact fetal membranes must be distinguished from those complicated by preterm prematurely ruptured membranes. Even so, those with spontaneous preterm labor do not constitute a homogeneous group. Among the more common associated findings are multifetal pregnancy, intrauterine infection, bleeding, placental infarction, premature cervical dilation, cervical insufficiency, hydramnios, uterine fundal abnormalities, and fetal anomalies. Severe maternal illness from infections, autoimmune diseases, and gestational hypertension also raises preterm labor risks.

Despite their diversity, these processes culminate in a common end point—premature cervical dilation and effacement and premature activation of uterine contractions. Importantly, the actual process of preterm labor should be considered a final step stemming from progressive or acute changes that could be initiated days or even weeks before labor onset. Indeed, many forms of spontaneous preterm labor that result from premature initiation of phase 2 of parturition may be viewed in this light (Chap. 21, Phase 2: Preparation for Labor). Although the end result in preterm birth is the same as at term with cervical ripening and myometrial activation, recent studies in animal models support the idea that preterm birth is not always an acceleration of the normal process. Diverse pathways to instigate parturition exist and are dependent on the etiology of preterm birth. Four major causes include uterine distention, maternal–fetal stress, premature cervical changes, and infection.

Uterine Distention

Multifetal pregnancy and hydramnios are well-recognized risks for preterm birth. Early uterine distention likely acts to initiate expression of contraction-associated proteins (CAPs) in the myometrium. The CAP genes that are influenced by stretch include those coding for gap-junction proteins such as connexin 43, for oxytocin receptors, and for prostaglandin synthase (Korita, 2002; Lyall, 2002; Sooranna, 2004). More recent reports suggest that levels of gastrin-releasing peptides (GRPs) are increased with stretch to promote myometrial contractility. GRP antagonists can inhibit uterine contractility (Tattershell, 2012). Also, a stretch-induced potassium channel—TREK-1—is upregulated during gestation and downregulated in labor. This suggests a potential role in uterine relaxation during pregnancy (Buxton, 2010).

Excessive uterine stretch also leads to early activation of the placental–fetal endocrine cascade shown in Figure 21-10. The resultant early rise in maternal corticotropin-releasing hormone and estrogen levels can further enhance the expression of myometrial CAP genes (Warren, 1990; Wolfe, 1988). Finally, the influence of uterine stretch should be considered with regard to the cervix. Prematurely increased stretch and endocrine activity may initiate events that shift the timing of uterine activation, including premature cervical ripening.

Maternal–Fetal Stress

Stress is defined as a condition or adverse circumstance that disturbs the normal physiological or psychological functioning of an individual. Examples of stressors are nutrient restriction, obesity, infection, and diabetes. Psychological duress can include racial discrimination, childhood stress, depression, or posttraumatic stress syndrome (Gillespie, 2017; Goldstein, 2017; Shaw, 2017). A quantitative measure of “stress” is difficult. Yet, considerable evidence shows a correlation between some degree of maternal stress and adverse birth outcomes that include stillbirth, preterm birth, and abnormal fetal development (Hobel, 2003; Ruiz, 2003). Factors that activate this cascade likely are broad and influence the stress response.

One potential mechanism for stress-induced preterm birth is premature activation of the placental–adrenal endocrine axis. One trigger may be elevations in cortisol from maternal psychological stress (Lockwood, 1999; Petraglia, 2010; Wadhwa, 2001). Activation of this axis yields rising maternal serum levels of placental-derived corticotropin-releasing hormone (CRH). This raises adult and fetal adrenal steroid hormone production and promotes early loss of uterine quiescence (Fig. 21-10).

If preterm delivery is associated with early activation of the fetal adrenal–placental endocrine axis, maternal estrogen levels would likely be prematurely elevated. Indeed, an early rise in serum estriol concentrations is noted in women with subsequent preterm labor (Heine, 2000; McGregor, 1995). Physiologically, this premature rise in estrogen levels may alter myometrial quiescence and accelerate cervical ripening.

Another mechanism by which stress may translate to preterm birth is premature cellular senescence. As part of normal physiology, aging of fetal and decidual cells precipitates the release of uterotonic signals for uterine activation at term (Menon, 2014a). Animal studies supported by correlative studies in women demonstrate that accelerated senescence of the decidua results in preterm birth (Cha, 2013; Hirota, 2010). In addition, premature cellular senescence may contribute to PPROM (Menon, 2016).

Cervical Dysfunction

In most cases, premature cervical remodeling precedes premature labor onset. In some instances, cervical dysfunction of either the epithelia or stromal extracellular matrix is the underlying cause. For example, an intact cervical epithelial barrier is critical to prevent ascending infection. Disruption of this barrier, such as that in mice lacking the glycosaminoglycan hyaluronan, predisposes mice to ascending infection and preterm birth (Akgul, 2014). Interestingly, the enhanced risk of preterm birth from group B streptococcal colonization may be in part due to the bacteria's ability to secrete hyaluronidase. This enzyme degrades hyaluronic acid in the cervicovaginal epithelia to aid bacterial ascension (Vornhagen, 2017).

Second, the mechanical competence of the cervix can be reduced. For example, genetic mutations in components of collagen and elastic fibers or proteins required for their assembly are risk factors for cervical insufficiency, PPROM, and preterm birth (Anum, 2009; Nallasamy, 2017; Pyeritz, 2000).

Infection

A patent female reproductive tract, although essential for conception and delivery, is theoretically problematic during phase 1 of parturition. Bacteria can gain access to intrauterine tissues through: (1) transplacental transfer of maternal systemic infection, (2) retrograde flow of infection into the peritoneal cavity via the fallopian tubes, or (3) ascending infection with bacteria from the vagina and cervix. Because the lower pole of the fetal membrane–decidual junction is contiguous with the cervical canal orifice, this anatomical arrangement provides a passageway for microorganisms. Ascending infection is considered to be the most common entry route. Ascending microorganisms colonize the cervix, decidua, and possibly the membranes, where they then may enter the amnionic sac.

Intraamnionic infection as a primary cause of preterm labor in pregnancies with intact membranes accounts for 25 to 40 percent of preterm births (Goncalves, 2002; Iams, 1987). In some instances, histological evidence of inflammation is found in the fetal membranes, decidua, or umbilical cord. Other cases are deemed "subclinical." Current data suggest that microbial invasion of the reproductive tract is sufficient to induce infection-mediated preterm birth. Affected women are more likely to develop clinical chorioamnionitis and PPROM compared with women with sterile cultures. Moreover, their neonates are also more likely to have perinatal complications that include RDS, intraventricular hemorrhage, and necrotizing enterocolitis (Hitti, 2001). Although the clinical course is more severe when intraamnionic infection is obvious, inflammation in the absence of detectable intraamnionic microorganisms—termed *sterile intraamnionic inflammation*—is also a risk factor for an inflammatory response, described in the next section (Lee, 2007, 2008; Romero, 2014). In sum, the earlier the onset of preterm labor, the greater the likelihood of underlying infection (Goldenberg, 2000; Goncalves, 2002; Watts, 1992).

The incidence of culture-positive amnionic fluid collected by amniocentesis during spontaneous term labor is similar to that with preterm labor (Gomez, 1994; Romero, 1993). It has been suggested that at term, amnionic fluid is infiltrated by bacteria as a consequence of labor, whereas in preterm pregnancies, bacteria represent an inciting cause of labor. Thus, fetal infection, as defined by bacteria detected within the amnionic fluid, has both differing etiologies and consequences.

Despite these observations, considerable data associate chorioamnionitis with preterm labor (Goldenberg, 2002; Üstün, 2001). With chorioamnionitis, microbes may invade maternal tissue only and not amnionic fluid. Despite this, endotoxins can stimulate amnionic cells to secrete cytokines that enter amnionic fluid. This scenario may serve to explain the apparently contradictory observations concerning an association between amnionic fluid cytokines and preterm labor in cases in which microbes are not detected in the amnionic fluid.

Inflammatory Responses

Inflammatory responses drive the pathogenesis of infection-induced preterm labor. Lipopolysaccharide (LPS) or other toxins elaborated by bacteria are recognized by pattern-recognition receptors such as *toll-like receptors* (Janssens, 2003). These receptors are present on mononuclear phagocytes, decidual cells, cervical epithelia, and trophoblasts (Chuang, 2000; Gonzalez, 2007; Holmlund, 2002). Loss of specific toll-like receptors results in delayed parturition in mouse models (Montalbano, 2013). Instead, activation of toll-like receptors induces a signaling cascade that activates production of chemokines such as interleukin 8 (IL-8) and cytokines such as IL-1β. Activation also recruits immune cells into the reproductive tract. Cytokines are produced by immune cells and by cells within the cervix, decidua, membranes, or fetus itself.

LPS-induced production of IL-1β in turn promotes a series of responses that include: (1) increased synthesis of others, that is, IL-6, IL-8, and tumor-necrosis factor alpha (TNF-α); (2) proliferation, activation, and migration of leukocytes; (3) modifications in extracellular matrix proteins; and (4) mitogenic and cytotoxic effects such as fever and acute-phase response (El-Bastawissi, 2000). Also, in many tissues, including myometrium, decidua, and amnion, IL-1β promotes prostaglandin formation that induces cervical ripening and loss of myometrial quiescence (Casey, 1990; Challis, 2002; Keelan, 2003). The importance of prostaglandins to infection-mediated preterm birth is supported by the observation that prostaglandin inhibitors can reduce the rate of LPS-induced preterm birth in both the mouse and nonhuman primate (Gravett, 2007; Timmons, 2014). Inhibition of

cyclooxygenase-2 prevents inflammation-mediated preterm labor in the mouse. And, immunomodulators plus antibiotics delay preterm delivery after experimental intraamnionic infection in a nonhuman primate model.

Proteases such as matrix metalloproteinases (MMPs) are also induced by IL-1β and function to break down extracellular matrix components such as collagen or elastic fibers. This disrupts the structural integrity of fetal membranes and the cervix. Current evidence from animal and human studies suggests that many aspects of infection-mediated preterm birth differ from pathways that regulate term parturition (Hamilton, 2012; Holt, 2011; Shynlova, 2013a,b; Timmons, 2014).

Origin of Cytokines

Uterine cytokines are likely important for preterm labor. For example, it appears that cytokines produced in maternal decidua and myometrium will have effects on that side, whereas cytokines produced in the membranes or in cells within the amnionic fluid will not be transferred to maternal tissues. The transfer of cytokines such as IL-1β from decidua across the membranes into amnionic fluid, however, appears to be severely limited. Additionally, the human myometrium expresses chemokine receptors that decline during labor (Hua, 2013).

The requirement of leukocytes for initiation of term labor in women remains inconclusive. In general, resident and invading leukocytes produce the bulk of cytokines in cases of inflammation resulting from infection. Indeed, with infection, leukocytes—mainly neutrophils, macrophages, and T lymphocytes—infiltrate the cervix, lower uterine segment, fundus, and membranes at the time of labor. Invading leukocytes and certain parenchymal cells produce cytokines and appear to be the primary source of myometrial cytokines (Young, 2002). By contrast, in the decidua, both stromal cells and leukocytes likely contribute. In the cervix, glandular and surface epithelial cells appear to produce cytokines.

The presence of cytokines in amnionic fluid and their association with preterm labor is well documented. But, their exact cellular origin—with or without recoverable microorganisms—is not well defined. Amnionic fluid cytokines are most likely secreted by mononuclear phagocytes or neutrophils activated and recruited into the amnionic fluid. Thus, the amount of amnionic fluid IL-1β would be determined by the number of leukocytes recruited, their activational status, or the effect of amnionic fluid constituents on their IL-1β secretion rate.

Vaginal Microbiota

Factors that predispose to ascending infection and then preterm birth are a key focus of ongoing basic research. Mucosal immunity and barrier function of the cervicovaginal epithelia, the microbiota composition in the vaginal tract, and their interplay are a major topic (Smith, 2017). From animal studies, mucosal immunity of the lower reproductive tract can be disrupted by viral infection with a subsequent enhanced susceptibility to ascending bacterial infection (Racicot, 2013, 2017). Along with the ability of the cervicovaginal epithelia to respond to environmental insults, the composition of the microbe ecosystem in the vaginal tract may also determine susceptibility to ascending infection.

New technologies based on genomic analysis have shown that the nonpregnant vaginal tract hosts a complex microbial community (Gajer, 2012; White, 2011). Also described in Chapter 65 (Vaginitis), these community state types can differ widely among women who are all healthy. And, the vaginal microbiome changes during normal pregnancy (Aagaard, 2012; Stout, 2017). Namely, the diversity and richness of microbe populations are reduced during pregnancy and become more stable. Compared with nonpregnant controls, *Lactobacillus* species show an enhanced dominance. Some but not all studies report an increased population of certain microbes—for example, *Gardnerella vaginalis* and *Ureaplasma urealyticum*—in women with preterm birth (Donders, 2009; Nelson, 2014). However, differences in populations of pregnant women studied, in definitions of preterm birth, and in data analysis may complicate interpretation of these data.

Some specific microorganisms are detected more frequently than others in amnionic fluid of women with preterm labor (Gerber, 2003; Hillier, 1988; Yoon, 1998). These include *G vaginalis, Fusobacterium* species*, Mycoplasma hominis*, and *U urealyticum.* Their identification was interpreted by some as presumptive evidence that specific microorganisms are more commonly involved as pathogens in the induction of preterm labor. Another interpretation, however, is that given direct access to the membranes after cervical dilation, selected microorganisms, such as fusobacteria, are more capable of burrowing through these exposed tissues and will do so. Fusobacteria are found in the vaginal fluid of only 9 percent of women but in 28 percent of positive amnionic fluid cultures from pregnancies with preterm labor and intact membranes (Chaim, 1992).

Preterm Premature Rupture of Membranes

This term defines spontaneous rupture of the fetal membranes before 37 completed weeks and before labor onset (American College of Obstetricians and Gynecologists, 2016d). Such rupture likely has various causes, but intrauterine infection, oxidative stress-induced DNA damage, and premature cellular senescence are major predisposing events (Dutta, 2016; Gomez, 1997; Mercer, 2003). Associated risk factors include lower socioeconomic status, body mass index <19.8, nutritional deficiencies, and cigarette smoking. Women with PPROM carry an enhanced risk for recurrence during a subsequent pregnancy (Bloom, 2001). Despite these known risk factors, none is identified in most cases of preterm rupture.

Molecular Changes

Increased apoptosis or necroptosis of membrane cellular components and greater levels of specific proteases in membranes and amnionic fluid are related to PPROM. Most tensile strength of the membranes is provided by the amnionic extracellular matrix and interstitial amnionic collagens that

are produced in mesenchymal cells (Casey, 1996). Thus, collagen degradation has been a focus of research. The MMP family is involved with normal tissue remodeling and particularly with collagen degradation. Some members are found in higher concentrations in amnionic fluid from pregnancies with PPROM (Maymon, 2000; Park, 2003; Romero, 2002). MMP activity is in part regulated by tissue inhibitors of matrix metalloproteinases—TIMPs. Several of these inhibitors are found in lower concentrations in amnionic fluid from women with ruptured membranes. Elevated MMP levels found at a time when protease inhibitor expression declines further supports that their expression alters amnionic tensile strength.

Studies of amniochorion explants show greater MMP expression following treatment with certain cytokines (Fortunato, 1999a,b, 2002). With membrane rupture, thrombin activity rises, which activates MMPs and prostaglandin synthesis. Studies by Mogami (2013) provide a mechanism by which bacterial endotoxin or TNF-α elicits release of fetal fibronectin (fFN) by amnion epithelial cells. The fFN then binds toll-like receptor 4 in the amnion mesenchymal cells to activate signaling cascades. These result in augmented prostaglandin E (PGE_2) synthesis and elevated activity of MMPs.

Higher prostaglandin levels promote cervical ripening and uterine contractions. Greater MMP concentrations allow collagen breakdown in the fetal membranes resulting in premature rupture.

In pregnancies with PPROM, the amnion exhibits a higher degree of cell death and more apoptosis markers than that in term amnion (Arechavaleta-Velasco, 2002; Fortunato, 2003). In vitro studies indicate that apoptosis is likely regulated by bacterial endotoxin, IL-1β, and TNF-α. In addition, oxidative stress initiated by events other than infection can induce DNA damage, premature senescence, and subsequent inflammation and proteolysis that leads to PPROM (Menon, 2014a,b). Last, there are proteins involved in the synthesis of mature cross-linked collagen or matrix proteins that bind collagen and thereby promote tensile strength. These proteins are altered in membranes with premature rupture (Wang, 2006).

Infection

Several studies have investigated the incidence of infection-induced PPROM. Bacterial cultures of amnionic fluid support a role for infection in a significant proportion. One review of 18 studies and almost 1500 women with PPROM found that bacteria were isolated from amnionic fluid in a third of cases (Goncalves, 2002). Accordingly, some have given antimicrobial treatment to women in spontaneous preterm labor with intact membranes, however, results have been disappointing as discussed later in Antimicrobials (Kenyon, 2008b).

The inflammatory response that leads to membrane weakening and mediators of this process are currently areas of research. One goal is to identify early risk markers for PPROM.

Multifetal Pregnancy

Twins and higher-order multifetal births account for approximately 3 percent of neonates born in the United States (Martin, 2017). Preterm delivery continues to be the major cause of the excessive perinatal morbidity and mortality with multifetal pregnancies. The effects of uterine stretch discussed in Causes of Preterm Birth are obvious. Many of these interrelationships are discussed in Chapter 45 (Preterm Birth).

CONTRIBUTING FACTORS

Pregnancy Factors

Several genetic and environmental factors affect the frequency of preterm labor. Of these, threatened abortion in early pregnancy is associated with higher rates of later adverse outcomes. Weiss (2004) reported outcomes with vaginal bleeding at 6 to 13 weeks' gestation in nearly 14,000 women. Both light and heavy bleeding were associated with subsequent preterm labor, placental abruption, and pregnancy loss before 24 weeks.

Birth defects in the fetus may also predispose to preterm birth. In a secondary analysis of data from the First- and Second-Trimester Evaluation of Risk (FASTER) Trial, birth defects were associated with preterm birth and low birthweight neonates (Dolan, 2007).

Lifestyle Factors

Cigarette smoking, inadequate maternal weight gain, and illicit drug use affect the incidence and outcome of low-birthweight neonates (Chap. 44, Accelerated Lung Maturation). Extremes of maternal weight—both underweight and obese mothers—have an enhanced risk of preterm birth (Cnattingius, 2013; Girsen, 2016). Other maternal factors implicated include young or advanced maternal age, poverty, short stature, and vitamin C deficiency (Casanueva, 2005; Gielchinsky, 2002; Kramer, 1995; Leveno, 2009; Meis, 1995).

As discussed in Causes of Preterm Birth, psychological factors such as depression, anxiety, and chronic stress are associated with preterm birth (Hoffman, 2016; Venkatesh, 2016). In one review of more than 50 studies, Donovan and coworkers (2016) found a significant link between low birthweight and preterm birth in women injured by physical abuse (Chap. 47, Trauma).

Studies of work and physical activity related to preterm birth have yielded conflicting results (Goldenberg, 2008). Some evidence suggests that working long hours and hard physical labor are probably linked to a higher risk of preterm birth (Luke, 1995). However, aerobic exercise in normal-

weight women with uncomplicated singleton pregnancies appears to be safe and not associated with preterm birth (American College of Obstetricians and Gynecologists, 2017d; Di Mascio, 2016). One metaanalysis of physical activity found that leisure-time physical activity was associated with a reduced risk of preterm birth (Aune, 2017).

Genetic Factors

The recurrent, familial, and racial nature of preterm birth suggests that genetics may play a causal role. Accumulating literature on genetic variants buttresses this concept (Gibson, 2007; Hampton, 2006; Macones, 2004; Velez, 2009). Several such studies have also implicated immunoregulatory genes in potentiating chorioamnionitis in cases of preterm delivery due to infection (Varner, 2005).

Periodontal Disease

Gum inflammation is a chronic anaerobic inflammation that affects as many as 50 percent of pregnant women in the United States (Goepfert, 2004). Vergnes and Sixou (2007) performed a metaanalysis of 17 studies and concluded that periodontal disease was significantly associated with preterm birth. To better study this relationship, Michalowicz (2006) randomly assigned 813 pregnant women between 13 and 17 weeks' gestation who had periodontal disease to treatment during pregnancy or postpartum. Treatment during pregnancy improved periodontal disease and was safe. However, treatment failed to significantly alter preterm birth rates. This position was reaffirmed by a joint workshop of the European Federation of Periodontology and the American Academy of Periodontology (Sanz, 2013).

Interval between Pregnancies

The intervals between pregnancies are linked with adverse perinatal outcomes. In a metaanalysis, intervals <18 months and >59 months were associated with greater risks for both preterm birth and small-for-gestational age newborns (Conde-Agudelo, 2006). The causal effect of short interpregnancy intervals, however, has been questioned (Ball, 2014).

Prior Preterm Birth

The most important risk factor for preterm labor is a prior preterm delivery. Data from nearly 16,000 women delivered at Parkland Hospital are instructive. Namely, the recurrent preterm delivery risk for women with a preterm first delivery was threefold greater than that of women whose first neonate was born at term. More than a third of women whose first two newborns were preterm subsequently delivered a third preterm newborn. Most—70 percent—of the recurrent births in this study occurred within 2 weeks of the gestational age of the prior preterm delivery. The causes of prior preterm delivery also recurred. Although women with prior preterm births are clearly at risk for recurrence, they represented only 10 percent of the total preterm births in this study. Expressed another way, 90 percent of the preterm births at Parkland Hospital could not be predicted based on a history of preterm birth. Laughon and associates (2014) confirmed the importance of prior *spontaneous* preterm birth. Notably, these investigators also found that prior *indicated* preterm birth was strongly associated with subsequent spontaneous preterm birth. Variations in the definition of spontaneous and indicated used may explain this association.

Ultimately, risk of recurrent preterm birth is influenced by three factors: the frequency of prior preterm deliveries, severity as measured by gestational age, and the order in which the prior preterm delivery occurred (McManemy, 2007). That is, an individual woman's risk for recurrent preterm birth is influenced by her past number and sequence of preterm and term births. For example, a risk of recurrent preterm birth for a gravida 3 para 2 woman with a prior preterm birth followed by a term birth differs from a woman with a prior term birth followed by preterm birth. Thus, the influence of reproductive history has a profound prognostic significance for risk of recurrence. Moreover, this may also influence the supposed benefit attributed to various interventions described later.

Infection

Antibiotic Prophylaxis

As discussed in Cervical Dysfunction, a link between some cases of preterm birth and infection seems irrefutable (Goldenberg, 2008). In several studies, antimicrobial treatment has been given to prevent preterm labor thought to be due to microbial invasion. These strategies especially targeted *Mycoplasma* species. Morency and colleagues (2007) performed a metaanalysis of 61 articles and suggested that antimicrobials given in the second trimester may prevent subsequent preterm birth. Andrews and associates (2006) reported results of a randomized trial in which they gave a course of azithromycin plus metronidazole every 4 months to 241 nonpregnant women whose last pregnancy resulted in spontaneous delivery before 34 weeks. Approximately 80 percent of the women with subsequent pregnancies had received study drug within 6 months of their subsequent conception. Such interconceptional antimicrobial treatment did not reduce the rate of recurrent preterm birth. Using a subgroup analysis of these same women, Tita and coworkers (2007) concluded that such use of antimicrobials may be harmful. In another randomized study, 2661 women received placebo or metronidazole plus erythromycin between 20 and 24 weeks' gestation followed by ampicillin plus metronidazole during labor

(Goldenberg, 2006). This antimicrobial regimen did not reduce the rate of preterm birth or that of histological chorioamnionitis. At this time, antibiotic prophylaxis to prevent preterm birth is not recommended in women with preterm labor and intact membranes (Flenady, 2013).

Bacterial Vaginosis

In this condition, normal, hydrogen peroxide-producing, lactobacillus-predominant vaginal flora is replaced with anaerobes (Hillier, 1995; Nugent, 1991). Its diagnosis and management are discussed in Chapter 65 (Vaginitis). Using Gram staining, relative concentrations of the bacterial morphotypes characteristic of bacterial vaginosis are determined and graded by the *Nugent score* or assessed clinically with *Amsel criteria*.

Bacterial vaginosis has been associated with spontaneous abortion, preterm labor, PPROM, chorioamnionitis, and amnionic fluid infection (Hillier, 1995; Kurki, 1992; Leitich, 2003a,b). Environmental factors appear to be important in bacterial vaginosis development. Exposure to chronic stress, ethnic differences, and frequent or recent douching are associated with higher rates of the condition (Culhane, 2002; Ness, 2002). A gene-environment interaction has also been described (Macones, 2004). Women with bacterial vaginosis and a susceptible TNF-α genotype had a ninefold increased incidence of preterm birth.

From all of these studies, adverse vaginal flora seems associated with spontaneous preterm birth. Unfortunately, to date, screening and treatment have not prevented preterm birth. These are discussed further in Chapter 65 (Trichomoniasis). Indeed, microbial resistance or antimicrobial-induced change in the vaginal flora results from regimens intended to eliminate bacterial vaginosis (Beigi, 2004; Carey, 2005).

DIAGNOSIS

Symptoms

Early differentiation between true and false labor is difficult—especially before demonstrable cervical effacement and dilation. Uterine activity alone can be misleading because of *Braxton Hicks contractions*. These irregular, nonrhythmical contractions can cause considerable confusion in the diagnosis of true labor. Not infrequently, women who deliver before term have uterine activity that is attributed to Braxton Hicks contractions that prompt an incorrect diagnosis of false labor. Accordingly, the American College of Obstetricians and Gynecologists (2016b) defines preterm labor to be regular contractions before 37 weeks that are associated with cervical change.

In addition to contractions, pelvic pressure, menstrual-like cramps, watery vaginal discharge, and lower back pain have been empirically associated with impending preterm birth. Such complaints are thought by some to be common in normal pregnancy and are therefore often minimized by patients and obstetrical care providers.

The importance of these symptoms as a harbinger of labor has been emphasized by some but not all investigators (Iams, 1990; Kragt, 1990). Iams and coworkers (1994) found that the signs and symptoms signaling preterm labor, including uterine contractions, appeared only within 24 hours of preterm labor.

Chao (2011) prospectively studied 843 women with a singleton fetus who presented to Parkland Hospital with preterm labor symptoms between $24^{0/7}$ and $33^{6/7}$ weeks, intact membranes, and cervical dilation <2 cm. Those whose cervix remained <2 cm were sent home with a diagnosis of false preterm labor. When analyzed against the general obstetrical population, women sent home had a similar rate of birth before 34 weeks—2 versus 1 percent. However, these women did have significantly higher rates of birth between 34 and 36 weeks—5 percent compared with 2 percent. Women with cervical dilation of 1 cm at discharge were significantly more likely to deliver before 34 weeks compared with women without cervical dilation—5 percent versus 1 percent. Importantly, almost 90 percent of the 1-cm group delivered within 21 days of the initial presentation.

Cervical Change

Researchers have evaluated asymptomatic cervical changes that may predict preterm labor. Asymptomatic cervical dilation after midpregnancy is suspected to be a risk factor for preterm delivery, although some clinicians consider it to be a normal anatomical variant. Moreover, study results have suggested that parity alone is not sufficient to explain cervical dilation discovered early in the third trimester.

Cook (1996) longitudinally evaluated cervical status with transvaginal sonography between 18 and 30 weeks in nulliparas and multiparas who all subsequently gave birth at term. Cervical length and diameter were identical in both groups throughout these critical weeks. In a study from Parkland Hospital, routine digital cervical examinations were performed between 26 and 30 weeks in 185 asymptomatic women. Approximately 25 percent of women whose cervix was dilated 2 or 3 cm delivered before 34 weeks (Leveno, 1986a). Other investigators have verified cervical dilation as a predictor of increased preterm delivery risk (Copper, 1995).

Although women with dilation and effacement in the third trimester are at greater risk for preterm birth, detection does not necessarily improve pregnancy outcome. Buekens and associates (1994) randomly assigned 2719 women to undergo routine cervical examinations at each prenatal visit

and compared them with 2721 women in whom serial examinations were not performed. Knowledge of antenatal cervical dilation did not affect any pregnancy outcome related to preterm birth or the frequency of interventions for preterm labor. The investigators also reported that cervical examinations were not related to PPROM. Thus, it seems that prenatal cervical examinations in asymptomatic women are neither beneficial nor harmful.

Ambulatory Uterine Monitoring

An external tocodynamometer belted around the abdomen and connected to an electronic waist recorder allows a woman to ambulate while uterine activity is recorded. Results are transmitted via telephone daily. Women are educated concerning signs and symptoms of preterm labor, and clinicians are kept apprised of their progress. The 1985 approval of this monitor by the Food and Drug Administration (FDA) prompted its widespread clinical use. Subsequently, it was proven that the use of this expensive and time-consuming system does not reduce preterm birth rates (Collaborative Home Uterine Monitoring Study Group, 1995; Iams, 2002; Urquhart, 2017). Despite improvements in technology with the internet and cellular telephones, use of such monitoring is discouraged (American College of Obstetricians and Gynecologists, 2016c).

Fetal Fibronectin

This glycoprotein is produced in 20 different molecular forms by various cell types, including hepatocytes, fibroblasts, endothelial cells, and fetal amnion cells. Present in high concentrations in maternal blood and amnionic fluid, fFN is thought to function in intercellular adhesion during implantation and in maintenance of placental adherence to uterine decidua (Leeson, 1996). Detected in cervicovaginal secretions in women who have normal pregnancies with intact membranes at term, fFN appears to reflect stromal remodeling of the cervix before labor.

Lockwood (1991) reported that fFN detection in cervicovaginal secretions before membrane rupture was a possible marker for impending preterm labor. Qualitative and quantitative fFN levels are measured using enzyme-linked immunosorbent assays, and values exceeding 50 ng/mL are considered positive. Sample contamination by amnionic fluid and maternal blood should be avoided. Interventional studies based on the use of fFN screening in asymptomatic women have not demonstrated improved perinatal outcomes (Andrews, 2003; Esplin, 2017; Grobman, 2004). The American College of Obstetricians and Gynecologists (2016c) does not recommend screening with fFN tests. Its use in conjunction with cervical length measurement is discussed next.

Cervical Length Measurement

Progressively shorter cervical canals assessed sonographically are associated with increased rates of preterm birth (Iams, 1996). The technique to measure cervical length with sonography is described in Chapter 10 (Cervical Length Assessment). When performed by trained operators, cervical length analysis using transvaginal sonography is safe, highly reproducible, and more sensitive than transabdominal sonographic screening (American College of Obstetricians and Gynecologists, 2016c). The Society for Maternal-Fetal Medicine (2016b) has provided guidance for the performance of proper cervical length measurement. The Society recommends that sonographers and practitioners obtain specific training in the acquisition and interpretation of cervical length imaging through accreditation programs.

Transvaginal cervical sonography is not affected by maternal obesity, cervix position, or shadowing from the fetal presenting part. Because of the inability to easily distinguish the lower uterine segment from the cervix in early gestation, transvaginal cervical length assessment is typically performed after 16 weeks' gestation. Such interrogation is currently limited to singleton gestations and not recommended for multifetal gestations outside of research trials (American College of Obstetricians and Gynecologists, 2016c).

Indications for cervical length measurement are somewhat controversial. For those women with a history of prior spontaneous preterm birth, the Society for Maternal-Fetal Medicine (2016b) recommends transvaginal cervical length screening. But, the American College of Obstetricians and Gynecologists (2016c) only recommends *consideration* of screening for this indication. In women with singleton pregnancies but without a history of prior preterm birth, the Society for Maternal-Fetal Medicine (2016b) views cervical length screening as reasonable yet acknowledges that this remains an area of debate.

A first concern with screening surrounds the efficacy of interventions to improve perinatal outcomes once cervical length screening has isolated at-risk gravidas. Of interventions, cervical cerclage and administration of vaginal progesterone have both been evaluated. Vaginal progesterone for this indication is discussed in Progesterone Use without Prior Preterm Birth. For prophylactic cerclage in women with prior preterm births and shortened cervices, many studies have failed to show superior primary outcomes. But, piecemeal subgroup analyses from the trials have been subsequently used as the basis for recommendations in current practice guidelines regarding cervical length assessment and consideration for cerclage placement. A second concern is the accuracy and utility of the screening test, especially in low-risk women, who represent most of the population with preterm birth (Interval between Pregnancies).

To address this issue in low-risk women, Esplin and colleagues (2017) prospectively studied 9410 nulliparas with singleton pregnancies. Universal screening of sonographically measured cervical length and quantitative measurement of vaginal fFN levels were evaluated as predictors of women

who would spontaneously deliver before 37 weeks. These measures had poor predictive performance as a screening test. In fact, all screening modalities had relative low sensitivity and low positive-predictive values. Based on these findings, routine use of these screening tests in this low-risk population is not recommended. Bloom and Leveno (2017) subsequently critiqued the use of transvaginal cervical length screening in low-risk women and the promulgation of consensus guidelines. As described in Chapter 1 (Repeal and Replace), they highlighted the staggering costs encumbering the health-care system in the United States as a result of such strategies.

PRETERM BIRTH PREVENTION

Cervical Cerclage

Prevention of preterm birth remains an elusive goal. Still, recent reports suggest that prevention in selected populations may be achievable.

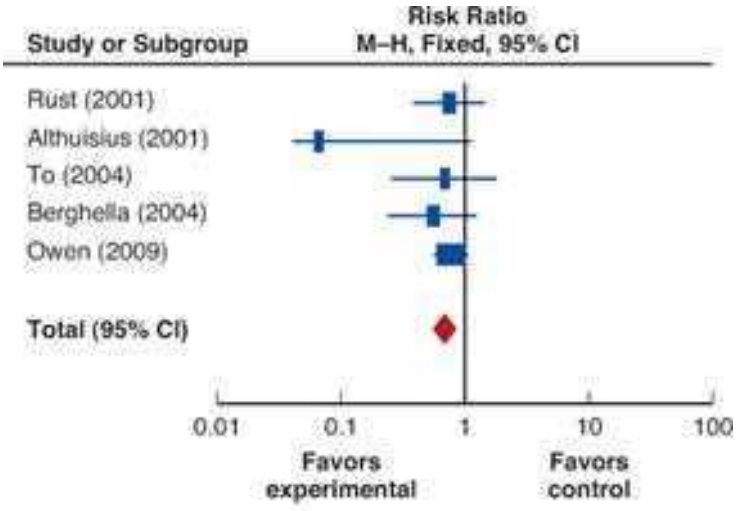
Of options, cerclage placement may be used to prevent preterm birth in at least three circumstances. First, the procedure may benefit women who have a history of recurrent midtrimester losses and who are diagnosed with cervical insufficiency. A second instance is the woman identified during sonographic examination to have a short cervix. The third indication is a "rescue" cerclage, done emergently when cervical incompetence is recognized in women with threatened preterm labor.

As is the case for virtually all obstetrical conditions, an accurate history is critical for management decisions. For recurrent abortion from cervical incompetence, historical clues are outlined in Chapter 18 (Management). For women with a short cervix incidentally detected by sonography, the benefit of cerclage placement appears directly related to whether the woman has a history of prior preterm birth. In those without a prior preterm birth, cerclage for a sonographically detected short cervix alone offers no advantage. To and associates (2004) screened 47,123 women and randomly assigned the 253 women with cervices <15 mm, with or without a history of preterm birth, to cerclage or no cerclage. The frequency of preterm delivery before 33 weeks did not differ significantly. In contrast, women with a sonographically diagnosed short cervix and a history of preterm birth may benefit. Owen and colleagues (2009) randomly assigned 302 women with prior preterm birth and with a short cervix—defined as length <25 mm—to cerclage or no procedure. The primary study outcome was not supported by the intervention. However, women with a cervical length <15 mm delivered before 35 weeks significantly less often following cerclage compared with women with no cerclage—30 versus 65 percent. This study suggested that recurrent preterm birth could be prevented in a subset of women with asymptomatic singleton gestations with both previous preterm birth and short cervical length.

These findings prompted a reassessment by Berghella and coworkers (2011), who performed a metaanalysis using individual patient data (Fig. 42-7). The primary outcomes from the included trials did not support cerclage placement. However, these investigators concluded that cerclage significantly prevented preterm birth and improved composite perinatal mortality and morbidity in women with prior spontaneous preterm birth, singleton gestation, and cervical length <25 mm.

FIGURE 42-7

Cerclage versus no cerclage for prevention of recurrent preterm birth in women with a cervical length <25 mm. Forest plot analysis of composite perinatal mortality and morbidity. CI = confidence index. (Adapted with permission from Berghella V, Rafael TJ, Szychowski JM, et al: Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis, Obstet Gynecol 117(3):663, 2011.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

One caveat in the interpretation of this cerclage data is the influence of obstetrical history. For example, all of the trials comprising the metaanalysis included preterm birth as early as 16 to 17 weeks' gestation. Defining these early second trimester losses as preterm births, rather than cervical

incompetence, is problematic. Thus, it is difficult to distinguish whether these women were treated in the context of cervical incompetence or of preterm labor at 16 weeks. Nonetheless, based on these findings, the American College of Obstetricians and Gynecologists (2016c) concluded that in women with a singleton pregnancy, prior spontaneous preterm birth before 34 weeks, cervical length <25 mm, and gestational age <24 weeks, cerclage placement may be considered.

Prophylaxis with Progestogen Compounds

In most mammals, *progesterone withdrawal* is considered to be a parturition-triggering event. During human parturition, however, maternal, fetal, and amnionic fluid progesterone levels remain elevated. It has been proposed that human parturition involves functional progesterone withdrawal mediated by decreased activity of progesterone receptors (Chap. 21, Sex Steroid Hormone Role). It follows conceptually that the administration of progesterone may block preterm labor. This hypothesis has stimulated several studies of both 17-alpha hydroxyprogesterone caproate (17-OHP-C) and vaginally administered progesterone in women with varying risks for preterm birth.

At present, the reported benefits of either of these progestogen therapies are limited to women with singleton pregnancies. Progesterone prophylaxis specifically in multifetal gestations has not lowered preterm birth rates (Caritis, 2009; Rouse, 2007). Accordingly, both the American College of Obstetricians and Gynecologists (2016c) and the Society for Maternal-Fetal Medicine (2017a) approve the use of progestogen therapy for prevention of preterm birth in select women with singleton pregnancies. Criteria are a history of prior preterm birth or no prior preterm birth but a sonographically identified short cervix.

Prior Preterm Birth and Progestogen Compounds

17-OHP-C is a synthetic progestogen, and the first and only drug approved by the FDA for prevention of recurrent preterm birth. The approval in 2011 was supported by a study by the Maternal-Fetal Medicine Units (MFMU) Network (Meis, 2003). In this trial, 463 women with a prior preterm birth were randomly assigned to receive weekly intramuscular injections of inert oil or 17-OHP-C from 16 through 36 weeks' gestation. They reported a significantly reduced recurrence of preterm birth in 36 percent of women receiving 17-OHP-C compared with 55 percent of those given placebo.

This MFMU study has been challenged because of the unexpectedly high preterm delivery rate in the placebo arm (Romero, 2013). One explanation for this high rate in the placebo group was asymmetry in the risks of recurrence. Indeed, 41 percent of the control group had ≥2 prior preterm births compared with only 28 percent in the 17-OHP-C group. Another concern was that the injection dosage of 17-OHP-C, which was 250 mg weekly, was empirically chosen (Caritis, 2014). Only later reports described the pharmacokinetics of 17-OHP-C (Caritis, 2012). Nonetheless, the Society for Maternal-Fetal Medicine (2017a) recently reaffirmed the use of 17-OHP-C, rather than vaginal progesterone, for prevention of recurrent preterm birth.

Metabolism

Sharma and associates (2008) reported that the metabolism of 17-OHP-C was predominantly mediated by the CYP3A enzymatic system. Thus, other agents that induce or inhibit this enzymatic system as well as hepatic impairment may alter drug levels. They also showed that 17-OHP-C is not converted after administration to the primary progesterone metabolite, 17α-hydroxyprogesterone. The relative binding affinity of 17-OHP-C to progesterone receptors approximates only 30 percent of that by progesterone (Attardi, 2007). Because synthetic 17-OHP-C is not converted to a naturally occurring progestogen and is not superior to progesterone in eliciting a hormonal response via the classic steroid-receptor mediated pathway, alternative pathways are now being considered to explain its efficacy (Manuck, 2011).

Caritis and colleagues (2012) examined 61 women receiving 17-OHP-C therapy and found that the half-life was relatively long (median 16.2 days). Pharmacokinetic parameters were affected by maternal body habitus and varied widely between subjects. In addition, 17-OHP-C crossed the placental barrier and was detectible in cord plasma 44 days after the last maternal injection (Caritis, 2012). Despite this, evidence to date suggests that 17-OHP-C is safe for the fetus. No abnormalities, including abnormal genitalia, were found in a 48-month follow-up study of infants exposed in the 2003 MFMU Network trial (Northen, 2007).

Pricing Concerns

There are special concerns involving 17-OHP-C and subsequent price-gouging claims (Cohen, 2011; Romero, 2013). In 2011, the FDA gave temporary approval to KV Pharmaceutical to market 17-OHP-C under the brand name *Makena*. Because regulations prohibited compounding, there was no competitor for this relatively inexpensive drug, and *Makena* was priced at $1500 per injection. This caused widespread concern because the cumulative cost of *Makena* would be more than $30,000 per pregnancy.

Use of 17-OHP-C at Parkland Hospital

A program for implementation of 17-OHP-C was incorporated at Parkland Hospital in 2012. Given the concerns above, a local compounding pharmacy provided 250-mg, single-dose vials of 17-OHP-C in sesame oil at a cost of $25 per dose. Nelson and colleagues (2017) recently reported their findings

from this program in a prospective study of 430 women given compounded 17-OHP-C. Use of 17-OHP-C was ineffective for prevention of recurrent preterm birth at 35 weeks or less compared with a historical cohort from Parkland. As shown in Table 42-6, 17-OHP-C did not significantly reduce the rates of recurrent preterm birth regardless of prior preterm birth number or sequence. Moreover, plasma concentrations of 17-OHP-C were not different at 24 weeks or 32 weeks between women delivered ≤35 weeks and those delivered later. Interestingly, levels were consistent with those previously reported using castor oil as a vehicle (Caritis, 2014). Last, the gestational age interval at which preterm birth recurred did not differ after use of 17-OHP-C. A side effect of 17-OHP-C was a significant increase in the rate of gestational diabetes. Taken together, 17-OHP-C use was ineffective to prevent recurrent preterm birth and was associated with a significant side effect.

TABLE 42-6

Prior Obstetrical History of 430 Women with Births ≤35 weeks and Recurrence Rates After 17-OHP-C at Parkland Hospital

	No 17-OHP-C	17-OHP-C Treated			
Prior Birth <35 Weeks	Historical Cohort		Recurrence		
	Recurrence Rate[a]	No.	No.	Rate	*p* value[b]
Overall	16.8%	430	106	25%	1.0
Para 1	18%	141	44	31%	1.0
Para 2:					
Both ≤35 weeks	43%	48	20	42%	0.49
Only 2nd birth ≤35 weeks	17%	52	11	21%	0.84
Only 1st birth ≤35 weeks	11%	39	2	5%	0.18
Para 3+:					
All ≤35 weeks	45%	27	12	44%	0.56
Other sequences of ≤35 weeks	12%	123	17	14%	0.78

[a]Recurrence rate is derived from the Parkland obstetrical population for 1988–2011 prior to introduction of 17-OHP-C.

[b]*p* values are one-sided.

Reproduced with permission from Nelson, 2017.

From the foregoing studies, evidence to support the use of 17-OHP-C to prevent recurrent preterm birth is problematic (Young, 2017). The mechanism of action remains unknown, and the pharmacological properties have yet to be established. Evidence of clinical effectiveness has yet to be replicated. A condition of the FDA approval for 17-OHP-C was that a confirmatory multicenter, double-blind randomized controlled trial be conducted with a preferred primary end point of delivery <35 weeks. This international trial—PROLONG—is currently underway with scheduled completion in 2018 and with an estimated enrollment of 1707 participants (PROLONG, 2014).

Progesterone Use without Prior Preterm Birth

Three randomized trials are at the center of whether progestogen therapy should be used in women without prior preterm births. These trials, shown in Table 42-7, hinge on sonographically determined cervical length. In the first trial, Fonseca and colleagues (2007) randomly assigned 250 women with short cervices measuring ≤15 mm identified during routine prenatal care. Women were given nightly 200-mg micronized progesterone vaginal capsules or placebo from 24 to 34 weeks' gestation. Spontaneous delivery <34 weeks was significantly reduced by progesterone therapy. Importantly, this trial included not only nulliparas but also those with twins or prior preterm birth.

TABLE 42-7

Randomized Trials of Progestogen Compounds Given Prophylactically to Prevent Preterm Labor

Investigator	Women Randomized	Cervical Length[a]	Progestogen Compound	Progestogen vs Placebo
Fonseca (2007)	n = 250; 5% nulliparous, 10% twins, 15% prior PTB; 8 hospitals: UK, Greece, Brazil, Chile	<15 mm	Progesterone, 200-mg vaginal capsules daily	Delivery <34 weeks: 19% vs 34%, $p = .02$
Hassan (2011)	n = 465; singletons only; 55% nulliparous; 13% prior PTB; 44 hospitals in 10 countries	10–20 mm	Progesterone, 90-mg vaginal gel daily	Delivery <33 weeks: 9% vs 16%, $p = .02$
Grobman (2012)	n = 657; singletons only; nulliparous only; 14 centers across US	<30 mm	17-OHP-C, 250 mg IM weekly	Delivery <37 weeks: 25% vs 24%, p = NS

[a]Determined sonographically.

17-OHP-C = 17-hydroxyprogesterone caproate; IM = intramuscularly; NS = nonsignificant; PTB = preterm birth; UK = United Kingdom; US = United States.

In the second trial, Hassan and coworkers (2011) randomly assigned 465 women with a short cervix—10 to 20 mm—to vaginal progesterone gel, 90 mg daily, or placebo. This trial also included nulliparas and women with prior preterm births.

From these studies, the FDA rejected progesterone gel for use because the results did not meet the level of statistical significance required to show efficacy in the subjects recruited in the United States. According to Likis and colleagues (2012), the heterogeneity of these first two studies that included women with varied indications for progestogen treatment, combined with the fact that outcomes were not reported by risk factors such as nulliparity, made it impossible to interpret the efficacy of progesterone for specific indications.

The third study randomly assigned administration of 17-OHP-C intramuscular injection or placebo between 16 and $22^{3/7}$ weeks to nulliparas with a singleton gestation and a cervical length <30 mm detected sonographically (Table 42-8) (Grobman, 2012). Treatment with 17-OHP-C given weekly did not reduce the frequency of preterm birth before 37 weeks. Regardless of cervical length, 17-OHP-C was ineffective.

TABLE 42-8

Comparison of 17-OHP-C versus Placebo to Prevent Preterm Birth at <37 and <34 Weeks

Variable	17-OHP-C N = 327	Placebo N = 330	RR (95% CI)	*p* value[a]
Preterm birth <37 wk:				
Cervical length, mm				.59
<10	5/9 (56)	10/16 (63)	0.89 (0.4–1.78)	
10–20	19/50 (38)	18/40 (45)	0.84 (0.52–1.38)	
>20	58/268 (21)	52/274 (19)	1.4 (0.82–1.52)	
Preterm birth <34 wk:				
Cervical length, mm				.49
<10	5/9 (56)	6/16 (38)	1.48 (0.63–3.51)	
10–20	11/50 (22)	12/40 (30)	0.73 (0.36–1.48)	
>20	25/268 (9)	30/274 (11)	0.85 (0.52–1.41)	

[a] *p* value for Breslow-Day interaction term.

Data are presented as n/N (%).

CI = confidence interval; RR = relative risk; 17-OHP-C = 17-hydroxyprogesterone caproate.

Data from Grobman, 2012.

Thus, vaginal progesterone, but not 17-OHP-C, appears to benefit women with a sonographically measured short cervix. Romero and Stanczyk (2013) provided a review to explain the conflicting evidence and argued that naturally occurring progesterone, which is used in the vaginal preparations, is not the same as synthetic 17-OHP-C. Likewise, Furcron and coworkers (2015) found that 17-OHP-C did not have local antiinflammatory effects at the maternal-fetal interface or cervix. Further, 17-OHP-C did not protect against endotoxin-induced preterm birth.

From all these studies, the American College of Obstetricians and Gynecologists (2016c) concluded that universal cervical length screening in women without a prior preterm birth is not mandatory. However, this screening strategy could be considered in the context of treatment with vaginal progesterone.

The OPPTIMUM Study

This study of 1228 high-risk women with singleton pregnancies is the largest to date for vaginal progesterone prophylaxis (Norman, 2016). This randomized trial of vaginal progesterone, 200 mg daily from 22–24 weeks to 34 weeks of gestation, was termed the OPPTIMUM study—*dOes Progesterone Prophylaxis To prevent preterm labor IMprove oUtcoMe?* High-risk women were defined as those with a prior spontaneous birth ≤34 weeks or with a cervical length ≤25 mm or a positive fFN test result combined with other clinical risk factors for preterm birth.

The primary outcomes of OPPTIMUM were unique in that both immediate obstetrical and childhood outcomes were examined. These were fetal death or birth <34 weeks; a composite of death, brain injury, or bronchopulmonary dysplasia; and a standardized cognitive score at 2 years of age. Contrary to earlier reports, vaginal progesterone was not associated with a lower risk of preterm birth or composite neonatal adverse outcomes. In children at 2 years of age, vaginal progesterone also had no long-term benefit or harm.

Thus, evidence is conflicting as to the efficacy of progestogens across the spectrum of the various specific indications. Some have attempted to resolve these issues through systematic review and metaanalysis (Prior, 2017; Romero, 2016, 2017). As outlined in this entire section, virtually all evidence supporting use of progestogens for a specific indication can be challenged in some way. We agree with the conclusions from the OPPTIMUM

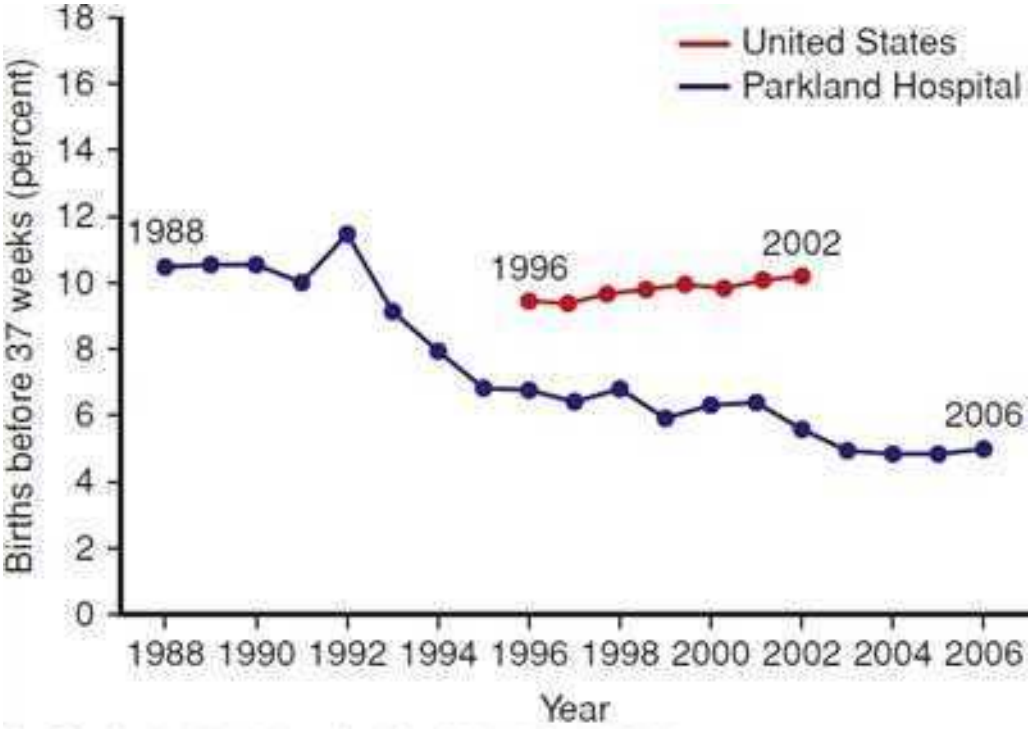
trial (Norman, 2016) that the results of recent studies should prompt a major review of progesterone use for preterm birth prophylaxis, a search to identify specific women who might specifically benefit, and a redoubling of efforts to find alternative strategies to prevent preterm birth in women at risk.

Geographic-Based Public Health-Care Programs

A well-organized prenatal system lowers the preterm birth rate in high-risk indigent populations (Creasy, 1980). One example is the Parkland Hospital prenatal clinic system (Leveno, 2009). As shown in Figure 42-8, the declining preterm birth rate between 1988 and 2006 coincided with a substantial rise in prenatal care attendance. In the early 1990s, a concerted effort was made to improve access to prenatal care by creating seamless care that began with antenatal enrollment and extended through delivery and the puerperium. Prenatal clinics were placed strategically throughout Dallas County to provide convenient access for our patients. Prenatal protocols are used by nurse practitioners at all clinic sites to guarantee homogeneous care. Women with high-risk pregnancy complications are referred to our hospital-based central clinic system. Here, Maternal-Fetal Medicine clinics operate each weekday and are staffed by residents and midwives and supervised by fellows and faculty.

FIGURE 42-8

Percentage of births before 37 weeks' gestation at Parkland Hospital from 1988 to 2006 compared with that in the United States from 1996 to 2002. Analysis in both cohorts was limited to singleton liveborn infants ≥500 g who received prenatal care. (Reproduced with permission from with permission from Leveno KJ, McIntire DD, Bloom SL, et al: Decreased preterm births in an inner-city public hospital, Obstet Gynecol. 2009 Mar;113(3):578–584.)



Thus, prenatal care is considered one component of a comprehensive and orchestrated public health-care system that is community-based. We believe that the drop in preterm births experienced at our inner-city hospital is at least partially attributable to a geographically based public health-care program specifically targeting minority populations of pregnant women. A similar obstetrical care system for indigent women at the University of Alabama at Birmingham has also produced salutary results (Tita, 2011).

MANAGEMENT OF PRETERM PREMATURE RUPTURE OF MEMBRANES

Methods used to diagnose ruptured membranes are detailed in Chapter 22 (Identification of Labor). A history of vaginal leakage of fluid, either as a continuous stream or a gush, should prompt a speculum examination to visualize gross vaginal pooling of amnionic fluid, clear fluid from the cervical canal, or both. Confirmation of PPROM is usually accompanied by sonographic examination to assess amnionic fluid volume, to identify the presenting part, and if not previously determined, to estimate gestational age. Once PPROM is identified, the general scheme shown in Table 42-9 can guide management.

TABLE 42-9

Management of Preterm Premature Rupture of Membranes

Gestational Age	Management
34 weeks or more	Plan delivery: labor induction unless contraindicated Group B streptococcal prophylaxis[a] Single corticosteroid course may be considered up to $36^{6/7}$ weeks[b]
32 weeks to 33 completed weeks	Expectant management Group B streptococcal prophylaxis[a] Single corticosteroid course[c] Antimicrobials to prolong latency
24 weeks to 31 completed weeks	Expectant management Group B streptococcal prophylaxis[a] Single corticosteroid course[c] Tocolytics: no consensus Antimicrobials to prolong latency Magnesium sulfate for neuroprotection may be considered[d]
<24 weeks	Expectant management or induction of labor[e] Group B streptococcal prophylaxis is not recommended[f] Single corticosteroid course may be considered[e,f] Tocolytics: no consensus[e,f] Antimicrobials: may be considered[e,g]

[a]Figure 64-7 outlines group B streptococcal prophylaxis for preterm gestations.

[b]May be considered between $34^{0/7}$ and $36^{6/7}$ weeks in those who have not received a previous course of antenatal corticosteroids.

[c]Repeat, or rescue, course of corticosteroids with preterm rupture of membranes is controversial.

[d]Magnesium sulfate for neuroprotection in accordance with one of the larger studies.

[e]See Periviable Neonatal Survival (Periviable Neonatal Survival) to aid patient counseling and decision making.

[f]Intervention not recommended before viability but may be considered as early as $23^{0/7}$ weeks of gestation.

[g]May be considered as early as $20^{0/7}$ weeks of gestation.

Data from American College of Obstetricians and Gynecologists 2016a, d, 2017a, e.

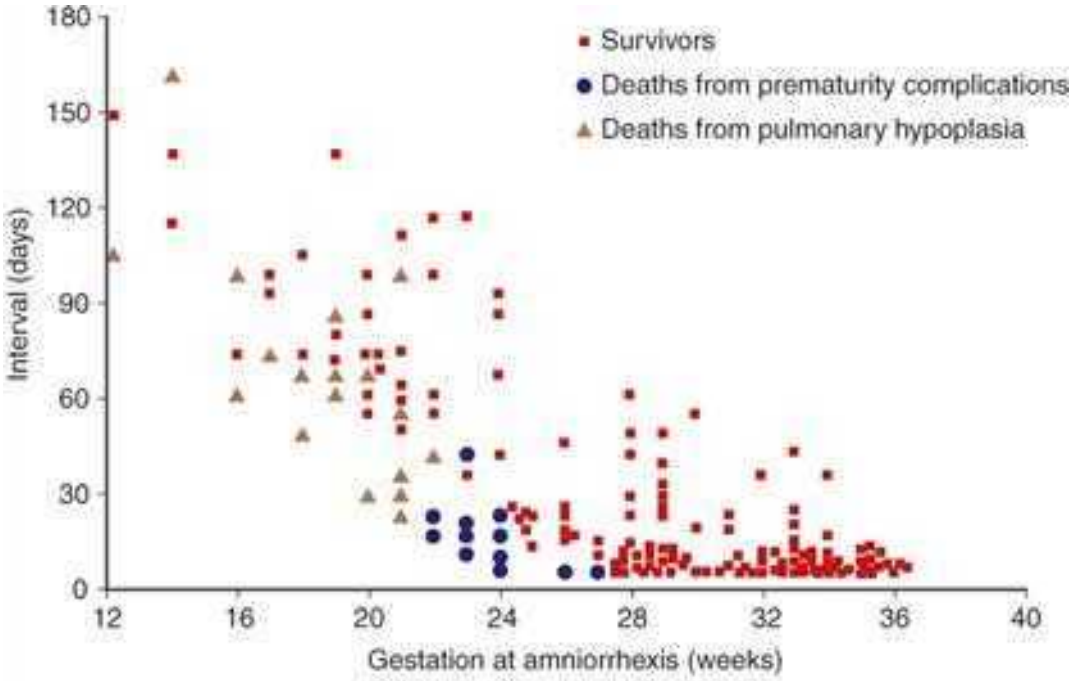
Natural History

Cox and associates (1988) described pregnancy outcomes of 298 consecutive women who gave birth following spontaneously ruptured membranes between 24 and 34 weeks' gestation at Parkland Hospital. Although this complication was identified in only 1.7 percent of pregnancies, it contributed to 20 percent of all perinatal deaths. By the time they presented, 76 percent of the women were already in labor, and 5 percent were delivered for other complications. Thus, only 19 percent initially were permitted expectant management. Ultimately, delivery was delayed 48 hours or more after membrane rupture in only 7 percent of the total study cohort. There was benefit noted from delayed delivery, however, as none of the neonates died in this group. This contrasted with a neonatal death rate of 80 per 1000 in preterm newborns delivered within 48 hours of membrane rupture. Nelson and colleagues later (1994) reported similar results.

The time from PPROM to delivery is inversely proportional to the gestational age when rupture occurs (Carroll, 1995). As shown in Figure 42-9, very few days are gained when membranes ruptured during the third trimester compared with midpregnancy.

FIGURE 42-9

Relationship of time between preterm membrane rupture and delivery in 172 singleton pregnancies. (Reproduced with permission from Carroll SG, Blott M, Nicolaides KH: Preterm prelabor amniorrhexis: Outcome of live births, Obstet Gynecol 1995 Jul;86(1):18–25.)



Hospitalization

Most clinicians hospitalize women with ruptured membranes. Concerns regarding the costs of lengthy hospitalizations are usually moot, because most women enter labor within a week or less after membrane rupture. Carlan and coworkers (1993) randomly assigned 67 women with ruptured membranes to home or hospital management. No benefits were found for hospitalization, and maternal hospital stays were reduced by 50 percent in those sent home—14 versus 7 days. Importantly, the investigators emphasized that this study was too small to conclude that home management was safe in regard to umbilical cord prolapse.

Intentional Delivery

Before the mid-1970s, labor was usually induced in women with preterm ruptured membranes because of fear of sepsis. Maternal infection risk and fetal prematurity risk vary according to the gestational age at membrane rupture, and management decisions hinge on this balance. With regard to periviable pregnancy, Morales (1993b) expectantly managed 94 singleton pregnancies with ruptured membranes before 25 weeks. The average time gained was 11 days. Although 41 percent of infants survived to age 1 year, only 27 percent of the original cohort were neurologically normal. Similar results were reported by Farooqi (1998) and Winn (2000) and their colleagues. Management of these early pregnancies is discussed in Late-Preterm Birth.

For PPROM in general, two randomized trials in the 1990s compared labor induction with expectant management (Cox, 1995; Mercer, 1993). In both of these studies, the balance of risk and benefit was difficult to ascertain, as neither immediate delivery nor expectant management were proven to be superior for neonatal outcomes. Lieman and associates (2005) found that neonatal outcomes did not improve with expectant management beyond 33 weeks. McElrath and coworkers (2003) found that prolonged latency after membrane rupture was not associated with a greater incidence of fetal neurological damage. An important correlate is that infection—specifically chorioamnionitis—is recognized as a risk factor for development of neonatal neurological injury (Gaudet, 2001; Wu, 2000).

Bond and colleagues (2017) recently compared planned early birth with expectant management for women with PPROM before 37 weeks' gestation. They evaluated 12 randomized trials totaling 3617 women and 3628 newborns. No clinically important differences in the incidence of neonatal sepsis between women who immediately delivered and those managed expectantly were identified. Although the incidence of chorioamnionitis was lower, neonates of women randomized to early birth were more likely to be born at an earlier gestational age and encountered attendant perinatal sequelae.

The authors concluded that in women with rupture of membranes before 37 weeks' gestation without contraindications to continuing the pregnancy, a policy of expectant management with careful monitoring was associated with better outcomes for both the mother and newborn.

The American College of Obstetricians and Gynecologists (2016d) has recognized the controversies of immediate delivery compared with expectant management. Clearly, gestational age is an important consideration. At $24^{0/7}$ to $33^{6/7}$ weeks, expectant management in the absence of nonreassuring fetal status, clinical chorioamnionitis, or placental abruption is recommended. At $34^{0/7}$ weeks of gestation or greater, delivery is still recommended by the College for all women with ruptured membranes. Our current practices at Parkland Hospital are consistent with these recommendations.

Considerations with Expectant Management

Several scenarios during expectant management merit consideration. One is performance of digital cervical examination. Alexander and colleagues (2000) analyzed findings in women with PPROM expectantly managed between 24 and 32 weeks' gestation. They compared those who had one or two digital cervical examinations with women who were not examined. Those who were examined had a rupture-to-delivery interval of 3 days compared with 5 days in those not examined. This difference did not worsen maternal or neonatal outcomes.

Rupture of membranes following second-trimester amniocentesis is uncommon (Chap. 14, Chorionic Villus Sampling). Compared with women with spontaneous rupture during the second trimester, Borgida and associates (2000) found that pregnancies complicated by PPROM after genetic amniocentesis resulted in significantly better perinatal outcomes. The perinatal survival rate was 91 percent. After counseling, affected women are typically managed expectantly as outpatients with serial surveillance of amnionic fluid volume (American College of Obstetricians and Gynecologists, 2016d). In the series cited above, the mean time to documentation of a normal amnionic fluid volume after amniocentesis approximated 2 weeks.

Tocolysis has been used in few studies. In women with ruptured membranes and lack of labor, prophylactic tocolysis does not improve neonatal outcomes but is associated with greater rates of chorioamnionitis (Mackeen, 2014). Similarly, therapeutic tocolysis—for those with ruptured membranes and labor—has also not provided significant perinatal benefit (Garite, 1987).

There is uncertainty regarding PPROM in the woman who has undergone cervical cerclage. McElrath and associates (2002) studied 114 women with a cerclage in place who later had ruptured membranes before 34 weeks. They were compared with 288 controls. Pregnancy outcomes were equivalent in both groups. Cerclage retention for more than 24 hours after preterm rupture of membranes may be associated with pregnancy prolongation, however, there is risk of intrauterine infection and its consequences (Giraldo-Isaza, 2011; Laskin, 2012). As discussed in Chapter 18 (Induced Abortion), such management is controversial.

With PPROM in general, the volume of amnionic fluid remaining after rupture appears to have prognostic importance in pregnancies before 26 weeks. Hadi and colleagues (1994) described 178 pregnancies with ruptured membranes between 20 and 25 weeks. Almost 40 percent developed oligohydramnios, defined by the absence of fluid pockets measuring 2 cm or more. Virtually all women with oligohydramnios delivered before 25 weeks, whereas 85 percent with adequate amnionic fluid volume were delivered in the third trimester. Carroll and coworkers (1995) observed no cases of pulmonary hypoplasia in fetuses born after membrane rupture at 24 weeks or beyond. This suggests that 23 weeks or less is the threshold for development of lung hypoplasia (Chap. 7, Respiratory System). Further, when contemplating early expectant management, consideration is also given to oligohydramnios and resultant limb compression deformities (Chap. 11, Management).

Other risk factors have also been evaluated. First, in neonates born to women with active herpetic lesions who were expectantly managed, the infectious morbidity risk appeared to be outweighed by risks associated with preterm delivery (Major, 2003). Second, Lewis and associates (2007) found that expectant management of women with PPROM and noncephalic presentation was associated with a higher rate of umbilical cord prolapse, especially before 26 weeks.

Clinical Chorioamnionitis

As discussed, infection is a major concern with membrane rupture. While some cases remain subclinical, if chorioamnionitis is diagnosed, prompt efforts to effect delivery, preferably vaginally, are initiated. Because maternal leukocytosis alone is not a consistent finding, *fever is the only reliable indicator for the diagnosis of chorioamnionitis*. Institutional practices and protocols vary in defining the temperature threshold. Traditionally, a temperature ≥38°C (100.4°F) accompanying ruptured membranes has implied infection. At Parkland Hospital, we still adhere to this criterion.

In 2015, a workshop sponsored by the NICHD was convened and suggested renaming this condition "intraamnionic infection and inflammation" (Higgins, 2016). The merits and clinical utility of this novel "triple I" terminology have been questioned (Barth, 2016). Nonetheless, the American College of Obstetricians and Gynecologists (2017b) recently revised both the definitions and temperature thresholds for intraamnionic infection. Using these new definitions, the diagnosis of suspected intraamniotic infection is made when the maternal temperature is ≥39.0°C or when the maternal temperature is 38.0 to 38.9°C and one additional clinical risk factor is present. Suggested factors include low parity, multiple digital examinations, use of internal uterine and fetal monitors, meconium-stained amnionic fluid, and the presence of certain genital tract pathogens.

Examples are group B streptococcus and sexually transmitted agents. Isolated maternal fever is defined as any maternal temperature between 38.0°C and 38.9°C with no additional risk factors present, and with or without persistent temperature elevation.

With chorioamnionitis, fetal and neonatal morbidity are substantively increased. Alexander and colleagues (1998) studied 1367 very-low-birthweight neonates delivered at Parkland Hospital. Approximately 7 percent were born to women with overt chorioamnionitis, and their outcomes were compared with similar newborns without clinical infection. Those in the infected group had higher incidences of sepsis, RDS, early-onset seizures, intraventricular hemorrhage, and periventricular leukomalacia. The investigators concluded that these very-low-birthweight newborns were vulnerable to neurological injury attributable to chorioamnionitis. Yoon and colleagues (2000) found that intraamnionic infection in preterm neonates was related to increased rates of cerebral palsy. Petrova and associates (2001) studied more than 11 million singleton live births in the United States from 1995 to 1997. During labor, 1.6 percent of all women had fever, and this was a strong predictor of infection-related death in both term and preterm neonates.

Antimicrobial Therapy

The proposed microbial pathogenesis for spontaneous preterm labor or ruptured membranes has prompted investigators to give various antimicrobials to forestall delivery. Mercer and associates (1995) reviewed 13 randomized trials performed before 35 weeks. Their metaanalysis indicated that only three of 10 outcomes were *possibly* benefited: (1) fewer women developed chorioamnionitis, (2) fewer newborns developed sepsis, and (3) pregnancy was more often prolonged 7 days in women given antimicrobials. Rates of neonatal survival, necrotizing enterocolitis, RDS, or intracranial hemorrhage, however, were unaffected.

To further address this issue, the MFMU Network designed a trial to study expectant management combined with placebo or with a 7-day antibiotic regimen. Treatment included intravenous ampicillin plus erythromycin every 6 hours for 48 hours, which was followed by oral amoxicillin plus erythromycin, every 8 hours for 5 days. The women had membrane rupture between 24 and 32 weeks' gestation. Neither tocolytics nor corticosteroids were given. Antimicrobial-treated women had significantly fewer newborns with RDS, necrotizing enterocolitis, and composite adverse outcomes (Mercer, 1997). The latency period was also significantly longer. Specifically, 50 percent of women given an antimicrobial regimen remained undelivered after 7 days of treatment compared with only 25 percent of those given placebo. Also, a significantly greater number of treated pregnancies were undelivered at 14 and 21 days. Cervicovaginal group B streptococcal colonization did not alter these results.

Other studies have examined the efficacy of shorter treatment lengths and different antimicrobial combinations. Three-day treatments compared with 7-day regimens using either ampicillin or ampicillin-sulbactam appear equally effective in regard to perinatal outcomes (Lewis, 2003; Segel, 2003). Similarly, erythromycin compared with placebo offered a range of significant neonatal benefits. The amoxicillin-clavulanate regimen was not recommended, however, because of its association with an increased incidence of neonatal necrotizing enterocolitis (Kenyon, 2004).

Some predicted that prolonged antimicrobial therapy in such pregnancies might have unwanted consequences (Carroll, 1996; Mercer, 1999). Stoll and associates (2002) studied 4337 neonates weighing from 400 to 1500 g and born from 1998 to 2000. Their outcomes were compared with those of 7606 neonates of similar birthweight born from 1991 to 1993 and prior to the practice of antibiotic prophylaxis. The overall rate of early-onset sepsis did not change between these two epochs. But, the rate of group B streptococcal sepsis dropped from 5.9 per 1000 births in the 1991 to 1993 group to 1.7 per 1000 births in the 1998 to 2000 group. Comparing these same epochs, the rate of *Escherichia coli* sepsis, however, rose from 3.2 to 6.8 per 1000 births. Almost 85 percent of coliform isolates from the more recent cohort were resistant to ampicillin. Neonates with early-onset sepsis were more likely to die, especially if they were infected with coliforms. Long term, Kenyon and coworkers (2008a) found that antimicrobials given for women with PPROM had no effect on the health of children at age 7 years.

Corticosteroids to Accelerate Fetal Lung Maturity

The use of antenatal corticosteroids in the setting of PPROM was once considered controversial as the magnitude of the benefits was not as great as when the membranes were intact. A single course of corticosteroids, however, is now recommended for pregnant women with ruptured membranes between $24^{0/7}$ and $34^{0/7}$ weeks' gestation (American College of Obstetricians and Gynecologists, 2017a). As with periviability (Late-Preterm Birth), a single course of corticosteroids as early as $23^{0/7}$ weeks in those who are at risk for preterm delivery within 7 days may be considered (American College of Obstetricians and Gynecologists, 2017e). A similar controversy is found at the other end of the gestational age spectrum, wherein corticosteroid administration in the late-preterm period is also under consideration (Corticosteroids for Fetal Lung Maturation).

Membrane Repair

Tissue sealants are used for various purposes in medicine, including achieving surgical hemostasis. As discussed in Chap. 18 (Inevitable Abortion), there are limited reports of sealants in the repair of fetal membranes. Crowley and coworkers (2016) recently reviewed the available evidence and concluded that data are currently insufficient to evaluate sealing procedures for ruptured membranes. At Parkland Hospital, we do not currently use these agents for this indication.

MANAGEMENT OF PRETERM LABOR WITH INTACT MEMBRANES

Women with signs and symptoms of preterm labor with intact membranes are managed similarly to those with PPROM. If possible, delivery before 34 weeks' gestation is delayed. Drugs used to abate or suppress preterm uterine contractions are subsequently discussed.

Amniocentesis to Detect Infection

Several tests have been used to diagnose intraamnionic infection (Andrews, 1995; Romero, 1993; Yoon, 1996). Although such infection can be confirmed with a positive test result, there is little utility for routine amniocentesis (American College of Obstetricians and Gynecologists (2017b).

Corticosteroids for Fetal Lung Maturation

Because glucocorticosteroids were found to accelerate lung maturation in preterm sheep fetuses, Liggins and Howie (1972) evaluated them to treat women. Corticosteroid therapy was effective in lowering the incidence of RDS and neonatal mortality rates if birth was delayed for at least 24 hours after *initiation* of betamethasone. Infants exposed to corticosteroids in these early studies have now been followed to age 31 years with no ill effects detected. In 1995, a National Institutes of Health (NIH) Consensus Development Conference panel recommended corticosteroids for fetal lung maturation in threatened preterm birth. In a subsequent meeting, another NIH Conference (2000) concluded that data were insufficient to assess corticosteroid effectiveness in pregnancies complicated by hypertension, diabetes, multifetal gestation, fetal-growth restriction, or fetal hydrops. It was concluded, however, that it was reasonable to administer corticosteroids to these women.

A recent metaanalysis by Roberts and associates (2017) of 30 studies totaling 7774 women and 8158 infants quantified the benefit of a single course of corticosteroids. Treatment was associated with lower rates of perinatal death, neonatal death, RDS, intraventricular hemorrhage, necrotizing enterocolitis, need for mechanical ventilation, and systemic infection in the first 48 hours of life. No obvious benefits were gained for chronic lung disease, death in childhood, or neurodevelopmental delay in childhood. Therapy was not associated with chorioamnionitis. Parenthetically, corticosteroids given prophylactically to women at risk of preterm birth in low- and middle-income countries actually *increase* perinatal mortality rates (Althabe, 2015).

A single course of corticosteroids is currently recommended by the American College of Obstetricians and Gynecologists (2017a) for women between 24 and 34 weeks who are at risk for delivery within 7 days. This recommendation for premature twins has been challenged (Viteri, 2016). Boundaries of gestational age for corticosteroid administration are also now being explored. For pregnancies at 23 weeks and at risk of delivery within 7 days, a single course of corticosteroids may be considered (Late-Preterm Birth). Administration of corticosteroids during the periviable period is linked to a family's decision regarding resuscitation and should be considered in that context (American College of Obstetricians and Gynecologists, 2017e).

Betamethasone and dexamethasone appear to be equivalent for fetal lung maturation (Murphy, 2007). These two drugs are comparable in reducing rates of major neonatal morbidities in preterm newborns (Elimian, 2007). A treatment course may be two 12-mg doses of betamethasone, and each dose is given intramuscularly 24 hours apart. With dexamethasone, 6-mg doses are given intramuscularly every 12 hours for four doses. Because treatment for less than 24 hours may be beneficial and reduce neonatal morbidity and mortality rates, a first dose of antenatal corticosteroids is administered regardless of the ability to complete additional doses before delivery (American College of Obstetricians and Gynecologists, 2017a).

Women at Risk for Late-Preterm Delivery

The MFMU Network conducted a randomized trial to assess whether administration of antenatal betamethasone to women who were likely to deliver in the late-preterm period would decrease respiratory and other neonatal complications (Gyamfi-Bannerman, 2016). Even though only 60 percent of the study cohort of 2831 women received both injections, the rate of respiratory complications measured as a composite outcome was lower with corticosteroid use compared with placebo—11.6 versus 14.4 percent. Because of these findings, *consideration* for administration of a single course of betamethasone for women between $34^{0/7}$ and $36^{6/7}$ weeks has been recommended by both the American College of Obstetricians and Gynecologists (2017a) and the Society for Maternal-Fetal Medicine (2016a).

Adoption of this practice has not been universal. Both short- and long-term neonatal safety are concerns (Crowther, 2016; Kamath-Rayne, 2016). Specifically, in the newborns receiving betamethasone, rates of hypoglycemia were significantly greater (Gyamfi-Bannerman, 2016). Neonatal hypoglycemia is particularly worrisome for possible adverse long-term consequences that include developmental delay (Kerstjens, 2012). Another caveat is that the largest effects of betamethasone included a reduction in transient tachypnea of the newborn—a self-limited condition with little clinical significance (Kamath-Rayne, 2016). Specifically, the rates of transient tachypnea of the newborn were 6.7 and 9.9 percent in those given betamethasone and placebo, respectively. These rates are three- to fourfold higher than those reported by the Consortium on Safe Labor (2010), which was a retrospective, observational study that abstracted detailed labor and delivery information from 19 hospitals across the United States on 233,844 deliveries. Because of these issues, we do not provide corticosteroids beyond 34 weeks at Parkland Hospital at this time.

Repeated Courses

Single versus additional courses of intramuscular corticosteroids for lung maturation has been the topic of two major trials. Although both found repeated courses to be beneficial in reducing neonatal respiratory morbidity rates, the long-term consequences were much different. In one randomized study by Crowther and associates (2007), all women at risk for preterm birth were given a primary course of betamethasone. Women were then given serial weekly doses of 11.4 mg of betamethasone for persistent risk or were given placebo. These investigators found no adverse effects in the infants followed to age 2 years. Wapner and coworkers (2007) studied infants born to 495 women who were randomly assigned to receive a single corticosteroid course that contained two doses or assigned to repeated courses that were given weekly. A nonsignificant rise in the cerebral palsy rate was identified in infants exposed to repeated courses. The doubled betamethasone dose in this study was worrisome because some experimental evidence supports the view that adverse effects are dose dependent (Bruschettini, 2006). Stiles (2007) summarized these two studies as "early gain, long-term questions." We agree, and at Parkland Hospital, we follow the recommendation by the American College of Obstetricians and Gynecologists (2017a) for single-course therapy.

Rescue Therapy

This refers to administration of a second corticosteroid dose when delivery becomes imminent and more than 7 days have elapsed since the initial dose. In one randomized trial, 326 women received placebo or a single 12-mg dose of betamethasone (Peltoniemi, 2007). Paradoxically, the rescue dose of betamethasone increased the risk of RDS. In another randomized study of 437 women with gestations <33 weeks, Garite and associates (2009) reported significantly lower rates of respiratory complications and neonatal composite morbidity with rescue corticosteroids versus placebo. Rates of perinatal mortality and other morbidities, however, did not differ. Last, McEvoy and colleagues (2010) found that treated infants had improved respiratory compliance.

Garite and coworkers (2009) randomly assigned 437 women with singletons or twins <33 weeks' gestation and with intact membranes to one rescue course of either betamethasone or dexamethasone or placebo. These women had all previously completed a single course of corticosteroids before 30 weeks' gestation and at least 14 days before the rescue course. RDS developed in 41 percent of the newborns given rescue corticosteroids compared with 62 percent of those randomized to placebo. Rates of other morbidities attributable to prematurity did not differ. In a metaanalysis, Crowther and colleagues (2011) concluded that a single course of corticosteroids should be considered in women whose prior course was administered at least 7 days previously and who were <34 weeks' gestation. The American College of Obstetricians and Gynecologists (2017a) has taken the position that a single rescue course of antenatal corticosteroids *be considered* in women before 34 weeks whose prior course was administered at least 7 days previously. Effects of rescue therapy beyond 34 weeks are currently unknown. At Parkland Hospital, we currently do not provide additional courses of corticosteroids beyond the initial single-course therapy.

Magnesium Sulfate for Neuroprotection

Very-low-birthweight neonates whose mothers were treated with magnesium sulfate for preterm labor or preeclampsia were found to have a reduced incidence of cerebral palsy at 3 years (Grether, 2000; Nelson, 1995). Because of this, randomized trials were designed to investigate this hypothesis. In one trial, 1063 women at risk of delivery before 30 weeks were given magnesium sulfate or placebo (Crowther, 2003). Magnesium exposure improved some perinatal outcomes. Namely, rates of both neonatal death and cerebral palsy were lower in the magnesium-treated group—but this study was not sufficiently powered. The multicenter French trial reported by Marret and associates (2008) had similar problems.

More convincing evidence for magnesium neuroprotection came from the MFMU Network study—*Beneficial Effects of Antenatal Magnesium Sulfate—BEAM—Study* (Rouse, 2008). This was a placebo-controlled trial in 2241 women at imminent risk for preterm birth between 24 and 31 weeks. Women randomized to magnesium sulfate were given a 6-g bolus over 20 to 30 minutes followed by a maintenance infusion of 2 g per hour. Magnesium sulfate was actually infusing at the time of delivery in approximately half of the treated women. A 2-year follow-up was available for 96 percent of the children. Results are shown in Table 42-10. This trial can be interpreted differently depending on statistical methodologies employed. Some interpret these findings to mean that magnesium infusion prevents cerebral palsy regardless of the gestational age at which therapy is given. Those with a differing view conclude that this trial only supports use of magnesium sulfate for prevention of cerebral palsy before 28 weeks.

TABLE 42-10

Magnesium Sulfate for the Prevention of Cerebral Palsy[a]

	Treatment		
Perinatal Outcome[a]	**Magnesium Sulfate No. (%)**	**Placebo No. (%)**	**Relative Risk (95% CI)**
Infants with 2-year follow-up	1041 (100)	1095 (100)	—
Fetal or infant death	99 (9.5)	93 (8.5)	1.12 (0.85–1.47)
Moderate or severe cerebral palsy:			
Overall	20/1041 (1.9)	3/1095 (3.4)	0.55 (0.32–0.95)
<28–31 weeks[b]	12/442 (2.7)	30/496 (6)	0.45 (0.23–0.87)
≥24–27 weeks[b]	8/599 (1.3)	8/599 (1.3)	1.00 (0.38–2.65)

[a]Selected results from the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) Study.

[b]Weeks' gestation at randomization.

CI = confidence index.

Data from Rouse, 2008.

Subsequent to these studies, Doyle and associates (2009) reviewed five randomized trials to assess neuroprotective effects. A total of 6145 infants were studied, and these reviewers concluded that magnesium exposure compared with no exposure significantly lowered risks for cerebral palsy. Rates of other neonatal morbidity did not differ significantly. It was calculated that treatment given to 63 women would prevent one case of cerebral palsy.

Controversy surrounding magnesium efficacy for neuroprotection prompted a debate at the 2011 annual meeting of the Society for Maternal-Fetal Medicine. Rouse (2011) spoke for the benefits of magnesium sulfate, whereas Sibai (2011) challenged that the reported benefits were false positive due to random statistical error in the metaanalysis by Doyle (2009). Another peculiarity is the apparent lack of dose-response for efficacy (McPherson, 2014). Because none of the individual studies found a benefit from magnesium sulfate for fetal neuroprotection, the American College of Obstetricians and Gynecologists (2016a) concluded that those electing prophylaxis should develop specific guidelines. To guide such therapy, the American College of Obstetricians and Gynecologists (2012) issued a *Patient Safety Checklist* for use of magnesium sulfate for neuroprotection. For those with PPROM, prophylaxis may similarly be considered. At Parkland Hospital, we provide magnesium sulfate for neuroprotection with threatened preterm delivery from $24^{0/7}$ to $27^{6/7}$ weeks.

Antimicrobials

Results have been disappointing in studies of antimicrobials given to arrest preterm labor. From one Cochrane metaanalysis, antimicrobial prophylaxis given to women with intact membranes did not reduce preterm birth rates or affect other clinically important short-term outcomes (Flenady, 2013). However, rates of short- and longer-term harm were higher for children of mothers exposed to antibiotics. Kenyon (2001) reported the ORACLE Collaborative Group study of 6295 women with spontaneous preterm labor and intact membranes, but without evidence of infection. Women were randomly assigned to receive antimicrobial or placebo therapy. The primary outcomes of neonatal death, chronic lung disease, and major cerebral abnormality were similar in both groups. In a follow-up of the ORACLE II trial, fetal exposure to antimicrobials in this clinical setting was associated with an increased cerebral palsy rate at age 7 years compared with that in children without fetal exposure (Kenyon, 2008b). Importantly, antimicrobial use described here is distinct from that given for group B streptococcal prophylaxis (Chap. 64, Methicillin-Resistant Staphylococcus aureus).

Bed Rest

This is one of the most often prescribed interventions during pregnancy, yet one of the least studied. One systematic review concluded that evidence neither supported nor refuted bed rest for prevention of preterm birth (Sosa, 2004). Goulet and coworkers (2001) randomly assigned 250 Canadian women to either home care or hospitalization after treatment of an acute episode of preterm labor and found no benefits. There have, however, been reports of possible harm. Kovacevich and associates (2000) reported that bed rest for 3 days or more increased thromboembolic complications to 16 per 1000 women compared with only 1 per 1000 with normal ambulation. Promislow and colleagues (2004) observed significant bone loss in pregnant women prescribed outpatient bed rest. More recently, Grobman and associates (2013) noted that women with activity restriction were nearly 2.5 times more likely to have a preterm birth before 34 weeks. This finding, however, may reflect ascertainment bias. That is, women with restricted activity may have been assigned to bed rest because they were viewed to be at more imminent risk of preterm delivery. McCall and coworkers (2013) summarized the literature on bed rest, and they found insufficient evidence to support its use. The American College of Obstetricians and Gynecologists (2017d) suggests that, although frequently prescribed, bed rest is only rarely indicated, and ambulation should be considered in most cases.

Cervical Pessaries

Silicone rings, such as the *Arabin pessary*, are being used to support the cervix in women with a sonographically short cervix. For 385 Spanish women with a cervical length ≤25 mm, Goya and associates (2012) provided a silicone pessary or expectant management. Newborns spontaneous delivered before 34 weeks' gestation in 6 percent of women in the pessary group compared with 27 percent in the expectant management group. Another trial randomly assigned almost 100 women with a cervix <25 mm at 20 to 24 weeks to silicone pessaries or expectant management (Hui, 2013). The pessary did not lower the rate of delivery <34 weeks. Similar findings were reported by Nicolaides and colleagues (2016). The Society for Maternal-Fetal Medicine (2017b) recently recognized the conflicting published reports and lack of an FDA-approved pessary for the indication of preterm birth prevention. They currently recommend pessary prophylaxis only within research protocols.

Emergency or Rescue Cerclage

Some evidence supports the concept that cervical incompetence and preterm labor lie along a spectrum leading to preterm delivery. Consequently, investigators have evaluated cerclage placement after preterm labor begins to manifest clinically. Althuisius and colleagues (2003) randomly assigned 23 women with cervical incompetence before 27 weeks to bed rest, with or without emergency McDonald cerclage. Delivery delay was significantly greater in the cerclage group compared with those assigned to bed rest—54 versus 24 days, respectively. Terkildsen and coworkers (2003) studied 116 women who underwent second-trimester emergency cerclage. Nulliparity, membranes extending beyond the external cervical os, and cerclage before 22 weeks were associated with a significantly decreased chance of significant pregnancy continuation. For women facing a poor pregnancy prognosis due to cervical dilation at midgestation, it seems reasonable to offer emergency or rescue cerclage with appropriate counseling. However, it is unclear if such interventions truly confer a benefit or merely increase the risk of membrane rupture and infection (Hawkins, 2017).

Tocolysis to Treat Preterm Labor

Although several drugs and other interventions have been used to prevent or inhibit preterm labor, none is completely effective. The American College of Obstetricians and Gynecologists (2016b) has concluded that tocolytic agents do not markedly prolong gestation but may delay delivery in some women for up to 48 hours. This may allow transport to an obstetrical center with higher-level neonatal care and permit time for a course of corticosteroid therapy. Although delivery may be delayed to administer corticosteroids, treatment has not improved perinatal outcome rates (Gyetvai, 1999).

Beta-adrenergic agonists, magnesium sulfate, calcium-channel blockers, or indomethacin are the recommended tocolytic agents for this short-term use. The gestational age range for tocolytic use is debatable. But, because corticosteroids are not generally used after 34 weeks, and because the perinatal outcomes in preterm neonates are generally good after this time, most do not recommend use of tocolytics after 33 weeks' gestation (Goldenberg, 2002).

In many women, tocolytics stop contractions temporarily but rarely prevent preterm birth. The College (2016b) notes that maintenance therapy with tocolytics is ineffective for preventing preterm birth. Importantly, no trial has ever convincingly shown reductions in rates of any important adverse outcome by a tocolytic drug compared with placebo (Walker, 2016). Maintenance tocolysis after acute therapy is not recommended.

β-Adrenergic Receptor Agonists

Several compounds react with β-adrenergic receptors to reduce intracellular ionized calcium levels and prevent activation of myometrial contractile proteins (Chap. 21, G-Protein–Coupled Receptors). Of β-mimetic drugs in the United States, ritodrine and terbutaline have been used in obstetrics, but only ritodrine is approved for preterm labor by the FDA.

Ritodrine was voluntarily withdrawn from the United States market in 2003, but a discussion of ritodrine is included here to present issues with β-mimetic drug use. In one early trial, neonates whose mothers were treated with ritodrine for threatened preterm labor had lower rates of preterm

birth and its complications (Merkatz, 1980). In a randomized trial at Parkland Hospital, intravenous ritodrine delayed delivery for 24 hours but without other benefits (Leveno, 1986b). Additional studies confirmed a delivery delay up to 48 hours (Canadian Preterm Labor Investigators Group, 1992).

β-Agonist drug infusion has resulted in serious and even fatal maternal side effects. Pulmonary edema is a special concern, and its contribution to morbidity is discussed in Chapter 47 (Acute Pulmonary Edema). In one early study, tocolysis was the third most common cause of acute respiratory distress and death in pregnant women during a 14-year period in Mississippi (Perry, 1998). The cause of pulmonary edema is multifactorial. Risk factors include tocolytic therapy with β-agonist drugs, multifetal gestation, concurrent corticosteroid therapy, tocolysis for more than 24 hours, and intravenous infusion of large volumes of crystalloid. β-Agonist agents cause retention of sodium and water, and with time—usually 24 to 48 hours—these can cause volume overload (Hankins, 1988). The drugs have been implicated in increased capillary permeability, cardiac rhythm disturbances, and myocardial ischemia.

Terbutaline is commonly used in the United States to forestall preterm labor. Like ritodrine, it may cause pulmonary edema (Angel, 1988). Low-dose terbutaline can be administered long-term by subcutaneous pump (Lam, 1988; Perry, 1995). But, randomized trials have shown no benefit for terbutaline pump therapy (Guinn, 1998; Wenstrom, 1997). Oral terbutaline given to prevent preterm delivery is also ineffective (How, 1995; Parilla, 1993). In one trial, 203 women with arrested preterm labor at 24 to 34 weeks' gestation were randomly assigned to receive 5-mg terbutaline tablets or placebo every 4 hours (Lewis, 1996). Of outcomes, delivery rates at 1 week, median latency duration, mean gestational age at delivery, and incidence of preterm labor relapse were similar in both groups. Because of reports of serious maternal side effects, the FDA (2011) issued a warning regarding the use of terbutaline to treat preterm labor. The American College of Obstetricians and Gynecologists (2016b) recommends only short-term inpatient use of terbutaline as a tocolytic or as acute therapy of uterine tachysystole. Subcutaneous dosages of 0.25 mg are commonly used for the latter indication. Terbutaline, used as a tocolytic prior to external cephalic version, is discussed in Chapter 28 (Tocolysis).

Magnesium Sulfate

Ionic magnesium in a sufficiently high concentration can alter myometrial contractility. Its role is presumably that of a calcium antagonist, and when given in pharmacological doses, it may inhibit labor. Intravenous magnesium sulfate, given as a 4-g loading dose and followed by a continuous infusion of 2 g/hr, usually arrests labor (Steer, 1977). Like β-mimetic agents, magnesium treatment can cause pulmonary edema (Samol, 2005). However, this has not been our experience at Parkland Hospital in the treatment of tens of thousands of preeclamptic women with intravenous magnesium sulfate. Pharmacology and toxicology of magnesium are considered in more detail in Chapter 40 (Pharmacology and Toxicology).

Only two randomized studies have evaluated tocolysis with magnesium sulfate. Cotton and colleagues (1984) compared magnesium sulfate, ritodrine, and placebo in 54 women with preterm labor. They identified few differences in outcomes. Cox and coworkers (1990) randomly assigned 156 women to receive magnesium sulfate or infusions of normal saline. Magnesium-treated women and their neonates had identical outcomes compared with those given placebo. Because of these findings, this method of tocolysis was abandoned at Parkland Hospital. Similarly, Crowther and associates (2014) reviewed magnesium sulfate as a tocolytic agent and concluded it was ineffective and potentially harmful. Last, the FDA (2013) has warned against prolonged use of magnesium sulfate given to arrest preterm labor because of bone thinning and fractures in fetuses exposed for more than 5 to 7 days. This was attributed to low calcium levels in the fetus.

Prostaglandin Inhibitors

These compounds are intimately involved in contractions of normal labor (Chap. 21, Uterotonins in Parturition Phase 3). Antagonists act by inhibiting prostaglandin synthesis or by blocking their action on target organs. A group of enzymes collectively termed *prostaglandin synthase* is responsible for the conversion of free arachidonic acid to prostaglandins. Several drugs block this system, including acetylsalicylate and indomethacin.

Indomethacin, a nonselective cyclooxygenase inhibitor, was first used as a tocolytic in one study of 50 women (Zuckerman, 1974). Studies that followed reported the efficacy of indomethacin in halting contractions and delaying preterm birth (Muench, 2003; Niebyl, 1980). Morales and coworkers (1989, 1993a), however, compared indomethacin with either ritodrine or magnesium sulfate and found no difference in their efficacy to forestall preterm delivery. Berghella and associates (2006) reviewed four trials of indomethacin given to women with a sonographically determined short cervix and found such therapy to be ineffective.

Indomethacin is administered orally or rectally. Most studies have limited indomethacin use to 24 to 48 hours because of concerns for oligohydramnios, which can develop with therapeutic doses. If amnionic fluid is monitored, oligohydramnios can be detected early, and it is reversible with drug discontinuation.

In a study of neonates born before 30 weeks, Norton and coworkers (1993) identified necrotizing enterocolitis in 30 percent of 37 indomethacin-exposed newborns compared with 8 percent of 37 control newborns. Higher incidences of intraventricular hemorrhage and patent ductus arteriosus were also documented in the indomethacin group. Several investigators have challenged the association between indomethacin exposure and necrotizing enterocolitis (Muench, 2001; Parilla, 2000). Similarly, Gardner (1996) and Abbasi (2003) and their colleagues found no link between indomethacin use and intraventricular hemorrhage, patent ductus arteriosus, sepsis, necrotizing enterocolitis, or neonatal death. Two metaanalyses

of the effects of antenatal indomethacin on neonatal outcomes had conflicting findings (Amin, 2007; Loe, 2005). Reinebrant and colleagues (2015) in a review of 20 studies reported no clear benefit from cyclooxygenase inhibitors, including indomethacin, compared with placebo or any other tocolytic agent.

Nitric Oxide Donors

These potent smooth-muscle relaxants affect the vasculature, gut, and uterus. In randomized clinical trials, nitroglycerin administered orally, transdermally, or intravenously was ineffective or showed no superiority over other tocolytics. In addition, maternal hypotension was a common side effect (Bisits, 2004; El-Sayed, 1999; Lees, 1999).

Calcium-Channel Blockers

Discussed in Chapter 21 (Actin-Myosin Interactions), myometrial activity is directly related to cytoplasmic free calcium, and reduced calcium concentrations inhibit contractions. Calcium-channel blockers act to inhibit, by various mechanisms, calcium entry through cell membrane channels. Although they were developed to treat hypertension, their ability to arrest preterm labor has been evaluated.

From study results, calcium-channel blockers, especially nifedipine, are safer and more effective tocolytic agents than β-agonist drugs (King, 2003; Papatsonis, 1997). Lyell and colleagues (2007) randomized 192 women at 24 to 33 weeks' gestation to either magnesium sulfate or nifedipine and found no substantial differences in efficacy or adverse effects. In another randomized study, 145 women with preterm labor between 24 and 33 weeks received nifedipine or atosiban. Neither proved superior to delay delivery, and neonatal morbidity was equivalent (Salim, 2012).

Flenady and coworkers (2014b) reviewed 38 trials of calcium- channel blockers (mainly nifedipine) for preterm labor. These investigators suggested that calcium-channel blockers have benefits compared with placebo or no treatment. But, this conclusion stemmed from a trial with unclear risk of selection bias and a three-arm study of 84 women that was not blinded (Ara, 2008; Zhang, 2002). We are currently performing a randomized, double-blind, placebo-controlled trial of nifedipine for acute tocolysis of preterm labor at Parkland Hospital.

Importantly, the combination of nifedipine with magnesium for tocolysis is potentially dangerous. Ben-Ami (1994) and Kurtzman (1993) and their coworkers reported that nifedipine enhances the neuromuscular blocking effects of magnesium, which can interfere with pulmonary and cardiac function. In one small study of 54 women with preterm labor who received either magnesium sulfate plus nifedipine or no tocolytic, neither benefit nor harm was found (How, 2006).

Atosiban

This nonapeptide oxytocin analogue is an oxytocin-receptor antagonist (ORA). Goodwin and colleagues (1995) described its pharmacokinetics in pregnant women. In randomized clinical trials, atosiban failed to improve relevant neonatal outcomes and was linked with significant neonatal morbidity (Moutquin, 2000; Romero, 2000). The FDA has denied approval of atosiban because of concerns regarding efficacy and fetal–newborn safety. Further, in 2014, a metaanalysis did not demonstrate superiority of ORAs (largely atosiban) as a tocolytic compared with placebo, β-mimetic drugs, or calcium-channel blockers in terms of pregnancy prolongation or neonatal outcomes. But, ORAs were associated with fewer maternal adverse effects (Flenady, 2014a). Recently, van Vliet and coworkers (2016) conducted a randomized trial comparing nifedipine with atosiban in 510 women with threatened preterm birth. Using a composite of adverse perinatal outcomes, no differences were reported between the two study groups.

Labor

Whether preterm labor is induced or spontaneous, abnormalities of fetal heart rate and uterine contractions are sought. We prefer continuous electronic monitoring. Fetal tachycardia, especially with ruptured membranes, is suggestive of sepsis. Some evidence supports that intrapartum acidemia may intensify some of the neonatal complications usually attributed to preterm delivery. For example, Morgan and associates (2017) found that metabolic acidemia significantly raised the risks related to prematurity in neonates delivered prior to 34 weeks' gestation. Low and colleagues (1995) observed that intrapartum acidosis—umbilical artery blood pH <7.0—had an important role in neonatal complications (Chap. 33, Neonatal Encephalopathy). Group B streptococcal infections are common and dangerous in the preterm neonate, and antimicrobial prophylaxis should be provided (Chap. 64, Methicillin-Resistant Staphylococcus aureus).

Delivery

In the absence of a relaxed vaginal outlet, an episiotomy for delivery may be necessary once the fetal head reaches the perineum. Perinatal outcome data do not support routine episiotomy or forceps delivery to protect the "fragile" preterm fetal head. Staff proficient in resuscitative techniques commensurate with the gestational age and fully oriented to any specific problems should be present at delivery. Principles of resuscitation described in Chapter 32 (Resuscitation Protocol) are applicable. The importance of specialized personnel and facilities for preterm newborn care is underscored by the improved survival rates of these neonates when delivered in tertiary-care centers.

Prevention of Intracranial Hemorrhage

Preterm newborns frequently have intracranial germinal matrix bleeding that can extend to more serious intraventricular hemorrhage (Chap. 34, Retinopathy of Prematurity). It was hypothesized that cesarean delivery to obviate trauma from labor and vaginal delivery might prevent these complications. This has not been validated by subsequent studies. Malloy (1991) analyzed 1765 newborns with birthweights <1500 g and found that cesarean delivery did not lower the risk of mortality or intracranial hemorrhage. Anderson and colleagues (1988), however, made an interesting observation regarding the role of cesarean delivery in intracranial hemorrhage prevention. These hemorrhages correlated with exposure to active-phase labor. However, they emphasized that avoidance of active-phase labor is impossible in most preterm births because decisions for delivery route are not required until active labor is firmly established.

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CHAPTER 43: Postterm Pregnancy

It must be admitted that the duration of pregnancy not infrequently exceeds 280 days from the last menstrual period, and that when it lasts much longer large children are developed, which are frequently delivered only after great difficulty. Thus, whenever the menstrual history of the patient indicates that she has passed much beyond the tenth and is approaching the eleventh lunar month, we should consider the propriety of the induction of labour, provided that examination shows the child is larger than usual.

—J. Whitridge Williams (1903)

INTRODUCTION

The above passage from Williams shows that pregnancies exceeding the expected normal length were problematic more than 100 years ago. These postterm pregnancies remain so today.

The adjectives *postterm, prolonged, postdates*, and *postmature* are often loosely used interchangeably to describe pregnancies that have exceeded a duration considered to be the upper limit of normal. We eschew use of the term *postdates* because the real issue in many postterm pregnancies is "post-*what* dates?" *Postmature* is reserved for the relatively uncommon specific clinical fetal syndrome in which the newborn has recognizable features indicating a pathologically prolonged pregnancy. Therefore, *postterm* or *prolonged pregnancy* is our preferred expression for an extended pregnancy.

The international definition of prolonged pregnancy, endorsed by the American College of Obstetricians and Gynecologists (2016b,d) is one that exceeds $42^{0/7}$ weeks, namely, 294 days or more from the first day of the last menstrual period. Importantly, this is 42 "completed weeks," as pregnancies between 41 weeks 1 day and 41 weeks 6 days, although in the 42nd week, do not complete 42 weeks until the seventh day has elapsed. The method that we use widely in this book is to divide the 42nd week into 7 days, that is, $42^{0/7}$ through $42^{6/7}$ weeks.

ESTIMATED GESTATIONAL AGE

The current definition of postterm pregnancy assumes that the last menses was followed by ovulation 2 weeks later. That said, some pregnancies may not actually be postterm. Instead, the calculation may reflect an error in gestational age estimation because of faulty menstrual date recall or delayed ovulation. Thus, the two categories of pregnancies that reach 42 completed weeks are those truly 40 weeks past conception and those of less-advanced gestation but with inaccurately estimated gestational age. Even with exactly recalled menstrual dates, there still is imprecision, and the American College of Obstetricians and Gynecologists (2016d, 2017b) considers first-trimester sonography to be the most accurate method to establish or confirm gestational age. Several clinical studies support this practice (Bennett, 2004; Blondel, 2002; Joseph, 2007).

INCIDENCE

Of the 3.93 million neonates born in the United States during 2015, 0.4 percent were delivered at 42 weeks or later (Martin, 2017). In the past, the proportion was much higher. This trend suggests earlier intervention, however, the added accuracy from earlier sonographic dating of gestational age is another factor.

To identify potential predisposing factors for postterm pregnancy, Olesen and associates (2006) analyzed various characteristics in the Danish Birth Cohort. Only prepregnancy body mass index (BMI) ≥25 and nulliparity were significantly associated with prolonged pregnancy. Mission (2015) and Arrowsmith (2011) and their coworkers also reported similar associations. In nulliparas, those whose cervical length at midpregnancy is longer, that is, in the third or fourth quartile, are twice as likely to deliver after 42 weeks (van der Ven, 2016).

The tendency for some mothers to have repeated postterm births suggests that some prolonged pregnancies are biologically determined. Oberg and colleagues (2013) reported that when mother and daughter had a prolonged pregnancy, the risk for the daughter to have a subsequent postterm pregnancy was significantly increased. Laursen and associates (2004) found that maternal, but not paternal, genes influenced prolonged pregnancy. As discussed in Chapter 5 (Placental Estriol Synthesis), rare fetal-placental factors that predispose to postterm pregnancy include anencephaly, adrenal hypoplasia, and X-linked placental sulfatase deficiency (Ayyavoo, 2014; MacDonald, 1965).

PERINATAL MORTALITY AND MORBIDITY

Rates of stillbirth, neonatal death, and infant morbidity all rise after the expected due date has passed. This is best seen when perinatal mortality rates are analyzed from times before widespread intervention for postterm pregnancies. In two large Swedish studies shown in Figure 43-1, after reaching a nadir at 39 to 40 weeks, the perinatal mortality rate rose as pregnancy duration exceeded 41 weeks. This trend is also reported for the United States (Cheng, 2008; MacDorman, 2009). As shown in Table 43-1, the major cause of death in these studies includes gestational hypertension, prolonged labor with cephalopelvic disproportion, birth injuries, and hypoxic-ischemic encephalopathy. Similar outcomes were reported by Olesen and colleagues (2003) in 78,022 women with postterm pregnancies delivered before routine labor induction was adopted in Denmark. Moster and associates (2010) found higher rates of cerebral palsy in postterm births, and Yang and coworkers (2010) reported lower intelligence quotient (IQ) scores at age 6.5 years in children born ≥42 weeks' gestation. Conversely, autism was not associated with postterm birth (Gardener, 2011).

TABLE 43-1

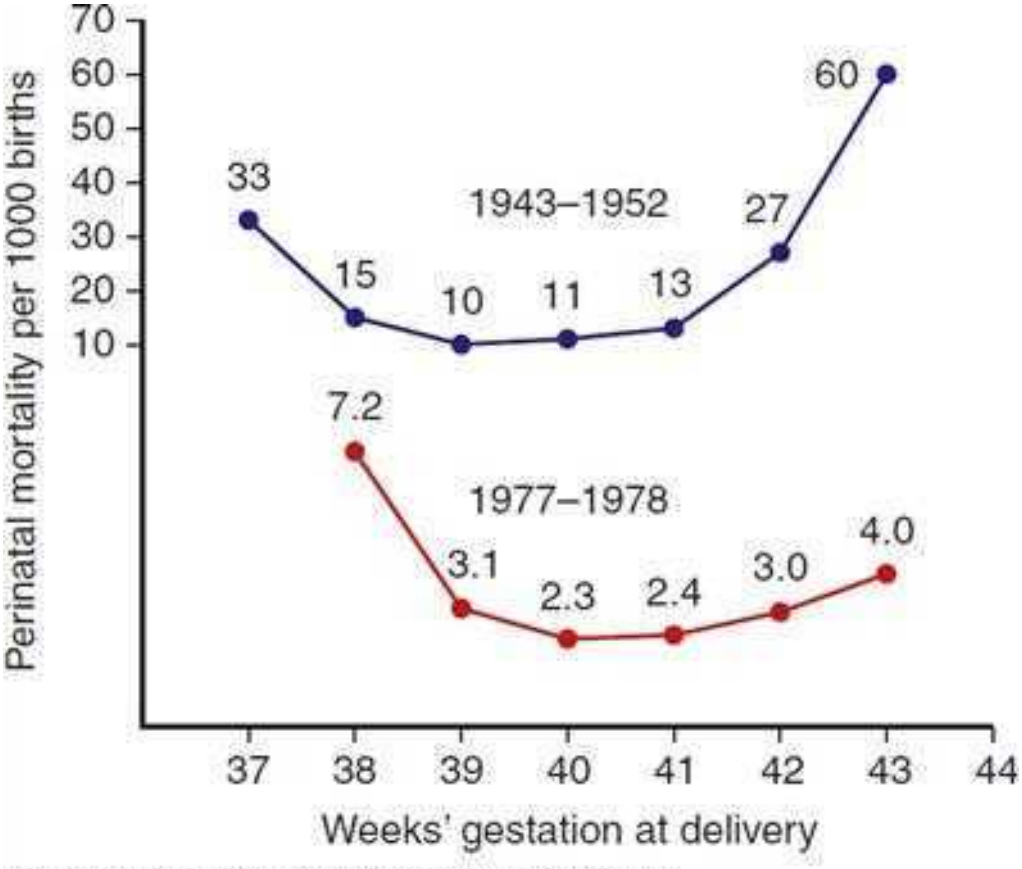
Adverse Maternal and Perinatal Outcomes Associated with Postterm Pregnancy

Maternal	Perinatal
Fetal macrosomia	Stillbirth
Oligohydramnios	Postmaturity syndrome
Preeclampsia	NICU admission
Cesarean delivery	Meconium aspiration
Dystocia	Neonatal convulsions
Fetal jeopardy	Hypoxic-ischemic encephalopathy
Shoulder dystocia	Birth injuries
Postpartum hemorrhage	Childhood obesity
Perineal lacerations	

NICU = neonatal intensive care unit.

FIGURE 43-1

Perinatal mortality rates in late pregnancy according to gestational age of all births in Sweden during 1943–1952 compared with those during 1977–1978. The partially compressed scale is used for convenience in depiction. (Adapted from Bakketeig, 1991; Lindell, 1956.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Alexander and colleagues (2000a) reviewed 56,317 consecutive singleton pregnancies delivered at ≥40 weeks between 1988 and 1998 at Parkland Hospital. Labor was induced in 35 percent of pregnancies completing 42 weeks. The rate of cesarean delivery for dystocia and fetal distress was significantly greater at 42 weeks compared with earlier deliveries. More newborns of postterm pregnancies were admitted to intensive care units. Importantly, the incidence of neonatal seizures and deaths was doubled at 42 weeks. Smith (2001) has challenged analyses such as these because the population at risk for perinatal mortality in a given week consists of all ongoing pregnancies rather than just the births in a given week. He calculated perinatal mortality rates calculated using only births in a given week of gestation from 37 to 43 completed weeks compared with the cumulative probability—the perinatal index—of death when all ongoing pregnancies are included in the denominator. Using this computation, delivery at 38 weeks had the lowest risk index for perinatal death.

PATHOPHYSIOLOGY

Postmaturity Syndrome

The postmature newborn is unique, and features include wrinkled, patchy, peeling skin; a long, thin body suggesting wasting; and advanced maturity in that the infant is open-eyed, unusually alert, and appears old and worried (Fig. 43-2). Skin wrinkling can be particularly prominent on the palms and soles. The nails are typically long. Most postmature neonates are not technically growth restricted because their birthweight seldom falls below the 10th percentile for gestational age (Chap. 44, Fetal-Growth Restriction). On the other hand, severe growth restriction—which logically must have preceded completion of 42 weeks—may be present.

FIGURE 43-2
Postmaturity syndrome. Neonate delivered at 43 weeks' gestation with thick, viscous meconium coating the desquamating skin. Note the long, thin appearance and wrinkling of the hands.

The incidence of postmaturity syndrome in newborns at 41, 42, or 43 weeks, respectively, has not been conclusively determined. From data, the syndrome complicates 10 to 20 percent of pregnancies at 42 completed weeks (American College of Obstetricians and Gynecologists, 2016d). Associated oligohydramnios substantially raises the likelihood of postmaturity. Trimmer and associates (1990) reported that 88 percent of fetuses were postmature if there was oligohydramnios defined by a sonographic maximal vertical amnionic fluid pocket that measured ≤1 cm at 42 weeks.

Placental Dysfunction

Many believe that postterm pregnancy is an abnormal state. Redman and Staff (2015) posit that limited placental capacity, which is characterized by dysfunctional syncytiotrophoblast, explains the greater risks of the postmaturity syndrome.

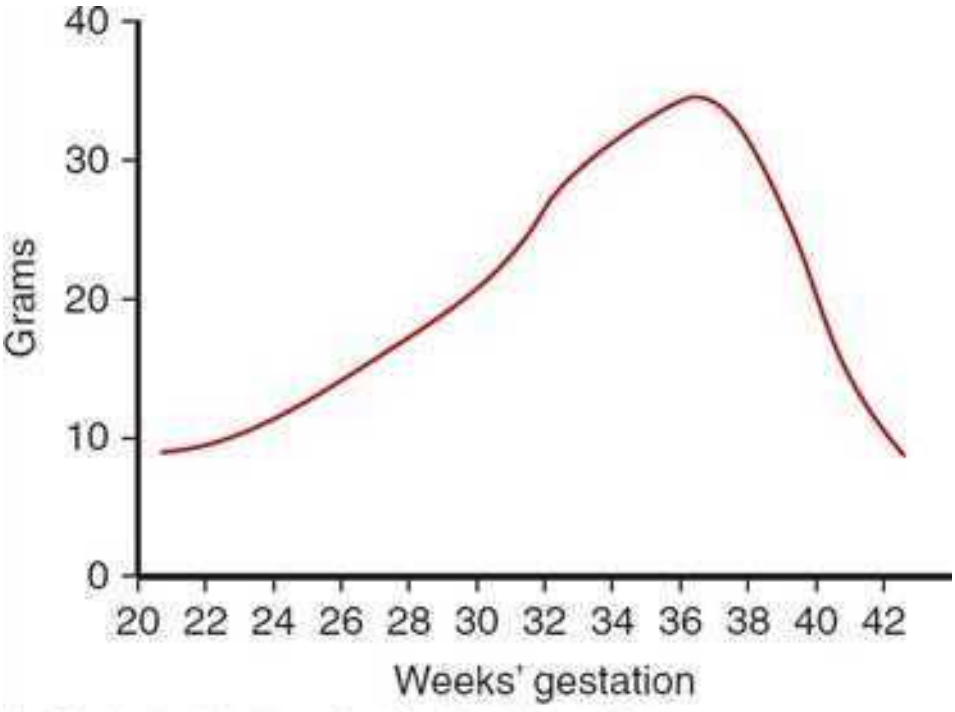
Clifford (1954) proposed that the associated skin changes were due to loss of the protective effects of vernix caseosa. He also attributed the postmaturity syndrome to placental senescence, although he did not find placental degeneration histologically. Still, the concept that postmaturity stems from placental insufficiency has persisted despite an absence of morphological or significant quantitative findings (Larsen, 1995; Redman, 2015; Rushton, 1991). There are findings that the rate of placental apoptosis—programmed cell death—is significantly greater at 41 to 42 completed weeks compared with that at 36 to 39 weeks (Smith, 1999). Several proapoptotic genes such as *kisspeptin* are upregulated in postterm placental explants compared with the same genes in term placental explants (Torricelli, 2012). The clinical significance of such apoptosis is currently unclear.

Jazayeri and coworkers (1998) investigated cord blood erythropoietin levels in 124 appropriately grown newborns delivered from 37 to 43 weeks. The only known stimulator of erythropoietin is decreased partial oxygen pressure. Thus, they sought to assess whether fetal oxygenation was compromised due to placental aging in postterm pregnancies. All women had an uncomplicated labor and delivery. These investigators found that cord blood erythropoietin levels were significantly higher in pregnancies reaching 41 weeks or more. Although Apgar scores and acid-base studies were normal, these researchers concluded that fetal oxygenation was decreased in some postterm gestations.

Another scenario is that the postterm fetus may continue to gain weight and thus be unusually large at birth. This at least suggests that placental function is not severely compromised. Indeed, continued fetal growth is the norm—albeit at a slower rate beginning at 37 completed weeks (Fig. 43-3). Nahum and colleagues (1995) confirmed that fetal growth continues until at least 42 weeks. However, Link and associates (2007) showed that umbilical blood flow did not increase concomitantly.

FIGURE 43-3

Mean daily fetal growth during previous week of gestation. (Redrawn from Hendricks CH: Patterns of fetal and placental growth: the second half of pregnancy. Obstet Gynecol 24:357, 1964.)



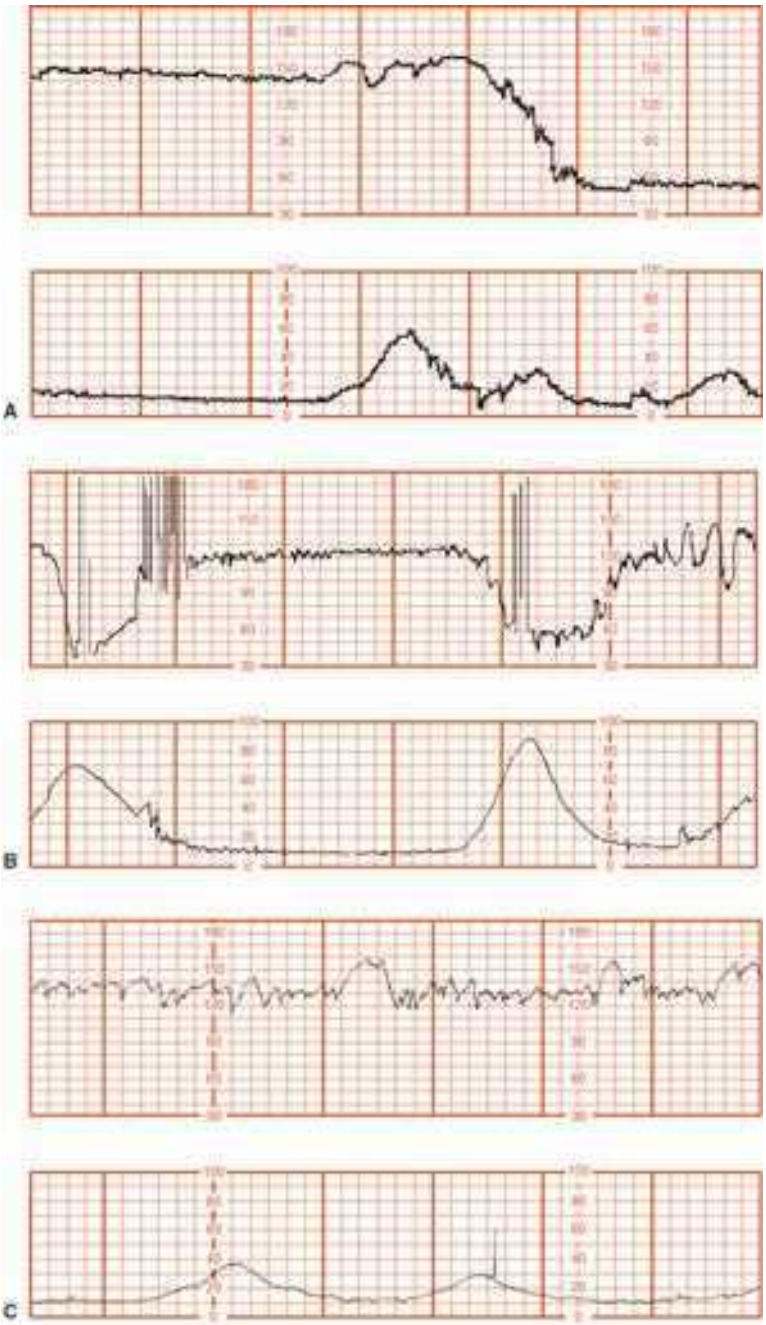
Fetal Distress and Oligohydramnios

The principal reasons for increased risks to postterm fetuses were described by Leveno and associates (1984). Both antepartum fetal jeopardy and intrapartum fetal distress were found to be the consequence of cord compression associated with oligohydramnios. In their analysis of 727 postterm pregnancies, intrapartum fetal distress detected with electronic monitoring was not associated with late decelerations characteristic of uteroplacental insufficiency. Instead, one or more prolonged decelerations such as shown in Figure 43-4 preceded three fourths of emergency cesarean deliveries for nonreassuring fetal heart rate tracings. In all but two cases, there were also variable decelerations. Another common fetal heart rate pattern, although not ominous by itself, was the saltatory baseline. As described in Chapter 24 (Prolonged Deceleration), these findings are consistent with cord occlusion as the proximate cause of the nonreassuring tracings. Other correlates included oligohydramnios and viscous meconium. Schaffer and

colleagues (2005) implicated a nuchal cord in abnormal intrapartum fetal heart rate patterns, meconium, and compromised newborn condition in prolonged pregnancies.

FIGURE 43-4

A. Prolonged fetal heart rate deceleration before emergency cesarean delivery in a postterm pregnancy with oligohydramnios. **B.** Severe—less than 70 bpm for 60 seconds or longer—variable decelerations in a postterm pregnancy with oligohydramnios. **C.** Saltatory baseline fetal heart rate showing oscillations exceeding 20 bpm and associated with oligohydramnios in a postterm pregnancy. (Reproduced with permission from Leveno KJ, Quirk JG, Cunningham FG, et al: Prolonged pregnancy, I. Observations concerning the causes of fetal distress, Am J Obstet Gynecol. 1984 Nov 1;150(5 Pt 1):465–473.)



The volume of amnionic fluid normally continues to decline after 38 weeks and may become problematic. Moreover, meconium release into an already reduced amnionic fluid volume results in thick, viscous meconium that may cause *meconium aspiration syndrome* (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy).

Trimmer and coworkers (1990) sonographically measured hourly fetal urine production using sequential bladder volume measurements in 38 postterm pregnancies. Diminished urine production was found to be associated with oligohydramnios. They hypothesized that decreased fetal urine flow was likely the result of preexisting oligohydramnios that limited fetal swallowing. Oz and associates (2002), using Doppler waveforms, concluded

that fetal renal blood flow is reduced in those postterm pregnancies complicated by oligohydramnios. As a possible cause, again, the study by Link and associates (2007) showed that umbilical blood flow did not increase past term.

Fetal-Growth Restriction

In the late 1990s, the clinical significance of fetal-growth restriction in the otherwise uncomplicated pregnancy became more fully appreciated. Divon (1998) and Clausson (1999) and their coworkers analyzed births between 1991 and 1995 in the National Swedish Medical Birth Registry. Stillbirths were more common among growth-restricted newborns who were delivered after 42 weeks. Indeed, a third of postterm stillborn neonates were growth restricted. During this time in Sweden, labor induction and antenatal fetal testing usually commenced at 42 weeks. In a study from Parkland Hospital, Alexander and colleagues (2000d) analyzed outcomes for 355 neonates from pregnancies ≥42 weeks and whose birthweights were <3rd percentile. They compared these with outcomes of 14,520 similarly aged newborns above the 3rd percentile and found that morbidity and mortality rates were significantly increased in the growth-restricted neonates. Notably, a fourth of all stillbirths associated with prolonged pregnancy were in this comparatively small number of growth-restricted fetuses.

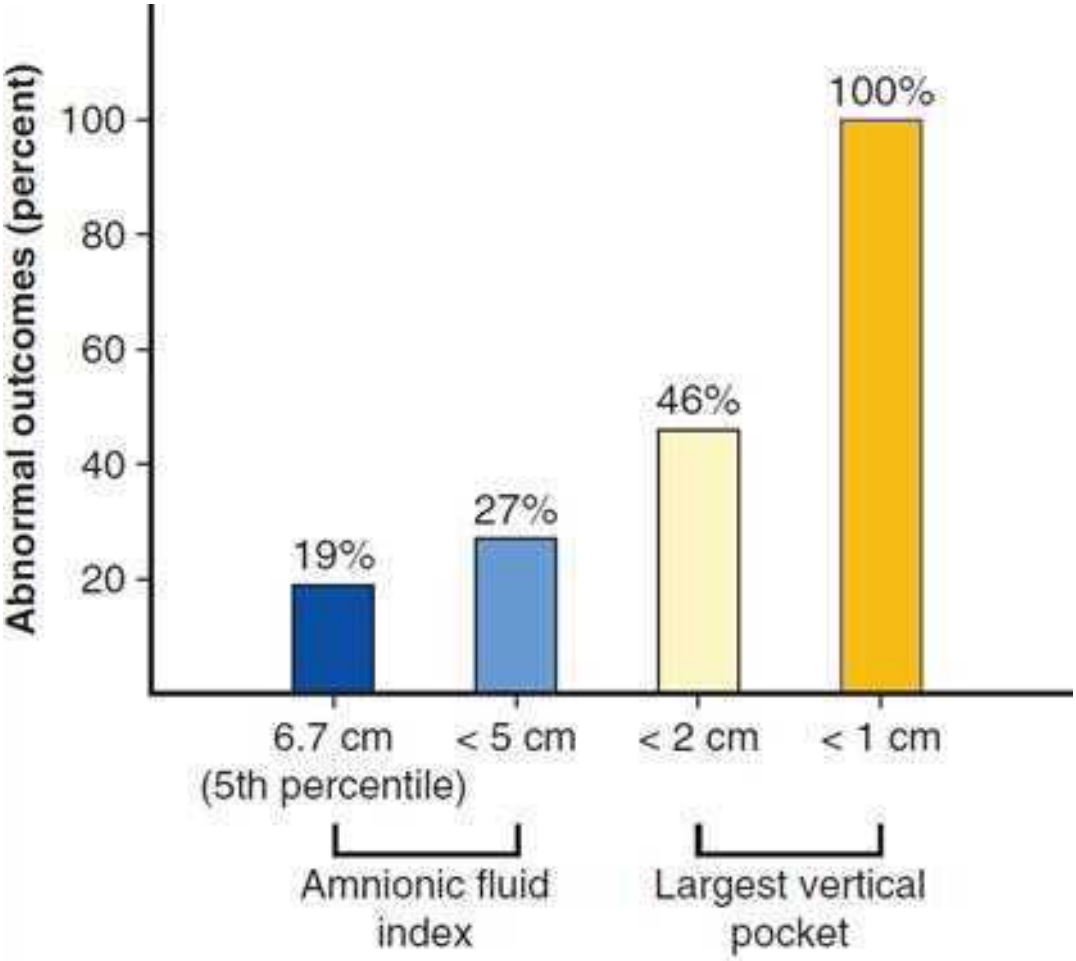
COMPLICATIONS

In the event of a medical or other obstetrical complication, it is generally not recommended that a pregnancy be allowed to continue past 42 weeks. Indeed, in many such instances, *earlier* delivery is indicated. Common examples include gestational hypertensive disorders, prior cesarean delivery, and diabetes. Other clinically important factors include amnionic fluid volume and potential fetal macrosomia.

Oligohydramnios

Most clinical studies support the view that diminished amnionic fluid determined by various sonographic methods identifies a postterm fetus with increased risks. Indeed, decreased amnionic fluid in any pregnancy signifies increased fetal risk (Chap. 11, Pregnancy Outcomes). Unfortunately, lack of an exact method to define “decreased amnionic fluid” has limited investigators, and many different criteria for sonographic diagnosis have been proposed. Fischer and colleagues (1993) attempted to determine which criteria were most predictive of normal versus abnormal outcomes in postterm pregnancies. As shown in Figure 43-5, the smaller the amnionic fluid pocket, the greater the likelihood that there was clinically significant oligohydramnios. Importantly, normal amnionic fluid volume did not preclude abnormal outcomes. Alfirevic and coworkers (1997) randomly assigned 500 women with postterm pregnancies to assessment using either the amnionic fluid index (AFI) or the deepest vertical pocket described in Chapter 11 (Measurement). They concluded that the AFI overestimated the number of abnormal outcomes in postterm pregnancies.

FIGURE 43-5
Comparison of the prognostic value of various sonographic estimates of amnionic fluid volume in prolonged pregnancies. Abnormal outcomes include cesarean or operative vaginal delivery for fetal jeopardy, 5-minute Apgar score ≤6, umbilical arterial blood pH <7.1, or admission to the neonatal intensive care unit. (Redrawn from Fischer RL, McDonnell M, Bianculli KW, et al: Amniotic fluid volume estimation in the postdate pregnancy: a comparison of techniques. Obstet Gynecol 81:698, 1993.)



Regardless of the criteria used to diagnose oligohydramnios in postterm pregnancies, most investigators have found a higher incidence of some measure of "fetal distress" during labor. Thus, oligohydramnios by most definitions is a clinically meaningful finding. Conversely, reassurance of continued fetal well-being in the presence of "normal" amnionic fluid volume is tenuous. This may be related to how quickly pathological oligohydramnios develops. Although such cases are unusual, Clement and coworkers (1987) described six postterm pregnancies in which amnionic fluid volume diminished abruptly over 24 hours, and in one of these, the fetus died.

Macrosomia

The velocity of fetal weight gain peaks at approximately 37 weeks (see Fig. 43-3). Although growth velocity slows at that time, most fetuses continue to gain weight. For example, the percentage of fetuses born in 2009 whose birthweight exceeded 4000 g was 8.2 percent at 37 to 41 weeks and increased to 11.0 percent at 42 weeks or more (Martin, 2011). According to Duryea and associates (2014), the 95th percentile at 42 weeks is 4475 g. Even so, in some studies, brachial plexus injury was not related to postterm gestation (Walsh, 2011). Intuitively, it seems that both maternal and fetal morbidity associated with macrosomia would be mitigated with timely induction to preempt further growth. This, however, does not appear to be the case. The American College of Obstetricians and Gynecologists (2016c) has concluded that current evidence does not support such a practice in women at term with suspected fetal macrosomia. Moreover, the College concluded that in the absence of diabetes, vaginal delivery is not contraindicated for women with an estimated fetal weight up to 5000 g (Chap. 27, Shoulder Dystocia). Obvious problems with all such recommendations are substantive variations in fetal weight estimation.

ANTEPARTUM MANAGEMENT

Although some intervention is indicated for prolonged pregnancies, the method and timing of this are not unanimous. The decision focuses on whether labor induction is warranted or if expectant management with fetal surveillance is best. In a survey done more than 10 years ago, Cleary-Goldman and associates (2006) reported that 73 percent of members of the American College of Obstetricians and Gynecologists routinely induced women at 41 weeks. Most of the remainder performed twice weekly fetal testing until 42 weeks.

Induction Factors

Although all obstetricians know what an “unfavorable cervix” is, the term unfortunately defies precise objective definition. Thus, investigators have used differing criteria for studies of prolonged pregnancies. Harris and coworkers (1983) defined an unfavorable cervix by a Bishop score <7 and reported this in 92 percent of women at 42 weeks (Chap. 26, Preinduction Cervical Ripening). Hannah and colleagues (1992) found that 40 percent of 3407 women with a 41-week pregnancy had an “undilated cervix.” In a study of 800 women undergoing induction for postterm pregnancy at Parkland Hospital, Alexander and associates (2000b) reported that women in whom there was no cervical dilation had a twofold higher cesarean delivery rate for “dystocia.” Yang and coworkers (2004) found that cervical length ≤3 cm measured with transvaginal sonography was predictive of successful induction. In a similar study, Vankayalapati and associates (2008) found that cervical length ≤25 mm was predictive of spontaneous labor or successful induction.

Several investigators have evaluated prostaglandin E_2 (PGE_2) and E_1 (PGE_1) for induction in women with an unfavorable cervix and prolonged pregnancies. A study by the Maternal–Fetal Medicine Units Network (1994) found that PGE_2 gel was not more effective than placebo. Alexander and associates (2000c) treated 393 women with a postterm pregnancy with PGE_2, regardless of cervical “favorability,” and reported that almost half of the 84 women with cervical dilatation of 2 to 4 cm entered labor with PGE_2 use alone. In another study, mifepristone was reported to increase uterine activity without uterotonic agents in women beyond 41 weeks (Fasset, 2008). Prostaglandins and other agents used for cervical ripening are discussed in Chapter 26 (Pharmacological Techniques).

Sweeping or stripping of the membranes to induce labor and thereby prevent postterm pregnancy was studied in 15 randomized trials during the 1990s. Boulvain and coworkers (2005) performed a metaanalysis of these and found that membrane stripping at 38 to 40 weeks lowered the frequency of postterm pregnancy. Although maternal and neonatal infection rates were not increased, this practice did not modify the cesarean delivery rate. Since then, randomized trials by Wong (2002), Kashanian (2006), Hill (2008), and their coworkers found that sweeping membranes did not reduce the need to induce labor. Drawbacks of membrane stripping included pain, vaginal bleeding, and irregular contractions without labor.

The station of the fetal head within the pelvis is another predictor of successful postterm pregnancy induction. Shin and colleagues (2004) studied 484 nulliparas who underwent induction after 41 weeks. The cesarean delivery rate was directly related to station. The rate was 6 percent if the vertex before induction was at −1 station; 20 percent at −2 station; 43 percent at −3 station; and 77 percent at −4 station.

Induction versus Fetal Testing

Because of the marginal benefits from induction with an unfavorable cervix, as just discussed, some clinicians prefer instead to implement a strategy of fetal testing beginning at 41 completed weeks. For example, in a Canadian study, 3407 women were randomly assigned at 41 or more weeks to induction or to fetal testing (Hannah, 1992). In the surveillance group, evaluation included: (1) counting fetal movements during a 2-hour period each day, (2) nonstress testing three times weekly, and (3) amnionic fluid volume assessment two to three times weekly, with pockets <3 cm considered abnormal. Labor induction resulted in a small but significant reduction in the cesarean delivery rate compared with fetal testing—21 versus 24 percent, respectively. This difference was due to fewer procedures for fetal distress. There were only two stillbirths in the fetal testing group.

The Maternal–Fetal Medicine Network performed a randomized trial of induction versus fetal testing beginning at 41 weeks (Gardner, 1996). Fetal surveillance included nonstress testing and sonographic estimation of amnionic fluid volume performed twice weekly in 175 women. Perinatal outcomes were compared with those of 265 women also at 41 weeks randomly assigned to induction with or without cervical ripening. There were no perinatal deaths, and the cesarean delivery rate was not different between management groups. The results of this study could be used to support the validity of either management scheme.

In an analysis of 22 trials, Gulmezoglu and colleagues (2012) found that induction after 41 weeks rather than surveillance was associated with significantly fewer perinatal deaths and meconium aspiration syndrome cases and a lower cesarean delivery rate. In a review of two metaanalyses and a randomized study, similar conclusions were reached (Mozurkewich, 2009).

In most studies, labor induction at $42^{0/7}$ weeks has a higher cesarean delivery rate compared with spontaneous labor. From Parkland Hospital, Alexander and coworkers (2001) evaluated pregnancy outcomes in 638 such women in whom labor was induced and compared them with outcomes of 687 women with postterm pregnancies who had spontaneous labor. Cesarean delivery rates were significantly increased—19 versus 14 percent—in the induced group because of failure to progress. When these investigators corrected for risk factors, however, they concluded that intrinsic maternal factors, rather than the induction itself, led to the higher rate. These factors included nulliparity, an unfavorable cervix, and epidural analgesia.

A large study from Denmark by Zizzo and associates (2017) is also instructive. In 2011, the Danish national guidelines were changed from labor induction at $42^{0/7}$ weeks with no fetal surveillance to labor induction at $41^{2/7}$ to $41^{6/7}$ weeks with fetal surveillance beginning at $41^{0/7}$ weeks. They compared two 3-year epochs—one before and one after 2011—and the results are shown in Table 43-2. The rate of pregnancies that progressed past $42^{0/7}$ weeks decreased from 2.85 to 0.62 percent. Concurrently, as expected, the induction rate rose significantly, and this was accompanied by a drop in the perinatal mortality rate—22 to 13 per 1000 births. The cesarean delivery rate was not changed. A similar before-and-after observational study reported that induction at ≥42 weeks was associated with a significantly lower cesarean delivery rate—15 versus 19.4 percent (Bleicher, 2017).

TABLE 43-2

National Death Cohort Study of 102,167 Pregnancies that Reached $41^{0/7}$ Weeks' Gestation

Factor	2008–2010[a]	2012–2014	*p* value
EGA >$42^{0/7}$	2.85%	0.62%	
Stillbirths	9/1000	5/1000	0.018
Neonatal deaths	13/1000	8/1000	.033
Cesarean delivery	15%	15%	NS
Vacuum delivery	11.3%	10.2%	<0.001
Induction	28%	43%	<0.001

[a]National guidelines changed between epochs as described in text.

NS = not significant.

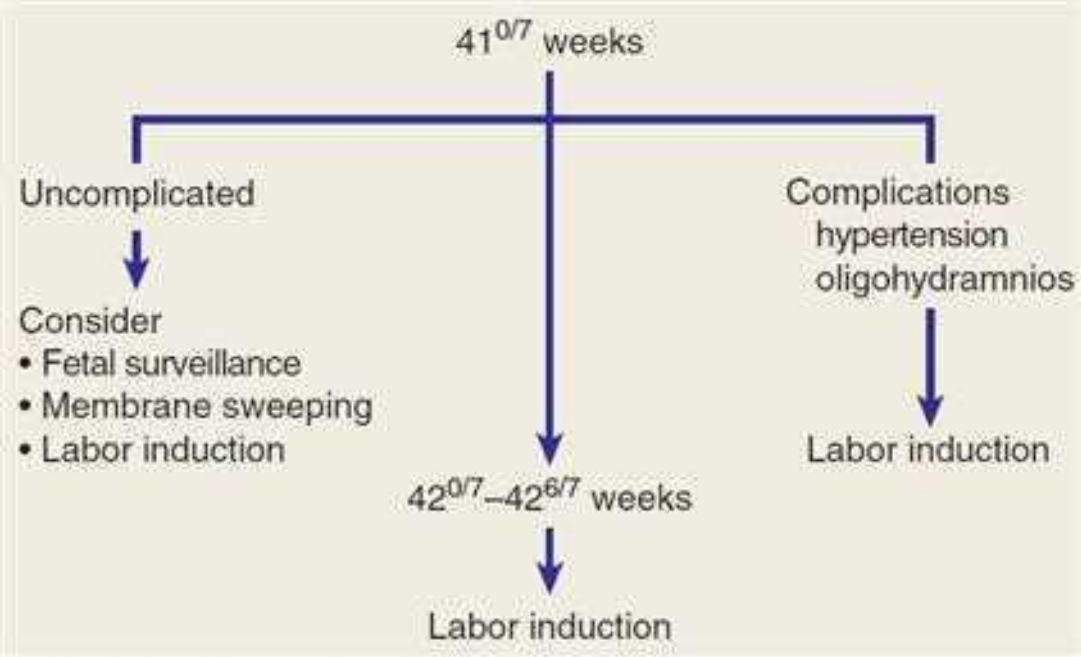
Data from Zizzo, 2017.

From the foregoing, evidence to substantiate intervention—whether induction or fetal testing—commencing at 41 versus 42 weeks is limited. Most evidence used to justify intervention at 41 weeks is from the randomized Canadian and American investigations cited earlier. No randomized studies have specifically assessed intervention at 41 weeks versus an identical intervention used at 42 weeks. A large Swedish multicenter randomized trial of more than 10,000 women at $41^{0/7}$ weeks has been designed to address the question (Elden, 2016).

Management Strategies

The American College of Obstetricians and Gynecologists (2016a) defines postterm pregnancies as having completed 42 weeks, namely, beyond $42^{0/7}$ weeks. There is insufficient evidence to mandate a management strategy between 40 and 42 completed weeks. Thus, although not considered mandatory, initiation of fetal surveillance at 41 weeks is a reasonable option. After completing 42 weeks, recommendations are for labor induction as summarized in Figure 43-6.

FIGURE 43-6
Algorithm for management of postterm pregnancy. (Summarized from American College of Obstetricians and Gynecologists, 2016d.)



When gestational age is uncertain, the American College of Obstetricians and Gynecologists (2017b) recommends delivery at 41 weeks' gestation using the best clinical estimate of gestational age. The College also recommends against amniocentesis for fetal lung maturity.

At Parkland Hospital, based on results from the trials just discussed, we consider 41-week pregnancies without other complications to be normal. Thus, no interventions are practiced solely based on fetal age until 42 completed weeks. With complications such as hypertension, decreased fetal movement, or oligohydramnios, labor induction is carried out. It is our view that large, randomized trials should be performed before otherwise uncomplicated 41-week gestations are routinely considered pathologically prolonged. In women in whom a *certain* gestational age is known, labor is induced at the completion of 42 weeks. Almost 90 percent of such women are induced successfully or enter labor within 2 days of induction. For those who do not deliver with the first induction, a second induction is performed within 3 days. Almost all women are delivered using this management plan, but in the unusual few who are not delivered, management decisions involve a third—or even more—induction versus cesarean delivery. Women classified as having *uncertain* postterm pregnancies are managed with weekly nonstress fetal testing and assessment of amnionic fluid volume. Women with an AFI ≤5 cm or with reports of diminished fetal movement undergo labor induction.

INTRAPARTUM MANAGEMENT

Labor is a particularly dangerous time for the postterm fetus. Therefore, women whose pregnancies are known or suspected to be postterm ideally come to the hospital as soon as they suspect labor. While being evaluated for active labor, we recommend that fetal heart rate and uterine contractions be monitored electronically for variations consistent with fetal compromise.

During labor, the decision to perform amniotomy is problematic. Further reduction in fluid volume following amniotomy can enhance the possibility of cord compression. Conversely, after membrane rupture, a scalp electrode and an intrauterine pressure catheter can be placed. These usually provide more precise data concerning fetal heart rate and uterine contractions. Amniotomy also aids identification of thick meconium.

Thick meconium in the amnionic fluid is particularly worrisome. The viscosity probably signifies the lack of liquid and thus oligohydramnios. Aspiration of thick meconium may cause severe pulmonary dysfunction and neonatal death (Chap. 33, Neonatal Encephalopathy and Cerebral Palsy). Because of this, amnioinfusion during labor has been proposed as a way of diluting meconium to lower the incidence of aspiration syndrome (Wenstrom, 1989). As discussed in Chapter 24 (Management Options), the benefits of amnioinfusion remain controversial. In a large randomized trial by Fraser and colleagues (2005), amnioinfusion did not reduce the risk of meconium aspiration syndrome or perinatal death. According to the American College of Obstetricians and Gynecologists (2016a), amnioinfusion does not prevent meconium aspiration, however, it remains a reasonable treatment approach for repetitive variable decelerations.

The likelihood of a successful vaginal delivery is reduced appreciably for the nullipara who is in early labor with thick, meconium-stained amnionic fluid. Therefore, if the woman is remote from delivery, strong consideration should be given to prompt cesarean delivery, especially when cephalopelvic disproportion is suspected or either hypotonic or hypertonic dysfunctional labor is evident. Some practitioners choose to avoid oxytocin use in these cases.

Until recently, it was taught—including at Parkland Hospital —that aspiration of meconium could be minimized but not eliminated by suctioning the pharynx as soon as the head was delivered. According to the American Heart Association guidelines, this in no longer recommended (Wyckoff, 2015). The American College of Obstetricians and Gynecologists (2017a) does not recommend routine intrapartum suctioning. Alternatively, if the depressed newborn has meconium-stained fluid, then intubation is carried out.

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CHAPTER 44: Fetal-Growth Disorders

> *When infants are of large size and abundant, they may mechanically throw out of function so great a portion of the placenta as seriously to interfere with the nutrition of the foetus, and sometimes cause its death. Excessive development of the foetus can usually be traced to prolongation of pregnancy, large size of one or both parents, advancing age, or multiparity of the mother.*
>
> —J. Whitridge Williams (1903)

INTRODUCTION

The concept of excessive or impaired fetal growth was not considered in detail by Williams in his first edition. Abnormally diminished fetal growth was attributed to placental lesions and fetal infections. Conversely, a large fetus was of obvious concern because of associated dystocia. Currently, fetal-growth disorders at both ends of the spectrum are major problems in obstetrics.

Nearly 20 percent of the almost 4 million neonates born in the United States are at the low and high extremes of fetal growth. In 2015, 8.1 percent of newborns weighed <2500 g at birth, whereas 8.0 percent weighed >4000 g. And, although almost 70 percent of low-birthweight neonates are born preterm, the balance of low-birthweight newborns accounted for approximately 3 percent of term births in 2015 (Martin, 2017). Between 1990 and 2006, the proportion of newborns with birthweights <2500 g grew by more than 20 percent when the rate peaked at 8.3 percent (Martin, 2012). This trend toward smaller babies has slowed since the mid- to late-2000s and might partly be explained by the concurrent movement toward fewer deliveries prior to 39 weeks' gestation (Richards, 2016). In contrast, between 1990 and 2006, the incidence of birthweights >4000 g declined approximately 30 percent to a nadir of 7.6 percent in 2010 (Martin, 2012). This trend away from the upper extreme is difficult to explain because it coincides with the epidemic prevalence of obesity, a known cause of macrosomia (Morisaki, 2013).

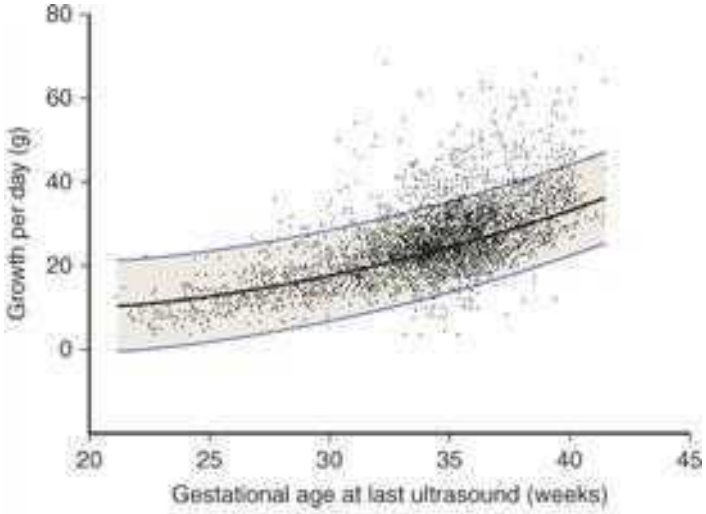
FETAL GROWTH

Pathophysiology

Human fetal growth is characterized by sequential patterns of tissue and organ growth, differentiation, and maturation. However, the "obstetrical dilemma" postulates a conflict between the need to walk upright—requiring a narrow pelvis—and the need to think—requiring a large brain, and thus a large head. Some speculate that evolutionary pressures restrict growth late in pregnancy (Mitteroecker, 2016). Thus, the ability to *growth restrict* may be adaptive rather than pathological.

Fetal growth has been divided into three phases. The initial phase of hyperplasia occurs in the first 16 weeks and is characterized by a rapid increase in cell number. The second phase, which extends up to 32 weeks' gestation, includes both cellular hyperplasia and hypertrophy. After 32 weeks, fetal mass accrues by cellular hypertrophy, and it is during this phase that most fetal fat and glycogen are accumulated. The corresponding fetal-growth rates during these three phases are 5 g/d at 15 weeks' gestation, 15 to 20 g/d at 24 weeks', and 30 to 35 g/d at 34 weeks' (Williams, 1982). As shown in Figure 44-1, the velocity of fetal growth varies considerably.

FIGURE 44-1
Increments in fetal weight gain in grams per day from 24 to 42 weeks' gestation. The black line represents the mean and the outer blue lines depict ±2 standard deviations. (Data from pregnancies managed at Parkland Hospital.)



Fetal development is determined by maternal provision of substrate and placental transfer of these, whereas fetal growth potential is governed by the genome. The precise cellular and molecular mechanisms by which normal fetal growth ensues are incompletely understood. That said, considerable evidence support an important role for insulin and insulin-like growth factors (IGFs) in regulation of fetal growth and weight gain (Luo, 2012). These growth factors are produced by virtually all fetal organs and are potent stimulators of cell division and differentiation.

Other hormones implicated in fetal growth have been identified, particularly hormones derived from adipose tissue. These hormones are known broadly as *adipokines* and include leptin, the protein product of the *obesity gene*. Fetal leptin concentrations rise during gestation, and they correlate both with birthweight and with neonatal fat mass (Briffa, 2015; Logan, 2017; Simpson, 2017). Other adipokines possibly involved include adiponectin, ghrelin, follistatin, resistin, visfatin, vaspin, omentin-1, apelin, and chemerin.

Fetal growth is also dependent on an adequate supply of nutrients. As discussed in Chapter 7 (Glucose and Fetal Growth), both excessive and diminished maternal glucose availability affect fetal growth. Reduced maternal glucose levels may result in a lower birthweight. Still, growth-restricted neonates do not typically show pathologically low glucose concentrations in cord blood (Pardi, 2006). Fetal-growth restriction in response to glucose deprivation generally results only after long-term severe maternal caloric deprivation (Lechtig, 1975).

Conversely, excessive glycemia produces macrosomia. Varying levels of glucose affect fetal growth via insulin and its associated IGFs. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study Cooperative Research Group (2008) found that elevated cord C-peptide levels, which reflect fetal hyperinsulinemia, are associated with greater birthweight. This relationship was noted even in women with maternal glucose levels below the threshold for diabetes. Overgrowth does occur in the fetuses of euglycemic women. Its etiology is thus likely more complicated than merely dysregulated glucose metabolism (Catalano, 2011). Genetic factors, including genomic imprinting and epigenetic modifications via gene methylation, are also important and emphasize the potential role of inheritance (Begemann, 2015; Nawathe, 2016).

Excessive transfer of lipids may also lead to fetal overgrowth (Higa, 2013). Free or nonesterified fatty acids in maternal plasma may be transferred to the fetus via facilitated diffusion or after liberation of fatty acids from triglycerides by trophoblastic lipases (Gil-Sánchez, 2012). Generally speaking, lipolytic activity is augmented in pregnancy, and fatty acid levels are increased in nonobese women during the third trimester (Diderholm, 2005). Independent of prepregnancy body mass index (BMI), higher free fatty acid levels during the latter half of pregnancy correlate with birthweight (Crume, 2015). Other studies have correlated maternal triglyceride levels with birthweight (Di Cianni, 2005; Vrijkotte, 2011). Greater intake of certain fatty acids, particularly omega-3, is also associated with greater birthweight (Calabuig-Navarro, 2016).

Placental fatty acid metabolism and transfer may be dysregulated in fetal-growth restriction and in maternal conditions associated with fetal overgrowth. For example, levels of endothelial lipase are reduced with deficient fetal growth, and this enzyme is overexpressed in placentas of women with diabetes (Gauster, 2007, 2011). Others have reported that diabetes and obesity are associated with altered placental lipid-transport gene expression (Radaelli, 2009). Obesity is also linked with greater expression of fatty acid binding/transport proteins within the trophoblast (Myatt, 2016; Scifres, 2011). The end result of these alterations is an abnormal accumulation of lipids that can result in pathological placental inflammation and dysfunction (Calabuig-Navarro, 2016; Myatt, 2016; Yang, 2016).

Amino acids undergo active transport, which explains the normally higher fetal concentrations compared with maternal levels. In growth restriction, this pattern is reversed. One possible mechanism is altered transport of these amino acids. Remember, amino acids that reach the fetus must first cross the microvillus membrane at the maternal interface. Amino acids then traverse the trophoblastic cell, and finally cross the basal membrane into fetal blood (Chap. 5, Placenta and Chorion). In human placentas, fetal growth correlates with peroxisome proliferator activator receptor gamma (PPAR-γ) activity, which governs placental regulation of L-type amino acid (LAT) receptors 1 and 2 (Chen, 2015b). Additional modulation is from rapamycin complex (mTORC) 1 and 2 receptors (Rosario, 2013). Placental mTORC activity is reduced in fetal-growth restriction. Others have shown that increasing birthweight and maternal BMI are linked to expression and activity of particular amino-acid transporters at the microvillus membrane (Jansson, 2013).

Normal Birthweight

Normative data for fetal growth based on birthweight vary with ethnicity and geographic region. Accordingly, researchers have developed fetal-growth curves using various populations and geographic locations throughout the United States (Brenner, 1976; Ott, 1993; Overpeck, 1999; Williams, 1975). Because these curves are based on specific ethnic or regional groups, they do not represent the entire population.

To address this, birthweights such as those shown in Table 44-1 are derived nationwide in the United States. Shown in Figure 44-2 are growth curves from more than 3.2 million mothers with singleton liveborn neonates in the United States during 1991 and 2011 (Duryea, 2014). These current curves plot birthweight against a gestational age based on an *obstetrical estimate*, formed in part by sonography. These curves are thought to be more accurate and reflect more precise pregnancy dating. Older curves used gestational age derived from a last menstrual period. Comparing birthweights from 1991 to data from 2011, the more recent growth curves indicate that the earlier assessments overestimated birthweights in the case of preterm birth. In particular, the 50th percentile for fetal growth that previously corresponded to 31 to 32 weeks' gestation now corresponds to 33 to 34 weeks' when improved obstetrical dating is used.

TABLE 44-1

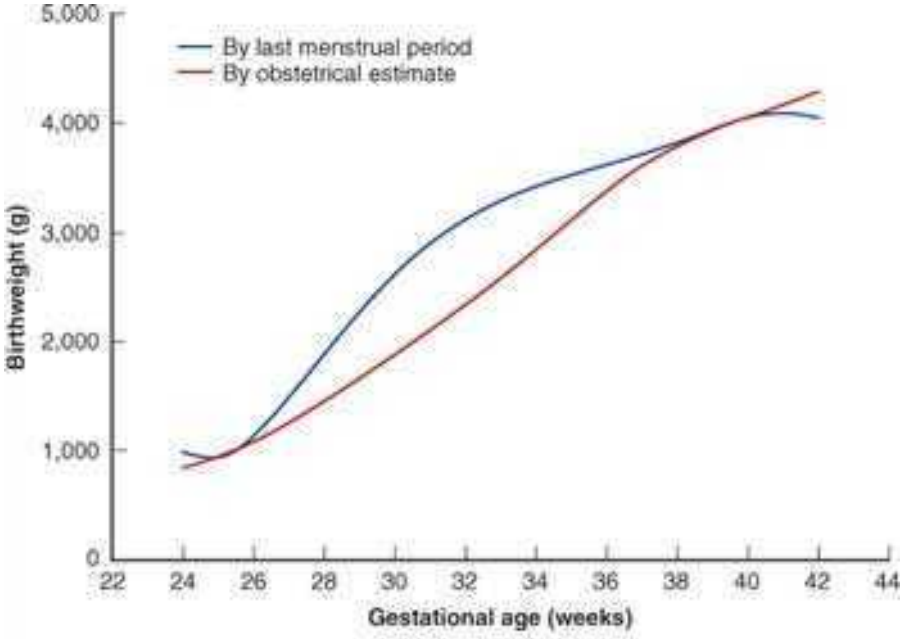
2011 Gestational Age Birthweight (g) Percentiles for 3,252,011 Singleton Live Births in the United States

	Percentile				
Age (wk)	**5th**	**10th**	**50th**	**90th**	**95th**
24	539	567	680	850	988
25	540	584	765	938	997
26	580	637	872	1080	1180
27	650	719	997	1260	1467
28	740	822	1138	1462	1787
29	841	939	1290	1672	2070
30	952	1068	1455	1883	2294
31	1080	1214	1635	2101	2483
32	1232	1380	1833	2331	2664
33	1414	1573	2053	2579	2861
34	1632	1793	2296	2846	3093
35	1871	2030	2549	3119	3345
36	2117	2270	2797	3380	3594
37	2353	2500	3025	3612	3818
38	2564	2706	3219	3799	3995
39	2737	2877	3374	3941	4125
40	2863	3005	3499	4057	4232
41	2934	3082	3600	4167	4340
42	2941	3099	3686	4290	4474

From Duryea, 2014, with permission.

FIGURE 44-2

Fetal-growth curves for births in the United States in 2011. Curves vary depending on whether gestational age was calculated from the last menstrual period or from an improved obstetrical estimate, derived in part using sonography. (Modified with permission from Duryea EL, Hawkins JS, McIntire DD, et al: A revised birth weight reference for the United States. Obstet Gynecol. 2014 Jul;124(1):16–22.)



The curves by Alexander (1996) and Duryea (2014) and their associates are most accurately termed a *population reference*, rather than a *standard*. A population reference incorporates pregnancies of varying risks, along with the resulting outcomes, both normal and abnormal. In contrast, a *standard* incorporates normal pregnancies with normal outcomes. Because population references include preterm births, which are more likely to be growth restricted, it has been argued that the associated birthweight data overestimate deficient fetal growth (Mayer, 2013; Zhang, 2010).

One recent project sought to define regional standards in eight countries and was based on data from optimal maternal health and socioeconomic conditions. Growth trajectories from the International Fetal and Newborn Growth Consortium for the 21st Century—INTERGROWTH 21 were similar in these eight: China, India, Kenya, Brazil, Oman, Italy, the United Kingdom, and the United States (Villar, 2014). However, an international standard based on the healthiest women is of questionable value (Hanson, 2015).

Fetal Growth versus Birthweight

Most of what is known regarding normal and abnormal human fetal growth is actually based on birthweights that are assembled as references for fetal growth at particular gestational ages. This is problematic, however, because birthweight does not define the *rate* of fetal growth. Indeed, such birthweight curves reveal compromised growth only at the extreme of impaired growth. Thus, they cannot be used to identify the fetus that fails to achieve an expected size but whose birthweight is above the 10th percentile. For example, a fetus with a birthweight in the 40th percentile may not have achieved its genomic growth potential for a birthweight in the 80th percentile.

The rate or *velocity* of fetal growth can be estimated by serial sonographic anthropometry. For example, Milovanovic (2012) demonstrated that the growth rate of intrinsically small-for-gestational-age (SGA) newborns (those below the 10th percentile) approximates that of appropriate-for-gestational-age neonates. However, diminished growth velocity may be linked to perinatal morbidity and adverse postnatal metabolic changes that are independent of birthweight. Recently, Sovio and colleageus (2015) demonstrated that growth velocity of the abdominal circumference in the lowest decile distinguishes SGA newborns who suffer increased morbidity. Conversely, an excessive fetal-growth velocity, particularly of the abdominal circumference—which may be correlated with increased hepatic blood flow—is associated with an overgrown neonate (American College of Obstetricians and Gynecologists, 2016a).

Several conditions or disorders can adversely affect the normal growth of a fetus. It is important clinically to distinguish between fetal-growth restriction and constitutional low birthweight.

FETAL-GROWTH RESTRICTION

Definition

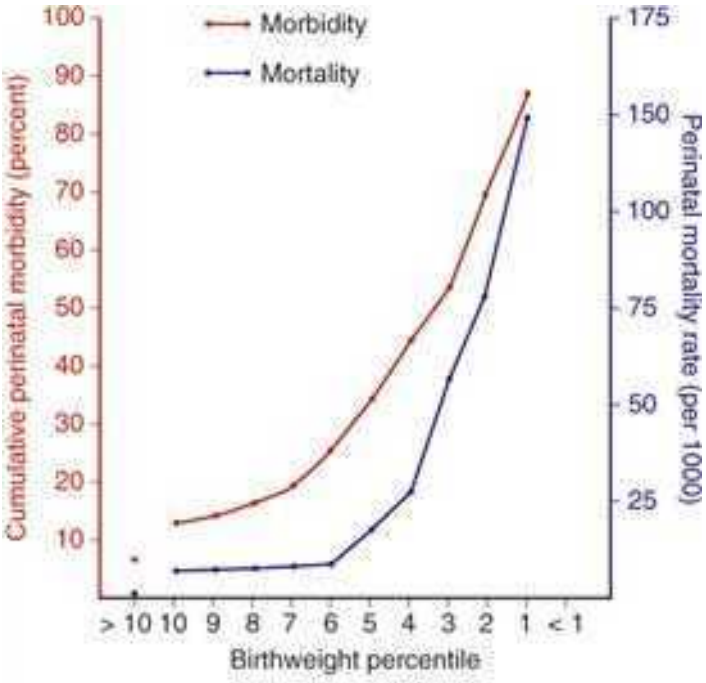
Lubchenco and coworkers (1963) published detailed comparisons of gestational ages with birthweights to derive norms for expected fetal size at a given gestational week. Battaglia and Lubchenco (1967) then classified *small-for-gestational-age* neonates as those whose weights were below the 10th percentile for their gestational age. Low-birthweight newborns who are small for gestational age are often designated as having *fetal-growth restriction.* Such infants were shown to be at increased risk for neonatal death. For example, the mortality rate of SGA neonates born at 38 weeks was 1 percent compared with 0.2 percent in those with appropriate birthweights.

Importantly, many neonates with birthweights <10th percentile are not pathologically growth restricted, but instead are small simply because of normal biological factors. As many as 70 percent of such SGA infants have normal outcomes and are thought to be appropriately grown when maternal ethnic group, parity, weight, and height are considered (Unterscheider, 2015). These small but normal infants also do not show evidence of the postnatal metabolic derangements commonly associated with deficient fetal growth. Moreover, intrinsically SGA newborns remain significantly smaller during surveillance to 2 years compared with appropriate-for-gestational age neonates, but they do not show differences in measures of metabolic risk (Milovanovic, 2012).

Because of these disparities, other classifications have been developed. Usher and McLean (1969) suggested that fetal growth standards should be based on mean weights-for-age, with normal limits defined by ±2 standard deviations. This definition would limit SGA infants to 3 percent of births instead of 10 percent. In a population-based analysis of 122,754 births at Parkland Hospital, McIntire and colleagues (1999) showed this definition to be clinically meaningful. Also, as shown in Figure 44-3, most adverse outcomes are in newborns smaller than the 3rd percentile. The importance of this cut-off has been independently confirmed in a prospective study by Unterscheider and colleagues (2013a).

FIGURE 44-3

Relationship between birthweight percentile and perinatal mortality and morbidity rates in 1560 small-for-gestational-age fetuses. A progressive increase in both mortality and morbidity rates is observed as birthweight percentile decreases.. (Data from Manning, 1995.)



More recently, individual or customized fetal-growth potential is proposed to replace a population-based threshold. In this model, a fetus that deviates from its individual optimal size at a given gestational age is considered either overgrown or growth restricted (Chiossi, 2017). Such optimal projections are based on maternal race or ethnicity. But, the superiority of customized growth curves has not been established (Chiossi, 2017; Costantine, 2013; Grobman, 2013; Zhang, 2011).

Symmetrical versus Asymmetrical Growth Restriction

Campbell and Thoms (1977) described the use of the sonographically determined *head-to-abdomen circumference ratio* (*HC/AC*) to differentiate growth-restricted fetuses. Those who were *symmetrical* were proportionately small, and those who were *asymmetrical* had disproportionately lagging abdominal growth compared with head growth. The onset or etiology of a particular fetal insult is hypothetically linked to either type of growth restriction. In the instance of *symmetrical growth restriction*, an early insult could result in a relative decrease in cell number and size. For example, early global insults such as those from chemical exposure, viral infection, or cellular maldevelopment with aneuploidy may cause a proportionate reduction of both head and body size. *Asymmetrical growth restriction* might follow a later pregnancy insult such as placental insufficiency from hypertension. In this variation, resultant diminished glucose transfer and hepatic storage would primarily affect cell size and not number. Thereby, fetal abdominal circumference—which reflects liver size—would be reduced.

Brain Sparing

Such somatic growth restriction is proposed to result from preferential shunting of oxygen and nutrients to the brain. This allows normal brain and head growth, that is—*brain sparing*. Accordingly, the ratio of brain weight to liver weight during the last 12 weeks—usually about 3 to 1—may be increased to 5 to 1 or more in severely growth-restricted infants. Because of brain-sparing effects, asymmetrical fetuses were thought to be preferentially protected from the full effects of growth restriction.

Considerable evidence has since accrued that fetal growth patterns are much more complex. For example, fetuses with aneuploidy typically have disproportionately large head sizes and thus are *asymmetrically* growth restricted, which is contrary to contemporaneous thinking (Nicolaides, 1991). Moreover, most preterm neonates with growth restriction due to preeclampsia and associated uteroplacental insufficiency are found to have more symmetrical growth impairment—again, a departure from accepted principles (Salafia, 1995).

More evidence of the complexity of growth patterns was presented by Dashe and associates (2000). These investigators analyzed 8722 consecutive liveborn singletons who had undergone sonographic examination within 4 weeks of delivery. Although only 20 percent of growth-restricted fetuses demonstrated sonographic head-to-abdomen asymmetry, these fetuses were at greater risk for intrapartum and neonatal complications. Symmetrically growth-restricted fetuses were not at increased risk for adverse outcomes compared with those appropriately grown. These investigators concluded that asymmetrical fetal-growth restriction represented significantly disordered growth, whereas symmetrical growth restriction more likely represented normal, genetically determined small stature.

Other data further challenge the concept of brain sparing. Roza and associates (2008) found that fetuses with circulatory redistribution—*brain sparing*—had a higher incidence of later behavioral problems. In another study, evidence of brain sparing was found in half of 62 growth-restricted fetuses with birthweights <10th percentile and who showed abnormal middle cerebral artery Doppler flow studies (Figueras, 2011). Compared with controls, these neonates had significantly lower neurobehavioral scores in multiple areas, suggesting profound brain injury. Zhu and coworkers (2016) prospectively compared late-onset growth restriction in 14 fetuses with that in 26 non-growth-restricted fetuses using magnetic resonance imaging to analyze hemodynamic flow. Despite the concept of brain sparing, growth-restricted infants had significantly smaller brains than controls. The complex effects of such insults—with respect to timing and severity—on brain structure, connectivity, and neurobehavioral outcomes have been recently reviewed by Miller and colleagues (2016).

Placental Abnormalities

Fetal-growth restriction is one of the "major obstetrical syndromes" associated with defects in early placentation (Brosens, 2015). Rogers and coworkers (1999) concluded that implantation-site disorders may be both a cause and consequence of hypoperfusion at the placental site. This comports with the association of certain placental angiogenic factors with pregnancy hypertensive disorders (Chap. 40, Endothelial Cell Injury). Thus, it may be that placentas from pregnancies complicated by hypertension elaborate these angiogenic factors in response to placental-site hypoperfusion, whereas pregnancies complicated by fetal-growth restriction without hypertension do not (Jeyabalan, 2008).

Mechanisms leading to abnormal trophoblastic invasion are likely multifactorial, and both vascular and immunological etiologies have been proposed. For example, *atrial natriuretic peptide converting enzyme*, also known as *corin*, plays a critical role in trophoblastic invasion and remodeling of the uterine spiral arteries (Cui, 2012). These processes are impaired in corin-deficient mice, which also develop evidence of preeclampsia. Moreover, mutations in the gene for corin have been reported in women with preeclampsia (Chen, 2015a).

Several immunological abnormalities are associated with fetal-growth restriction. This raises the prospect of maternal rejection of the "paternal semiallograft." Rudzinski and colleagues (2013) studied C4d, a component of complement that is associated with humoral rejection of transplanted tissues. They found this to be highly associated with chronic villitis—88 percent of cases versus only 5 percent of controls—and with reduced placental weight. In a study of 10,204 placentas, chronic villitis was associated with placental hypoperfusion, fetal acidemia, and fetal-growth restriction and its sequelae (Greer, 2012). Kim and coworkers (2015) extensively reviewed chronic inflammatory placental lesions and their association with fetal-growth restriction, preeclampsia, and preterm birth.

Perinatal Morbidity and Mortality

Several short-term and long-term adverse sequelae are linked with fetal-growth restriction. First, perinatal morbidity and mortality rates are substantive (see Fig. 44-3). Rates of stillbirth and adverse neonatal outcomes that include birth asphyxia, meconium aspiration, hypoglycemia, and hypothermia are all increased, as is the prevalence of abnormal neurological development. This is true for both term and preterm growth-restricted newborns. In one analysis of nearly 3000 newborns born before 27 weeks' gestation, those weighing <10th percentile had a nearly fourfold higher risk of neonatal death or neurodevelopmental impairment and a 2.6-fold increased risk of cerebral palsy compared with non-SGA neonates (De Jesus, 2013). In another analysis of more than 91,000 uncomplicated pregnancies, newborns with weights <5th percentile had a higher risk of low 5-minute Apgar score, respiratory distress, necrotizing enterocolitis, and neonatal sepsis than appropriate-weight neonates. The risks of stillbirth and neonatal death were sixfold and fourfold higher, respectively (Mendez-Figueroa, 2016).

The most severely growth-impaired newborns also have the worst outcomes. In one study of more that 44,561 neonates, only 14 percent of those weighing <1st percentile at birth survived to discharge (Griffin, 2015). For those infants who survive, the risks of adverse neurodevelopmental outcomes are substantial, especially for growth-impaired fetuses with either brain sparing or a major birth defect (Meher, 2015; Nelson, 2015b). Poor motor, cognitive, language and attention, and behavioral outcomes in growth-restricted newborns unfortunately persist into early childhood and adolescence (Baschat, 2014; Levine, 2015; Rogne, 2015).

Long-Term Sequelae

Fetal Undergrowth

Barker (1992) hypothesized that *adult* mortality and morbidity are related to fetal and infant health. This includes both under- and overgrowth. In the context of fetal-growth restriction, numerous reports describe a relationship between suboptimal fetal nutrition and an increased risk of subsequent adult hypertension, atherosclerosis, type 2 diabetes, and metabolic derangement (Burton, 2016; Jornayvaz, 2016). The degree to which low birthweight mediates adult disease is controversial, as weight gain in early life also appears important (Breij, 2014; Kerkhof, 2012; McCloskey, 2016).

Mounting evidence suggests that fetal-growth restriction may affect organ development, particularly that of the heart. Individuals with low birthweight demonstrate cardiac structural changes and dysfunction persisting through childhood, adolescence, and adulthood. In one study, 80 infants who were born SGA before 34 weeks' gestation were compared at 6 months with 80 normally grown children (Cruz-Lemini, 2016). The heart in the SGA children had a more globular ventricle that resulted in systolic and diastolic dysfunction. In another study, echocardiography in 418 adolescents showed that low birthweight was associated with a thicker left ventricular posterior wall (Hietalampi, 2012). In their review, Cohen and colleagues (2016) concluded, however, that these findings have unclear long-term significance.

Deficient fetal growth is also associated with postnatal structural and functional renal changes. In a review by Luyckx and Brenner (2015), birthweight abnormalities were evaluated for linkage with disordered nephrogenesis, renal dysfunction, chronic kidney disease, and hypertension. Both low and high birthweight, as well as maternal obesity and gestational diabetes, affect in-utero development of the kidney and its health into adulthood. However, other variables that include childhood nutrition, acute kidney injury, excessive childhood weight gain, and obesity also worsen long-term renal function.

Fetal Overgrowth

Particularly in women with diabetes and elevated cord blood levels of IGF-1, fetal overgrowth is associated with greater neonatal fat mass and morphological heart changes. Pedersen (1954) first proposed that hyperglycemia leads to fetal hyperinsulinemia and fetal overgrowth. This has been extended to organ dysmorphia, for example, increased interventricular septal thickness in neonates of mothers with gestational diabetes (Aman, 2011; Garcia-Flores, 2011). The cardiopulmonary vasculature is also adversely affected by diabetes in pregnancy. In 3277 cases of persistent pulmonary hypertension of the newborn (PPHN), maternal obesity, diabetes, and both deficient and excessive fetal growth were independent risk factors (Steurer, 2017). Long-term consequences of fetal overgrowth from obesity and diabetes are discussed in Chapters 48 (Antepartum Management) and 57 (Types of Diabetes).

Accelerated Lung Maturation

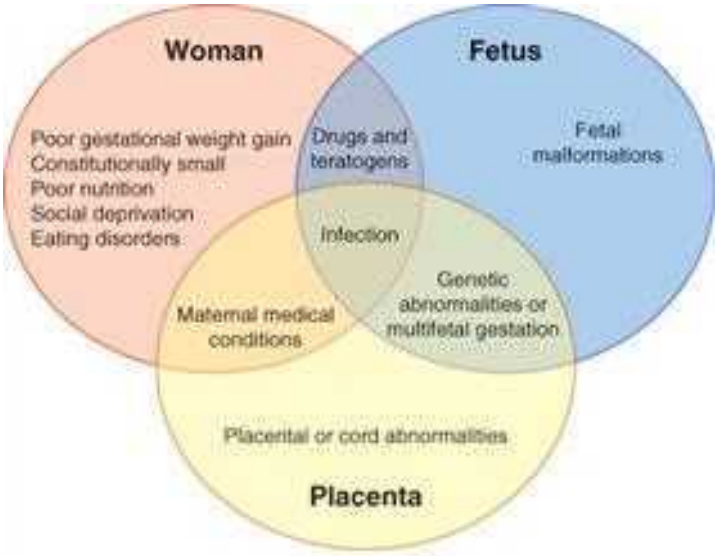
Numerous reports have described accelerated fetal pulmonary maturation in complicated pregnancies associated with growth restriction (Perelman, 1985). One possible explanation is that the fetus responds to a stressed environment by augmenting adrenal glucocorticoid secretion, which leads to accelerated fetal lung maturation (Laatikainen, 1988). Although this concept pervades modern perinatal thinking, evidence to support it is negligible.

To examine this hypothesis, Owen and associates (1990) analyzed perinatal outcomes in 178 women delivered because of hypertension. They compared these with outcomes in newborns of 159 women delivered because of spontaneous preterm labor or ruptured membranes. They concluded that a "stressed" pregnancy did not confer an appreciable survival advantage. Similar findings were described by Friedman and colleagues (1995) in women with severe preeclampsia. Two studies from Parkland Hospital also substantiate that the preterm infant accrues no apparent advantages from fetal-growth restriction (McIntire, 1999; Tyson, 1995).

Risk Factors and Etiologies

Risk factors for impaired fetal growth include potential abnormalities in the mother, fetus, and placenta. These three "compartments" are depicted in Figure 44-4. Some of these factors are known causes of fetal-growth restriction and may affect more than one compartment. For instance, cytomegalovirus infections can affect the fetus directly. In contrast, bacterial infections such as tuberculosis may have significant maternal effects that lead to poor fetal growth. Similarly, malaria, a protozoal infection, is a recognized cause of fetal-growth restriction (Briand, 2016). Importantly, many causes of diminished fetal growth are prospectively considered risk factors, because impaired fetal growth is not consistent in all affected women.

FIGURE 44-4
Risk factors and causes of impaired fetal growth centering on the mother, her fetus, and the placenta.



Constitutionally Small Mothers

It is axiomatic that small women typically have smaller newborns. As discussed subsequently, both prepregnancy weight and gestational weight gain modulate this risk. Durie and colleagues (2011) showed that the risk of delivering an SGA neonate was highest among underweight women who gained less weight than recommended by the Institute of Medicine (Chap. 9, Severe Undernutrition). Also, both maternal and paternal size influences birthweight. In a Swedish study of 137,538 term births, it was estimated that the maternal and paternal birthweights explained 6 and 3 percent of variance in birthweight, respectively (Mattsson, 2013).

Gestational Weight Gain and Nutrition

In the study by Durie (2011) cited above, gestational weight gain during the second and third trimesters that was less than that recommended by the Institute of Medicine was associated with SGA neonates in women of all weight categories except class II or III obesity. Conversely, excessive gestational weight gain was associated with an overgrown newborn in all weight categories (Blackwell, 2016).

As perhaps expected, eating disorders are linked with significantly higher risks for low birthweight and preterm birth (Micali, 2016). Marked weight gain restriction after midpregnancy should not be encouraged even in obese women (Chap. 48, Antepartum Management). Even so, it appears that food restriction to <1500 kcal/d adversely affects fetal growth minimally (Lechtig, 1975). The best documented effect of famine on fetal growth was in the *Hunger Winter* of 1944 in Holland. For 6 months, the German occupation army restricted dietary intake to 500 kcal/d for civilians, including pregnant women. This resulted in an average birthweight decline of only 250 g (Stein, 1975).

It is unclear whether undernourished women may benefit from micronutrient supplementation. In one study, almost 32,000 Indonesian women were randomly assigned to receive micronutrient supplementation or only iron and folate tablets (Prado, 2012). Offspring of those receiving the supplement had lower risks of early infant mortality and low birthweight and had improved childhood motor and cognitive abilities. Conversely, Liu and coworkers (2013) randomly assigned 18,775 nulliparas to folic acid alone; folic acid and iron; or folic acid, iron, and 13 other micronutrients. Folic acid and iron, with or without the additional micronutrients, resulted in a 30-percent reduction in risk of third-trimester anemia. But, supplementation did not affect other maternal or neonatal outcomes. A Cochrane database review of 19 trials involving 138,538 women concluded that supplementation of iron and folic acid improved birth outcomes, including lower risks of low birthweight and SGA (Haider, 2017). The importance of antenatal vitamins and trace metals is further discussed in Chapter 9 (Minerals).

Exercise in pregnancy may be beneficial for optimal fetal growth. One metaanalysis of 28 studies involving 5322 women concluded that exercise reduces the risk of fetal overgrowth without raising the risk of poor growth (Wiebe, 2015). Another metaanalysis concluded that aerobic exercise did not result in low-birthweight neonates (Di Mascio, 2016).

Social Issues

The effect of social deprivation on birthweight is interconnected with lifestyle factors such as smoking, alcohol or other substance abuse, and poor nutrition. With appropriate modifying interventions, women with psychosocial factors were significantly less likely to deliver a low-birthweight infant and also had fewer preterm births and other pregnancy complications (Coker, 2012).

Women who are immigrants may be at particular risk for poor fetal growth. In one study of 56,443 singleton pregnancies in Rotterdam, social deprivation was associated with adverse perinatal outcomes that included SGA newborns (Poeran, 2013). That said, a similar linkage was not found in socially deprived

women of non-Western origin. The effect of immigration, however, is complex and dependent on the population studied (Howell, 2017; Sanchez-Vaznaugh, 2016).

Vascular and Renal Disease

Especially when complicated by superimposed preeclampsia, chronic vascular disease commonly causes growth restriction (Chap. 50, Management During Pregnancy). In a study of more than 2000 women, vascular disease as evidenced by abnormal uterine artery Doppler velocimetry early in pregnancy was associated with higher rates of preeclampsia, SGA neonates, and delivery before 34 weeks (Groom, 2009). Using Washington state birth certificate data, Leary and colleagues (2012) found that maternal ischemic heart disease was linked to SGA infants in 25 percent of 186 births. Roos-Hesselink and coworkers (2013) described similar pregnancy outcomes in 25 women with ischemic heart disease.

Chronic renal insufficiency is frequently associated with underlying hypertension and vascular disease. Nephropathies are commonly accompanied by restricted fetal growth (Cunningham, 1990; Feng, 2015; Saliem, 2016). These relationships are considered further in Chapter 53 (Chronic Kidney Disease).

Pregestational Diabetes

Fetal-growth restriction in the newborns of women with diabetes may be related to congenital malformations or may follow substrate deprivation from advanced maternal vascular disease (Chap. 57, Preterm Delivery). Also, the likelihood of restricted growth increases with worsening White classification, particularly nephropathy (Klemetti, 2016). That said, the prevalence of serious vascular disease associated with diabetes in pregnancy is low, and the primary effect of overt diabetes, especially type 1, is fetal *overgrowth*. For example, in a prospective study of 682 consecutive pregnancies complicated by diabetes, women with type 1 diabetes were significantly more likely than women with type 2 diabetes to have a neonate weighing above the 90th and 97.7th percentiles (Murphy, 2011). Additionally, women with type 1 diabetes were significantly less likely to deliver an SGA newborn. In a recent study of 375 term singleton pregnancies complicated by type 1 diabetes, the risk of fetal overgrowth correlated with rising third-trimester glycemic values (Cyganek, 2017). Nearly a fourth of neonates were macrosomic. And, third-trimester hemoglobin A1c and fasting glucose values were independent predictors for the risk of macrosomia.

Chronic Hypoxia

Conditions associated with chronic uteroplacental hypoxia include preeclampsia, chronic hypertension, asthma, maternal cyanotic heart disease, smoking, and high altitude. When exposed to a chronically hypoxic environment, some fetuses have significantly reduced birthweight. In more than 1.8 million births in Austria, the birthweight declined 150 g for each 1000-meter rise in altitude (Waldhoer, 2015). In 63,620 Peruvian live births, the mean birthweight was significantly decreased at higher compared with lower altitudes—3065 g ± 475 g versus 3280 g ± 525 g (Gonzales, 2009). In this study, the rate of birthweights <2500 g was 6.2 percent at low altitudes, and it was 9.2 percent at high altitudes. In contrast, the rate of birthweights >4000 g was 6.3 percent at low altitudes and 1.6 percent at high altitudes.

Anemia

In most cases, maternal anemia does not restrict fetal growth. Exceptions include sickle-cell disease and some other inherited anemias (Desai, 2017; Thame, 2016). Importantly, curtailed maternal blood-volume expansion is linked to fetal-growth restriction (de Haas, 2017; Stott, 2017). This is further discussed in Chapter 40 (Blood Volume).

Antiphospholipid Syndrome

Adverse obstetrical outcomes including fetal-growth restriction have been associated with three species of antiphospholipid antibodies: *anticardiolipin antibodies, lupus anticoagulant,* and *anti-β2 glycoprotein-I antibodies.* Mechanistically, a “two-hit” hypothesis suggests that initial endothelial damage is then followed by intervillous placental thrombosis. More specifically, oxidative damage to certain membrane proteins such as β2 glycoprotein-I is followed by antiphospholipid antibody binding, which leads to immune complex formation and ultimately to thrombosis (Giannakopoulos, 2013). This syndrome is considered in detail in Chapters 52 (Acquired Thrombophilias) and 59 (Antiphospholipid Syndrome). Pregnancy outcomes in women with these antibodies may be poor and include fetal-growth restriction and fetal demise (Cervera, 2015). The primary autoantibody that predicts obstetrical antiphospholipid syndrome appears to be lupus anticoagulant (Yelnik, 2016).

Infertility

It is controversial whether pregnancies in women with prior infertility with or without treatment have an increased risk of SGA newborns (Zhu, 2007). Dickey and colleagues (2016) compared birthweight curves for singletons conceived by in vitro fertilization to the birthweight curves of Duryea (2014), described in Fetal Growth versus Birthweight. They found no reduction in fetal growth. Kondapalli and Perales-Puchalt (2013) reviewed possible links between low birthweight and infertility with its various interventions and concluded that any association remains unexplained for singletons.

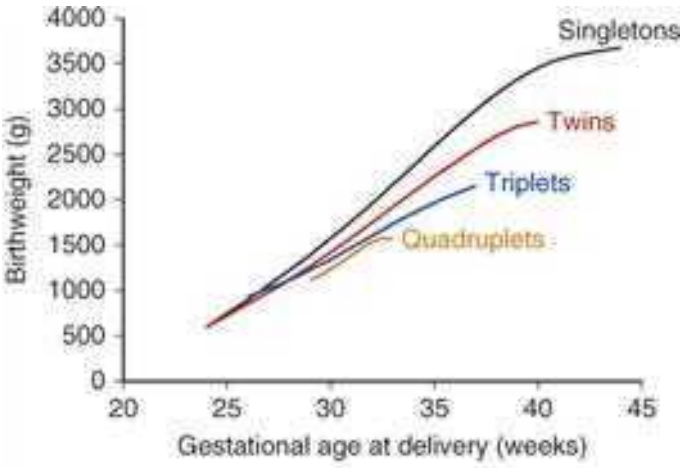
Placental, Cord, and Uterine Abnormalities

Several placental abnormalities may cause poor fetal growth. These are discussed further throughout Chapter 6 and include chronic placental abruption, extensive infarction, chorioangioma, velamentous cord insertion, placenta previa, and umbilical artery thrombosis. Growth failure in these cases is presumed secondary to uteroplacental insufficiency. Abnormal placental implantation leading to endothelial dysfunction may also limit fetal growth (Brosens, 2015). This pathology is implicated in pregnancies complicated by preeclampsia (Chap. 40, Etiology). If the placenta is implanted outside the uterus, the fetus is usually growth restricted (Chap. 19, Abdominal Pregnancy). Finally, some uterine malformations have been linked to impaired fetal growth (Chap. 3, Unicornuate Uterus (Class II)).

Multifetal Gestation

Pregnancy with two or more fetuses is more likely to be complicated by diminished growth of one or more fetuses compared with that of normal singletons. This is illustrated in Figure 44-5 and discussed in Chapter 45 (Low Birthweight).

FIGURE 44-5
Birthweight and gestational age relationships in multifetal gestations without malformations delivered at Parkland Hospital.



Drugs with Teratogenic and Fetal Effects

Several drugs and chemicals are capable of limiting fetal growth. Some are teratogenic and affect the fetus before organogenesis is complete. Some exert—or continue to exert—fetal effects after embryogenesis ends at 8 weeks. Many of these are considered in detail in Chapter 12, and examples include anticonvulsants and antineoplastic agents. Cigarette smoking, opiates and related drugs, alcohol, and cocaine may also cause growth restriction, either primarily or by decreasing maternal food intake. The link with caffeine use and fetal-growth restriction remains speculative (American College of Obstetricians and Gynecologists, 2016b). In contrast, Cyganek and colleagues (2014) studied growth restriction in pregnancies complicated by renal and liver transplants and concluded that common immunosuppressive drugs—prednisone, azathioprine, cyclosporine A, and tacrolimus—did not significantly affect fetal-growth rates.

Maternal and Fetal Infections

Viral, bacterial, protozoan, and spirochetal infections have been implicated in up to 5 percent of fetal-growth restriction cases and are discussed throughout Chapters 64 and 65. The best known of these are *rubella* and *cytomegalovirus infection*. Both promote calcifications in the fetus that are associated with cell death, and infection earlier in pregnancy correlates with worse outcomes. Toda and colleagues (2015) described a Vietnamese epidemic in which 39 percent of 292 term newborns with congenital rubella syndrome were low birthweight. In one study of 238 primary cytomegalovirus infections, no severe cases were observed when infection occurred after 14 weeks' gestation (Picone, 2013). These investigators later identified sonographic findings in 30 of 69 cases of congenital infection, and growth restriction was noted in 30 percent of these 30 cases (Picone, 2014).

Tuberculosis and *syphilis* have also both been associated with poor fetal growth. Both extrapulmonary and pulmonary tuberculosis are linked with low birthweight (Chap. 51, Tuberculosis). Sobhy (2017) analyzed 13 studies that included a total of 3384 women with active tuberculosis. The odds ratio was 1.7 for low birthweight. The etiology is uncertain, however, the adverse effects on maternal health, compounded by effects of poor nutrition and poverty, are important (Jana, 2012). Congenital syphilis is more common, and paradoxically, the placenta is almost always larger and heavier due to edema and perivascular inflammation (Chap. 65, Diagnosis). Congenital syphilis is strongly linked with preterm birth and thus low-birthweight newborns (Sheffield, 2002).

Toxoplasma gondii can also cause congenital infection, and Paquet and Yudin (2013) describe its classic association with fetal-growth restriction. Capobiango (2014) described 31 Brazilian pregnancies complicated by congenital toxoplasmosis. Only 13 percent were treated antepartum for toxoplasmosis, and low

birthweight complicated nearly 40 percent of all the pregnancies. *Congenital malaria* also causes low birthweight and poor fetal growth. Briand and colleagues (2016) emphasize the importance of prophylaxis early in pregnancy for women at risk.

Congenital Malformations

In a study of more than 13,000 fetuses with major structural anomalies, 22 percent had accompanying growth restriction (Khoury, 1988). In one study of 111 pregnancies complicated by fetal gastroschisis, a third had birthweights <10th percentile (Nelson, 2015a). As a general rule, the more severe the malformation, the more likely it is that the fetus will be SGA. This is especially evident in fetuses with chromosomal abnormalities or those with serious cardiovascular malformations.

Chromosomal Aneuploidies

Depending on which chromosome is redundant, fetuses with autosomal trisomies may display poor fetal growth. For example, in *trisomy 21*, fetal-growth restriction is generally mild. By contrast, fetal growth in *trisomy 18* is virtually always significantly limited. The crown-rump length in fetuses with trisomy 18 and 13, unlike that with trisomy 21, is typically shorter than expected (Bahado-Singh, 1997; Schemmer, 1997). By the second trimester, long-bone measurements usually are below the 3rd percentile. In one group of 174 children with trisomy 13, the mean birthweight with trisomy 13 was 2500 g, and in 254 children with trisomy 18, it was 1800 g (Nelson, 2016).

Poor fetal growth also complicates Turner syndrome, and the severity correlates with increasing haploinsufficiency of the short arm of the X chromosome (Fiot, 2016). In contrast, poor growth is not characteristic of an increased number of X chromosomes (Ottesen, 2010; Wigby, 2016). As discussed in Chapter 13 (Chromosomal Mosaicism), aneuploidic patches in the placenta—*confined placental mosaicism (CPM)*—is a recognized cause of fetal-growth restriction. Evidence suggests that aneuploidy affecting both the cytotrophoblast and mesenchymal core of the placenta, which is type 3 CPM, is associated with fetal-growth restriction (Toutain, 2010).

First-trimester prenatal programs that screen for fetal aneuploidy may incidentally identify pregnancies at risk for fetal-growth restriction unrelated to karyotype. In their analysis of 8012 women, the risk for growth restriction was higher in eukaryotic fetuses with extremely low free β-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) levels (Krantz, 2004). From her review, Dugoff (2010) concluded that a low PAPP-A level is strongly associated with poor fetal growth, but studies of free β-hCG are conflicting.

Second-trimester analytes, including elevated alpha-fetoprotein and inhibin A levels and low unconjugated serum estriol concentrations, are significantly associated with birthweight below the 5th percentile. An even greater risk of poor growth is linked with certain combinations of these analytes. Still, these markers are poor screening tools for complications such as fetal-growth restriction due to low sensitivity and positive-predictive values (Dugoff, 2010). Nuchal translucency is also not predictive of fetal-growth restriction. The role of all these markers in aneuploidy screening is discussed in Chapter 14 (Traditional Aneuploidy Screening Tests).

Fetal-Growth Restriction Recognition

Identification of the inappropriately growing fetus remains a challenge. *Early* establishment of gestational age, ascertainment of maternal weight gain, and careful measurement of uterine fundal growth throughout pregnancy will identify many cases of abnormal fetal growth in low-risk women. Risk factors, including a *prior growth-restricted fetus*, raise the recurrence risk to nearly 20 percent (American College of Obstetricians and Gynecologists, 2015). In women with risk factors, serial sonographic evaluation is considered. Although examination frequency varies depending on indications, an initial early dating examination followed by an examination at 32 to 34 weeks, or when otherwise clinically indicated, will identify many growth-restricted fetuses. Even so, *definitive diagnosis* frequently cannot be made until delivery.

Uterine Fundal Height

According to one systematic review, insufficient evidence supports the utility of fundal height measurement to detect fetal-growth restriction (Robert Peter, 2015). Nonetheless, carefully performed serial fundal height measurements are recommended as a simple, safe, inexpensive, and reasonably accurate *screening* method to detect growth-restricted fetuses. As a screening tool, its principal drawback is imprecision. Haragan and coworkers (2015) reported sensitivities of 71 and 43 percent for detecting excessive or deficient fetal growth. Specificities were 85 and 66 percent, respectively.

The method used by most for fundal height measurement is described in Chapter 9 (Subsequent Prenatal Visits). Between 18 and 30 weeks' gestation, the uterine fundal height in centimeters coincides within 2 weeks of gestational age. Thus, if the measurement is more than 2 to 3 cm from the expected height, inappropriate fetal growth is suspected and sonography is considered.

Sonographic Measurement

One supporting point for routine sonographic evaluation of all pregnancies is the opportunity to diagnose growth restriction. Typically, such routine screening incorporates an early initial sonographic examination—usually at 16 to 20 weeks' gestation. Increasingly, a first-trimester examination is added to establish gestational age and identify anomalies. Some then recommend repeat sonographic evaluation at 32 to 34 weeks to evaluate fetal growth.

First-trimester sonography has limited accuracy to predict SGA newborns. For example, Crovetto and associates (2017) reported detection rates of 35 and 42 percent with false-positive rates of 5 and 10 percent, respectively. From nearly 9000 screened pregnancies, Tuuli and colleagues (2011) concluded that second-trimester sonography is superior to first-trimester scans for predicting SGA neonates. At Parkland Hospital, we provide midpregnancy sonographic screening examination of all pregnancies. Additional sonographic evaluations of fetal growth are performed as clinically indicated.

With sonography, the most common method for identifying poor fetal growth is estimation of weight using multiple fetal biometrical measurements. Combining head, abdomen, and femur dimensions provides optimum accuracy, whereas little incremental improvement is gained by adding other biometrical measurements (Platz, 2008). Of the dimensions, femur length measurement is technically the easiest and the most reproducible. Biparietal diameter and head circumference measurements are dependent on the plane of section and may also be affected by deformative pressures on the skull. Last, abdominal circumference measurements are more variable. However, these are most frequently abnormal with fetal-growth restriction because soft tissue predominates in this dimension (Fig. 44-6). Shown in Figure 44-7 is an example of a severely growth-restricted newborn.

FIGURE 44-6

Correlation of sonographic fetal weight estimation using abdominal circumference (AC) and actual birthweight. (Data from pregnancies managed at Parkland Hospital.

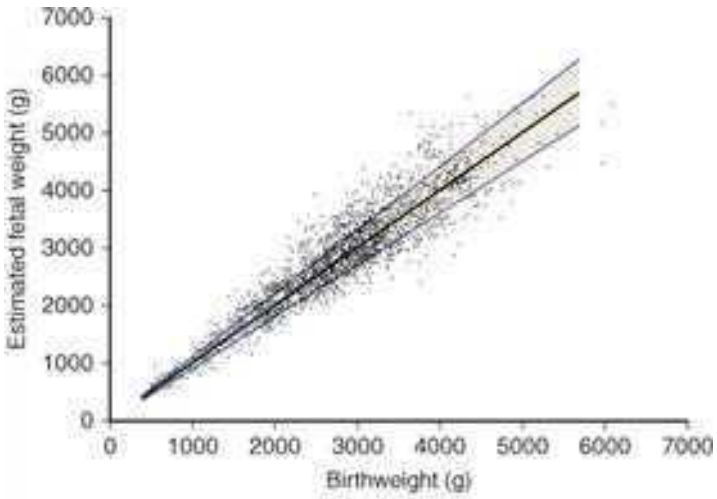


FIGURE 44-7

A 36-week newborn with severe fetal-growth restriction. (Used with permission from Dr. Roxane Holt.)

Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Some studies have reported a significant predictive value for small abdominal circumference with respect to lagging fetal growth. One study screened nearly 4000 pregnancies using either clinically indicated or universal sonography in the third trimester (Sovio, 2015). Universal sonography raised the rate of detection of SGA from 20 percent to 57 percent. Importantly, however, the neonatal morbidity rate was increased only if the abdominal circumference growth velocity was in the lowest decile.

Sonographic estimates of fetal weight and actual weight may be discordant by 20 percent or more, leading to both false-positive and false-negative findings. Dashe and associates (2000) studied 8400 live births at Parkland Hospital in which fetal sonographic evaluation had been performed within 4 weeks of delivery. They reported that 30 percent of growth-restricted fetuses were not detected. In a study of 2586 women with low-risk pregnancies randomly assigned to sonography at 32 or 36 weeks' gestation, sensitivity to identify grow restriction was improved at the later gestational age (Roma, 2015). Still, nearly 40 percent of cases of growth restriction defined as birthweight <3rd percentile were missed. A Cochrane database analysis of 13 trials with 34,980 women concluded that routine late pregnancy ultrasound for a low-risk or an unselected population is not associated with maternal or fetal benefit (Bricker, 2015).

Amnionic Fluid Volume Measurement

An association between pathological fetal-growth restriction and oligohydramnios has long been recognized. Petrozella and associates (2011) reported that decreased amnionic fluid volume between 24 and 34 weeks' gestation was significantly associated with malformations. In the absence of malformations, a birthweight <3rd percentile was seen in 37 percent of pregnancies with oligohydramnios, in 21 percent with borderline amnionic fluid volume, but in only 4 percent with normal volumes. Also, from a recent metaanalysis of 15 studies involving more than 35,000 pregnancies, high-risk pregnancies with oligohydramnios were more likely to be complicated by low birthweight compared with low-risk pregnancies with oligohydramnios (Rabie, 2017). Hypoxia and diminished renal blood flow are proposed explanations for oligohydramnios.

Doppler Velocimetry

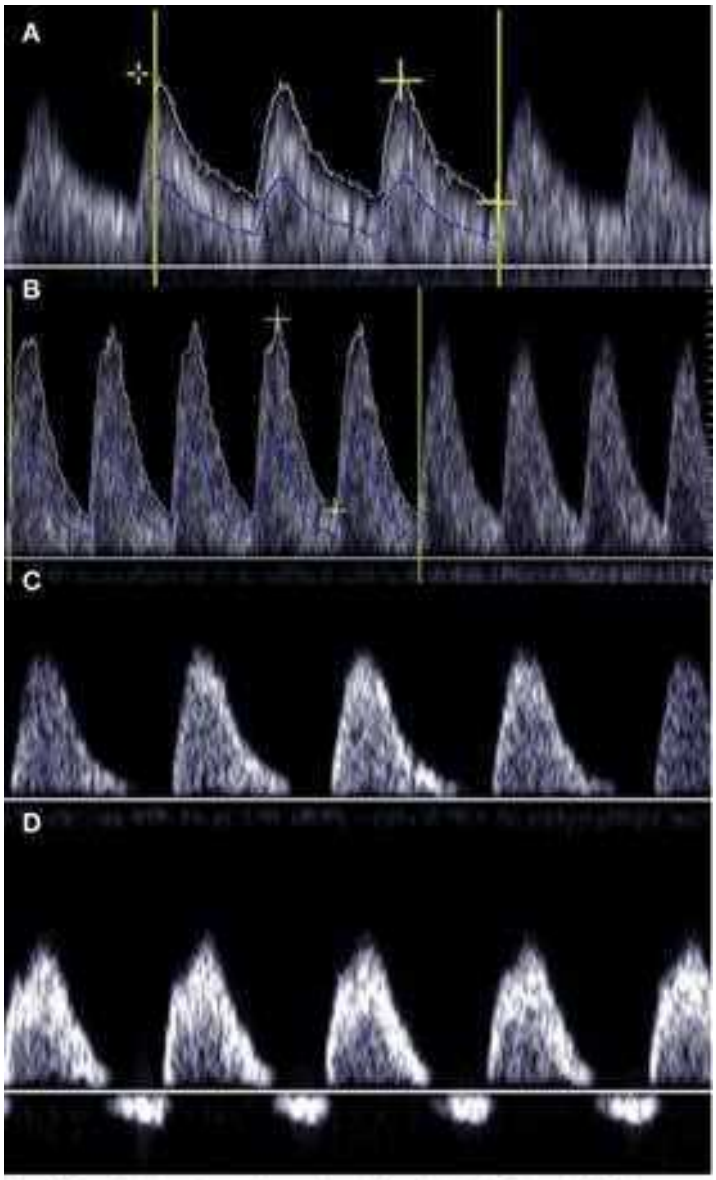
With this technique, early changes in placenta-based growth restriction are detected in peripheral vessels such as the umbilical and middle cerebral arteries. Late changes are characterized by reversal of umbilical artery flow and by abnormal flow in the ductus venosus and fetal aortic and pulmonary outflow tracts.

Of these, abnormal umbilical artery Doppler velocimetry findings—characterized by absent or reversed end-diastolic flow—are uniquely linked with fetal-growth restriction (Chap. 10, Doppler). These abnormalities highlight early versus severe growth restriction and represent the transition from fetal

adaptation to failure. Thus, persistently absent or reversed end-diastolic flow, such as that shown in Figure 44-8, has long been correlated with hypoxia, acidosis, and fetal death. In one prospective sonographic examination of 1116 fetuses with estimated fetal weights <10th percentile, only 1.3 percent of fetuses with normal umbilical artery Doppler studies had adverse outcomes compared with 11.5 percent of those with Doppler abnormalities (O'Dwyer, 2014). Unterscheider and associates (2013a) reported that abnormal umbilical artery Doppler velocimetry combined with an estimated fetal weight <3rd percentile is most strongly associated with poor obstetrical outcome.

FIGURE 44-8

Doppler velocity waveforms. **A.** Normal waveform with normal S/D ratio. **B.** Increased impedance to flow with abnormally elevated S/D ratio. **C.** Absent end-diastolic flow. **D.** Reversed end-diastolic flow.



Because of these findings, umbilical artery Doppler velocimetry is considered standard in the evaluation and management of the growth-restricted fetus. The American College of Obstetricians and Gynecologists (2015) has concluded that umbilical-artery Doppler velocimetry improves clinical outcomes. It is recommended in the management of fetal-growth restriction as an adjunct to standard surveillance techniques such as nonstress testing and biophysical profile.

Other Doppler assessments are still investigational. Interrogation of the ductus venosus was evaluated in a series of 604 fetuses <33 weeks' gestation who had an abdominal circumference <5th percentile (Baschat, 2007). Ductus venosus Doppler parameters were the primary cardiovascular factor in predicting neonatal outcome. These late changes are felt to reflect myocardial deterioration and acidemia, which are major contributors to adverse perinatal and neurological outcome. In another study of 46 growth-restricted fetuses, Doppler flow abnormalities of the aortic valve isthmus preceded those in the ductus venosus by 1 week (Figueras, 2009). In their evaluation of several fetal vessels, Turan and associates (2008) described the sequence of changes characteristic of mild placental dysfunction, progressive placental dysfunction, and severe, early-onset placental dysfunction. However, Unterscheider and colleagues (2013b) questioned whether a predictable progression of Doppler indices actually exists in fetal-growth restriction.

Prevention

Fetal-growth restriction prevention ideally begins before conception. Maternal medical conditions, medications, and nutrition are optimized, and smoking cessation is critical. Other risk factors are tailored to the maternal condition, such as antimalarial prophylaxis for women living in endemic areas and correction of nutritional deficiencies. Of note, treatment of mild-to-moderate hypertension does not reduce the incidence of growth-restricted newborns (Chap. 50, Antihypertensive Treatment in Pregnancy).

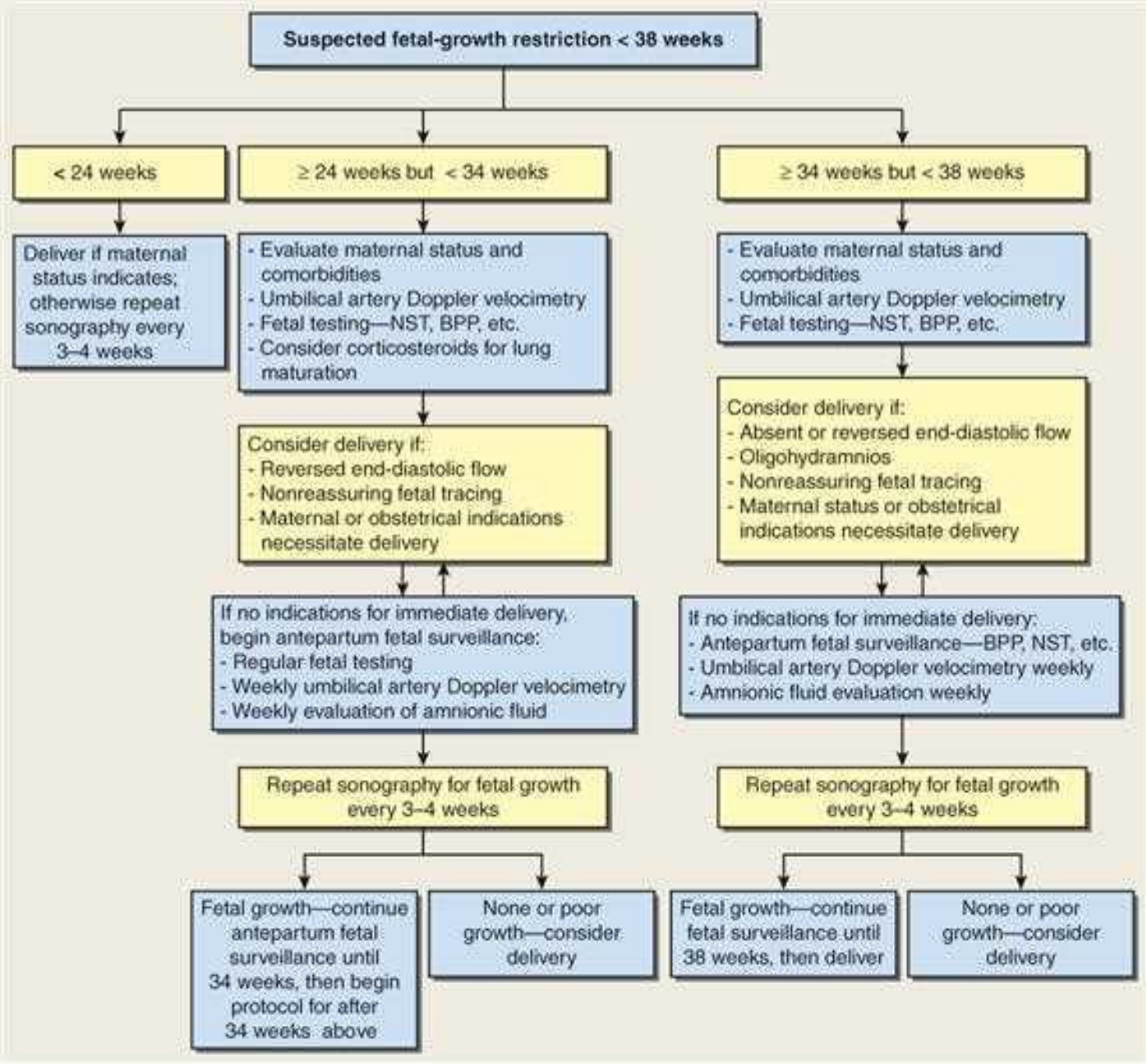
Accurate dating is essential during early pregnancy. Serial sonographic evaluations are typically used, but the best interval between assessments has not been clearly established. Given that a prior SGA newborn is associated with other adverse outcomes in a subsequent pregnancy, particularly stillbirth and preterm birth, surveillance during a subsequent pregnancy may be beneficial (Mendez-Figueroa, 2016; Spong, 2012). The American College of Obstetricians and Gynecologists (2015) notes that if growth is normal during a pregnancy following a prior pregnancy complicated by fetal-growth restriction, then Doppler velocimetry and fetal surveillance are not indicated. A recent metaanalysis of 45 trials involving 20,909 women reported that low-dose aspirin initiated prior to 16 weeks' gestation was associated with a significantly lower risk of fetal-growth restriction (Roberge, 2017). Moreover, they described a dose-response effect. The American College of Obstetricians and Gynecologists (2015) has not endorsed prophylaxis with low-dose aspirin for women with a prior growth-restricted fetus.

Management

If fetal-growth restriction is suspected, then efforts are made to confirm the diagnosis, assess fetal condition, and search for possible causes. Early-onset growth restriction is especially problematic. In pregnancies in which fetal anomalies are suspected, patient counseling and prenatal diagnostic testing are indicated (American College of Obstetricians and Gynecologists, 2015).

One management algorithm is shown in Figure 44-9. In pregnancies with suspected fetal-growth restriction, antepartum fetal surveillance includes periodic Doppler velocimetry of the umbilical arteries in addition to more frequent fetal testing. At Parkland Hospital, for women whose fetus measures ≤3rd percentile and has reached a viable age, we encourage hospitalization on our High-Risk Pregnancy Unit. Daily fetal heart rate tracings, weekly Doppler velocimetry, and sonographic assessment of fetal growth every 3 to 4 weeks are initiated. Other modalities of Doppler velocimetry, such as middle cerebral arteries or ductus venosus assessment, are considered experimental. The American College of Obstetricians and Gynecologists (2015) recommends that antenatal corticosteroids for pulmonary maturation be given to pregnancies complicated by fetal-growth restriction and at risk for birth before 34 weeks' gestation.

FIGURE 44-9
Algorithm for management of fetal-growth restriction at Parkland Hospital. BPP = biophysical profile; NST = nonstress test.



The timing of delivery is crucial, and the risks of fetal death versus the hazards of preterm birth must be considered. Several multicenter studies address these problems, but unfortunately, none have elucidated the optimal timing of delivery. For the preterm fetus, the only randomized trial of delivery timing is the Growth Restriction Intervention Trial (GRIT) (Thornton, 2004). This trial involved 548 women between 24 and 36 weeks' gestation with clinical uncertainty regarding delivery timing. Women were randomly assigned to immediate delivery or to delayed delivery until the situation worsened. The primary outcome was perinatal death or disability after reaching age 2 years. Mortality rates did not differ through 2 years of age. Moreover, children aged 6 to 13 years did not show clinically significant differences between the two groups (Walker, 2011).

In the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE), ductus venosus Doppler evaluation was compared with fetal heart rate monitoring. There were 310 pregnancies between 26 and 32 weeks' gestation with fetuses displaying an abdominal circumference <10th percentile and an umbilical artery pulsatility index >95th percentile (Lees, 2015). Delivery timing was determined by the results of three differing antenatal fetal assessment arms that were: short-term fetal heart rate variability, early ductus venosus Doppler velocimetry changes, or late ductus changes. The proportion of children with neuroimpairment at 2 years of age was not different among the groups. Of note, only 32 percent of the newborns overall were delivered according to this randomization. Safety net criteria and other maternal/fetal indications prompted these protocol deviations (Visser, 2016). In a post-hoc analysis, these authors concluded that before 32 weeks, delaying delivery until ductus venosus Doppler or fetal heat rate abnormalities occur is likely safe and possibly benefits long-term outcome (Ganzevoort, 2017).

The Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT) study examined the delivery timing of growth-restricted fetuses who were 36 weeks' gestation or older. In these 321 women who were randomized to induction or to expectant management, composite neonatal morbidity did not differ, except that neonatal admissions were lower after 38 weeks in a secondary analysis (Boers, 2010, 2012). Another secondary analysis of DIGITAT did not identify a clear subgroup that benefited from labor induction (Tajik, 2014). Other secondary analyses included assessment of neurodevelopmental and behavioral outcomes at age 2, and these also were similar between the randomized groups (Van Wyk, 2012).

Management of the Near-Term Fetus

As shown in Figure 44-9, delivery of a suspected growth-restricted fetus with normal umbilical artery Doppler velocimetry, normal amnionic fluid volume, and reassuring fetal heart rate testing can likely be deferred until 38 weeks' gestation. Said another way, uncertainty regarding the diagnosis should preclude intervention until fetal lung maturity is assured. Expectant management can be guided using antepartum fetal surveillance techniques described in Chapter 17. Most clinicians, however, recommend delivery at 34 weeks or beyond if there is clinically significant oligohydramnios. Consensus statements by the Society for Maternal-Fetal Medicine (Spong, 2011) and the American College of Obstetricians and Gynecologists (2017a) are similar. These recommend delivery between 34 and 37 weeks when there are comorbid conditions such as oligohydramnios. With a reassuring fetal heart rate pattern, vaginal delivery is planned. Notably, some of these fetuses do not tolerate labor.

Management of the Fetus Remote from Term

If growth restriction is identified in an anatomically normal fetus before 34 weeks, and amnionic fluid volume and fetal surveillance findings are normal, observation is recommended. Screening for toxoplasmosis, cytomegalovirus infection, rubella, herpes, and other infections is recommended by some. However, we and others have not found this to be productive (Yamamoto, 2013).

As long as interval fetal growth and fetal surveillance test results are normal, pregnancy is allowed to continue until fetal lung maturity is reached (see Fig. 44-9). Reassessment of fetal growth is typically made no sooner than 3 to 4 weeks. Weekly assessment of umbilical artery Doppler velocimetry and amnionic fluid volume is combined with periodic nonstress testing, although the optimal frequency has not been determined. As mentioned, we hospitalize these women in our High-Risk Pregnancy Unit and monitor their fetuses daily. If interval growth, amnionic fluid volume, and umbilical artery Doppler velocimetry are normal, then the mother is discharged home and seen intermittently for outpatient surveillance.

With growth restriction remote from term, no specific treatment ameliorates the condition. For example, evidence does not support diminished activity or bed rest to accelerate growth or improve outcomes. Despite this, many clinicians intuitively advise a program of modified rest. Nutrient supplementation, attempts at plasma volume expansion, oxygen therapy, antihypertensive drugs, heparin, and aspirin are all ineffective (American College of Obstetricians and Gynecologists, 2015).

In most cases diagnosed before term, neither a precise etiology nor a specific therapy is apparent. Management decisions hinge on assessment of the relative risks of fetal death during expectant management versus the risks from preterm delivery. Although reassuring fetal testing may allow observation with continued maturation, long-term neurological outcome is a concern (Baschat, 2014; Lees, 2015; Thornton, 2004). Baschat and associates (2009) showed that neurodevelopmental outcome at 2 years in growth-restricted fetuses was best predicted by birthweight and gestational age. Doppler abnormalities are generally not associated with poor childhood cognitive developmental scores among low-birthweight fetuses delivered in the third trimester (Llurba, 2013). These findings emphasize that adverse neurodevelopmental outcomes cannot always be predicted.

Labor and Delivery

Fetal-growth restriction is commonly the result of placental insufficiency due to faulty maternal perfusion, reduction of functional placenta, or both. If present, these conditions are likely aggravated by labor. Equally important, diminished amnionic fluid volume raises the likelihood of cord compression during labor. For these and other reasons, the frequency of cesarean delivery is increased. Accordingly, a woman with a suspected growth-restricted fetus should undergo "high-risk" intrapartum monitoring (Chap. 24, Intrapartum Surveillance of Uterine Activity).

The risk of neonatal hypoxia or meconium aspiration is also greater. Thus, care for the newborn should be provided immediately by an attendant who can skillfully clear the airway and ventilate a neonate as needed (Chap. 32, Resuscitation Protocol). The severely growth-restricted newborn is particularly susceptible to hypothermia and may also develop other metabolic derangements such as hypoglycemia, polycythemia, and hyperviscosity. In addition, low-birthweight newborns are at higher risk for motor and other neurological disabilities. Risk is greatest at the lowest extremes of birthweight (Baschat, 2009, 2014; Llurba, 2013).

FETAL OVERGROWTH

The term *macrosomia* is used rather imprecisely to describe a very large fetus or newborn. Although there is general agreement among obstetricians that neonates weighing <4000 g are not excessively large, a similar consensus has not been reached for the definition of macrosomia. Newborn weight rarely exceeds 11 pounds (5000 g), and excessively large infants are a curiosity. The largest newborn cited in the *Guinness Book of World Records* was a 23-lb 12-oz (10,800 g) infant boy born in 1879 to a Canadian woman (Barnes, 1957).

In the United States in 2015, of more than 4 million births, 6.9 percent weighed 4000 to 4499 g; 1 percent weighed 4500 to 4999 g; and 0.1 percent were born weighing 5000 g or more (Martin, 2017). To be sure, the incidence of excessively large infants grew during the 20th century. According to Williams (1903), at the beginning of the 20th century, the incidence of birthweight >5000 g was 1 to 2 per 10,000 births. This compares with 16 per 10,000 births at Parkland Hospital from 1988 through 2008 and with 11 per 10,000 in the United States in 2010. The influence of increasing maternal obesity rates is overwhelming, and its association with diabetes is well known. Of Parkland mothers with newborns weighing >5000 g, more than 15 percent were diabetic.

Definition

Several terms currently describe pathological fetal overgrowth. The most common of these—*macrosomia*—is defined by birthweights that exceed certain percentiles for a given population. Another commonly used scheme is to define macrosomia by an empirical birthweight threshold.

Birthweight Distribution

Macrosomia is frequently defined based on mathematical distributions of birthweight. Those newborns exceeding the 90th percentile for a given gestational week are usually used as the threshold for macrosomia or large-for-gestational age (LGA) birthweight. For example, the 90th percentile at 39 weeks is 4000 g. If, however, birthweights that are 2 standard deviations above the mean are used, then thresholds lie at the 97th percentile. Thus, substantially larger newborns are considered macrosomic compared with those at the 90th percentile. Specifically, the birthweight threshold at 39 weeks to be macrosomic would be approximately 4500 g for the 97th percentile rather than 4000 g for the 90th percentile.

Empirical Birthweight

Newborn weight exceeding 4000 g (8 lb 13 oz) is also a frequently used threshold to define macrosomia. Others use 4250 g or even 4500 g (10 lb). As shown in Table 44-2, birthweights ≥4500 g are uncommon. During a 30-year period at Parkland Hospital, during which there were more than 350,000 singleton births, only 1.4 percent of newborns weighed 4500 g or more. We are of the view that the upper limit of fetal growth, above which growth can be deemed abnormal, is likely two standard deviations above the mean, representing perhaps 3 percent of births. At 40 weeks, such a threshold would correspond to approximately 4500 g. The American College of Obstetricians and Gynecologists (2016a) concludes that the term *macrosomia* was an appropriate appellation for newborns who weigh 4500 g or more at birth.

TABLE 44-2

Birthweight Distribution of 354,509 Liveborn Infants at Parkland Hospital between 1988 and 2012

Birthweight (g)	Births		Maternal Diabetes	
	No.	%	No.	%
500–3999	322,074	90.9	13,365	4
4000–4249	19,106	5.4	1043	5
4250–4499	8391	2.4	573	7
4500–4649	3221	0.9	284	9
4750–4999	1146	0.3	134	12
5000–5249	385	0.1	57	15
5250–5499	127	0.04	31	24
5500 or more	59	0.02	14	24
Total	354,509		15,501	

Risk Factors

Some factors associated with fetal overgrowth are listed in Table 44-3. Many are interrelated and thus likely are additive. For example, advancing age is usually related to multiparity and diabetes, and obesity is related to diabetes. In one study, the incidence of macrosomia exceeded 24 percent in China among obese women, and macrosomia rates were also significantly higher (approximately 2.5-fold) for prolonged pregnancy and gestational diabetes (Wang, 2017). Of these, maternal diabetes is an important risk factor for fetal overgrowth (Chap. 57, Preterm Delivery). As shown in Table 44-2, the incidence

of maternal diabetes grows as birthweights >4000 g rise. It should be emphasized, however, that maternal diabetes is associated with only a small percentage of the total number of such large newborns.

TABLE 44-3

Risk Factors for Fetal Overgrowth

Obesity
Diabetes
Postterm gestation
Multiparity
Large size of parents
Advancing maternal age
Previous macrosomic infant
Racial and ethnic factors

Maternal and Perinatal Morbidity

The adverse consequences of excessive fetal growth are considerable. Neonates with a birthweight of at least 4000 g have cesarean delivery rates >50 percent. This is particularly true with maternal obesity or diabetes or with birthweights >5000 g (Cordero, 2015; Crosby, 2017; Gaudet, 2014; Hehir, 2015). One study found a higher risk for traumatic neonatal morbidity in LGA neonates compared with normal-weight ones (Chauhan, 2017). Rates of shoulder dystocia vary greatly and can reach nearly 30 percent for macrosomic neonates when maternal diabetes is comorbid (Cordero, 2015). In general obstetrical populations that include diabetic mothers, dystocia rates are at least 5 percent for neonates with birthweights ≥5000 g (Crosby, 2017; Hehir, 2015). Rates of postpartum hemorrhage, perineal laceration, and maternal infection, which are related complications, are also higher in mothers delivering overgrown newborns. Maternal and neonatal outcomes by birthweight for large babies >4000 g delivered at Parkland Hospital are shown in Table 44-4.

TABLE 44-4

Maternal and Fetal Outcomes for 208,090 Pregnancies Delivered at Parkland Hospital from 1998 through 2012

Outcome[a]	<4000 g n = 187,119	4000–4499 g n = 17,750	4500–4999 g n = 2849	≥5000 g n = 372	*p* value
Cesarean total	46,577 (25)	5,362 (30)	1204 (42)	224 (60)	<0.001
Scheduled	12,564 (7)	1,481 (8)	316 (11)	65 (17)	<0.001
Dystocia	7589 (4)	1388 (8)	337 (12)	46 (12)	<0.001
Shoulder dystocia	437 (0)	366 (2)	192 (7)	56 (15)	<0.001
3rd- or 4th-degree laceration	7296 (4)	932 (5)	190 (7)	37 (10)	<0.001
Labor induction	26,118 (13)	2499 (14)	420 (15)	39 (10)	0.141
Prolonged second stage	6905 (4)	899 (5)	147 (5)	14 (4)	<0.001
Chorioamnionitis	13,448 (7)	1778 (10)	295 (10)	35 (9)	<0.001
pH <7.0	925 (0.5)	96 (0.6)	20 (0.7)	4 (1.1)	0.039
Apgar <7 @ 5 minutes	1898 (1.0)	80 (0.5)	22 (0.8)	10 (2.7)	<0.001
ICN admission	4266 (2.2)	123 (0.7)	36 (1.3)	9 (2.4)	<0.001
Fractured clavicle	1880 (1.0)	616 (3.5)	125 (4.4)	16 (4.3)	<0.001
Mechanical ventilation	2305 (1.2)	54 (0.3)	11 (0.4)	9 (2.4)	<0.001
Hypoglycemia	480 (0.2)	89 (0.5)	31 (1.1)	12 (3.2)	<0.001
Hyperbilirubinemia	5829 (3.0)	305 (1.7)	60 (2.1)	12 (3.2)	<0.001
Erb palsy	470 (0.2)	224 (1.3)	74 (2.6)	22 (5.9)	<0.001
Neonatal death	402 (0.2)	3 (0)	2 (0.1)	1 (0.3)	<0.001

[a]Outcome data presented as n (%).

ICN = intensive care nursery.

Diagnosis

Because current methods fail to accurately estimate excessive fetal size, macrosomia cannot be definitively diagnosed until delivery. Inaccuracy in clinical estimates of fetal weight by physical examination is often attributable, at least in part, to maternal obesity. Numerous attempts have been made to improve the accuracy of sonographic fetal-weight estimation. Several formulas have been proposed to calculate fetal weight using measurements of the head, femur, and abdomen. Estimates provided by these computations are reasonably accurate for predicting the weight of small, preterm fetuses but are less valid in predicting the weight of large fetuses. In one study of 248 LGA and 655 non-LGA newborns from pregnancies complicated by diabetes, only 23 percent of women diagnosed with an LGA fetus before delivery actually delivered an LGA infant (Scifres, 2015). This resulted in a more than threefold rise in the cesarean delivery rate for suspected LGA birthweights.

From the foregoing, it is apparent that sonographic estimation of fetal weight is unreliable, and its routine use to identify macrosomia is not recommended. Indeed, the American College of Obstetricians and Gynecologists (2016a) concludes that clinical fetal weight estimates are just as accurate as sonographic ones.

Management

Several interventions have been proposed to interdict fetal overgrowth. Some include prophylactic labor induction for poorly defined indications such as "impending macrosomia," or elective cesarean delivery to avoid difficult delivery and shoulder dystocia. For women with diabetes in pregnancy, insulin therapy and close attention to good glycemic control reduces birthweight. However, this has not consistently translated into reduced cesarean delivery rates. Furthermore, as noted above, erroneous diagnosis of fetal overgrowth among women with diabetes raises cesarean delivery rates (Scifres, 2015). Also previously mentioned, fetal overgrowth irrespective of the diagnosis of diabetes mellitus is strongly associated with maternal obesity and excessive gestational weight gain (Durie, 2011; Durst, 2016; Harper, 2015). Dietary intervention to limit fetal overgrowth by curbing gestational weight gain, for example, is an active area of research. Currently recommended weight gains for pregnancy according to maternal BMI are described in Chapter 9 (Nutritional Counseling).

"Prophylactic" Labor Induction

Some clinicians induce labor when fetal macrosomia is suspected in nondiabetic women. This approach is suggested to obviate further fetal growth and thereby reduce potential delivery complications. Such prophylactic induction should theoretically reduce the risk of shoulder dystocia and cesarean delivery. In one systematic review of 11 studies of expectant management versus labor induction for suspected macrosomia, labor induction increased cesarean delivery rates without improving perinatal outcomes (Sanchez-Ramos, 2002). In contrast, Magro-Malosso and colleagues (2017) performed a metaanalysis of four randomized trials involving 1190 women and concluded that labor induction at 38 or more weeks for suspected macrosomia significantly reduces the frequency of fetal overgrowth and fractures. In one of these studies, 822 women with suspected LGA fetuses were randomly assigned either to early term delivery ($37^{0/7}$ to $38^{6/7}$ weeks) or to expectant management (Boulvain, 2015). There was a higher rate of vaginal delivery that was marginally significant and a lower composite measure of morbidity. These authors cautioned that any benefits should be balanced with the risks of early-term labor induction and delivery. Namely, a review of early-term births indicates that elective delivery before 39 weeks' gestation does not improve maternal outcomes and is associated with worse neonatal outcomes (Tita, 2016). We agree with the American College of Obstetricians and Gynecologists (2016a, 2017a,b) that current evidence does not support a policy for early labor induction or delivery before 39 weeks' gestation. It remains unclear whether delivery or induction for suspected macrosomia at term is better than expectant management.

Elective Cesarean Delivery

With the delivery of macrosomic infants, shoulder dystocia and its attendant risks described in Chapter 27 (Shoulder Dystocia) are major concerns. That said, the American College of Obstetricians and Gynecologists (2017b) concluded that fewer than 10 percent of all shoulder dystocia cases result in a persistent brachial plexus injury, and 4 percent of these injuries still follow cesarean delivery.

For prevention, planned cesarean delivery on the basis of suspected macrosomia to prevent brachial plexopathy is an unreasonable strategy in the *general population* (Chauhan, 2005). Ecker and coworkers (1997) analyzed 80 cases of brachial plexus injury in 77,616 consecutive infants born at Brigham and Women's Hospital. They concluded that an excessive number of otherwise unnecessary cesarean deliveries would be needed to prevent a single brachial plexus injury in neonates born to women without diabetes. Rouse and colleagues (1996) echoed these sentiments in their analysis of nondiabetic mothers.

Conversely, planned cesarean delivery may be a reasonable strategy for *diabetic* women with an estimated fetal weight >4250 or >4500 g. Conway and Langer (1998) described a protocol of routine cesarean delivery for sonographic estimates of ≥4250 g in diabetic women. This management significantly lowered the shoulder dystocia rate from 2.4 to 1.1 percent.

In summary, we agree with the College that elective delivery for the fetus that is suspected to be overgrown is inadvisable, particularly before 39 weeks' gestation. Finally, we also conclude that elective cesarean delivery is not indicated when estimated fetal weight is <5000 g among women without diabetes and <4500 g among women with diabetes (American College of Obstetricians and Gynecologists, 2016a, 2017b).

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CHAPTER 45: Multifetal Pregnancy

In single-ovum twins, there is always a certain area of the placenta in which there is anastomosis between vascular systems which is never present in the fused placenta of double-ovum twins. Thus, if at an early period the heart of one embryo is considerably stronger than that of the other, a gradually increasing area of the communicating portion of the placenta is monopolized by the former, so that its heart increases rapidly in size, whilst that of the latter receives less blood and eventually atrophies.

—J. Whitridge Williams (1903)

INTRODUCTION

In Williams' time, a great deal concerning the embryological and morphological development of multifetal pregnancies was unknown. These pregnancies may result from two or more fertilization events, from a single fertilization followed by a splitting of the zygote, or from a combination of both. Multifetal gestations were problematic during those times and remain so today for both the mother and her fetuses. For example, in this country, approximately a fourth of very-low-birthweight neonates—those born weighing <1500 g—are from multifetal gestations (Martin, 2017).

Fueled largely by infertility therapy, both the rate and the number of twins and higher-order multifetal births grew dramatically during the 1980s and 1990s in the United States. National data from Martin and coworkers (2017) presented here is informative. The twinning rate rose 76 percent from 18.9 per 1000 live births in 1980 to 33.2 in 2009. During the same time, the number of higher-order multifetal births peaked in 1998 at a rate of 1.9 per 1000 total births. Since then, however, evolving infertility management has lowered rates of higher-order multifetal births—especially among non-Hispanic white women. For example, the rate of triplets or more declined by more than 50 percent from 1998 to 2015 in this demographic group. And, in 2015, the overall multifetal birth rate was 34.5 per 1000, with twins representing nearly 97 percent of these births.

These rates of multifetal pregnancies have a direct effect on the rates of preterm birth and its comorbidities. In addition, the risks for congenital malformation and its consequences are greater with multifetal gestations. Importantly, this increased risk applies to *each* fetus and is not simply the result of more fetuses. In sum, in 2013 in the United States, multifetal births accounted for 3 percent of all live births but for 15 percent of all infant deaths. Moreover, the risk of infant death rose proportionally with the number of fetuses in the pregnancy (Matthews, 2015). Specifically, the infant mortality rate for twins was more than four times the rate for single births. In the same year, the infant mortality rate for triplets was nearly 12 times the rate for singletons, and for quadruplets, it was a staggering 26 times that for singletons! From Parkland Hospital, a comparison of singleton and twin outcomes is shown in Table 45-1. These risks are magnified further with higher-order births.

TABLE 45-1

Selected Outcomes in Singleton and Twin Pregnancies Delivered at Parkland Hospital from 1988 through 2016

Outcome	Singletons (No.)	Twins (No.)
Pregnancies	202,306	2412
Births[a]	202,306	4824
Stillbirths	1011 (5.0)	114 (23.6)
Neonatal deaths	590 (2.9)	92 (19.5)
Perinatal deaths	1601 (7.9)	206 (42.7)
Very low birthweight (<1500 g)	1927 (9.6)	507 (107.6)

[a]Birth data are represented as number (per 1000).

[b]Denominator for neonatal deaths and very low birthweight is liveborn infants.

Data from Dr. Don McIntire.

The mother may also experience higher obstetrical morbidity and mortality rates. These rates also rise with the number of fetuses (Mhyre, 2012; Young, 2012). In one study of more than 44,000 multifetal pregnancies, the risks for preeclampsia, postpartum hemorrhage, and maternal death were twofold higher than these rates in singleton gestations (Walker, 2004). The risk for peripartum hysterectomy is also greater. Francois and associates (2005) reported this to be threefold for twins and

24-fold for triplets or quadruplets. Last, compared with women with a singleton pregnancy, these mothers are at increased risk for depression as well as parental divorce (Choi, 2009; Jenna, 2011).

MECHANISMS OF MULTIFETAL GESTATIONS

Twin fetuses usually result from fertilization of two separate ova, which yields *dizygotic* or *fraternal twins*. Less often, twins arise from a single fertilized ovum that then divides to create *monozygotic* or *identical twins*. Either or both processes may be involved in the formation of higher numbers. Quadruplets, for example, may arise from as few as one to as many as four ova. These traditional models of twinning discussed in the next sections have been taught for more than 50 years and remain the widely accepted theory. More recently, Herranz (2015) offered a provocative alternative hypothesis, which posits that monozygotic twinning occurs with splitting at the postzygotic two-cell stage. Notably, data are not robust in support of either the traditional or the newly proposed model (Denker, 2015).

Dizygotic versus Monozygotic Twinning

Dizygotic twins are not in a strict sense true twins because they result from the maturation and fertilization of two ova during a single ovulatory cycle. Moreover, from a genetic perspective, dizygotic twins are like any other pair of siblings.

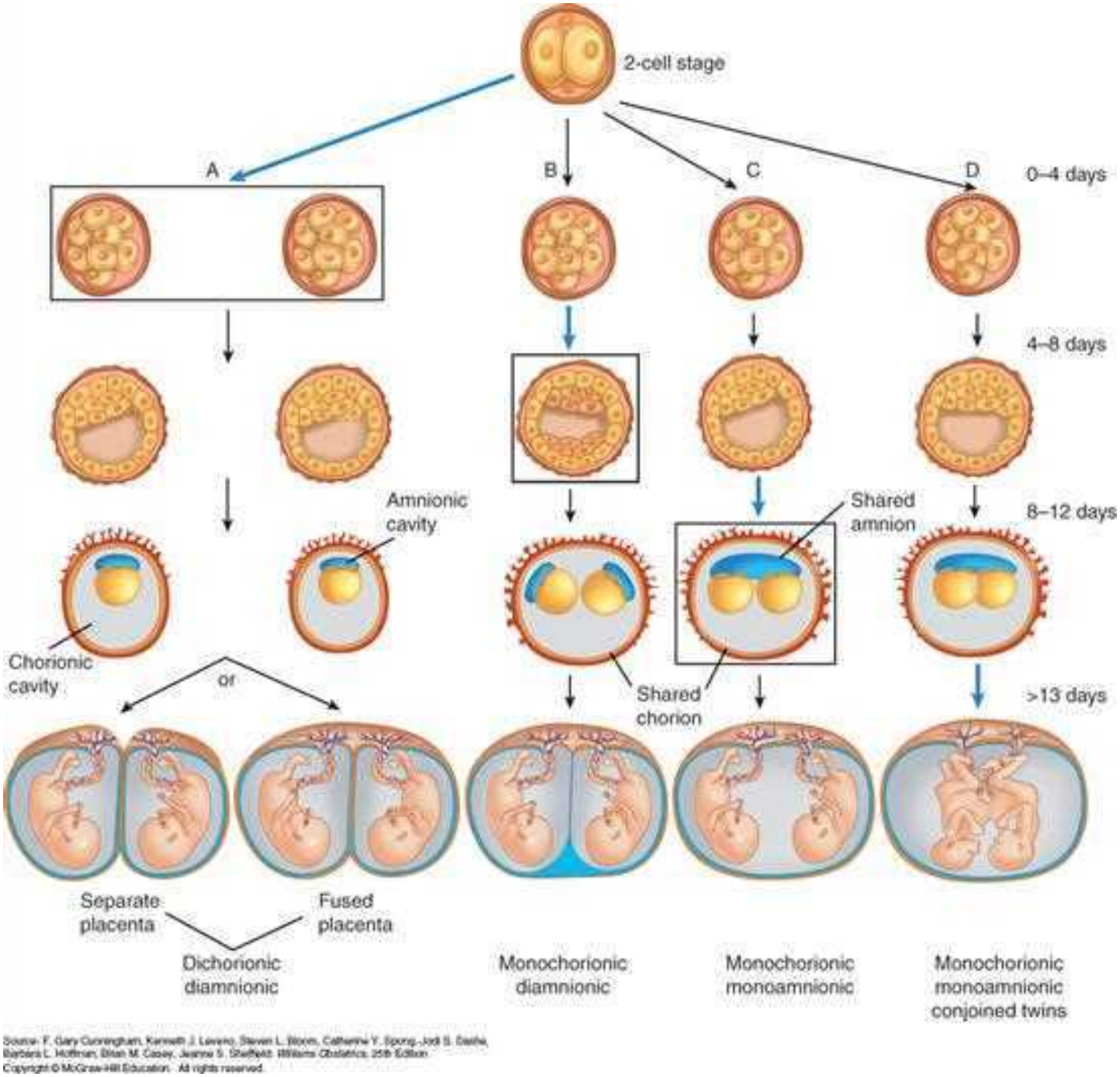
On the other hand, monozygotic or identical twins, although they have virtually the same genetic heritage, are usually not identical. Namely, the division of one fertilized zygote into two does not necessarily result in equal sharing of protoplasmic material. Monozygotic twins may actually be discordant for genetic mutations because of a postzygotic mutation, or may have the same genetic disease but with marked variability in expression. In female fetuses, skewed lyonization can produce differential expression of X-linked traits or diseases. Further, the process of monozygotic twinning is in a sense a teratogenic event, and monozygotic twins have a higher incidence of often discordant malformations (Glinianaia, 2008). For example, in one study of 926 monozygotic twins, the prevalence of congenital heart defects was 12-fold greater than the general population rate, but 68 percent of affected infants had a normal sibling (Pettit, 2013). From any of these mechanisms, dizygotic twins of the same sex may appear more nearly identical at birth than monozygotic twins.

Genesis of Monozygotic Twins

The developmental mechanisms underlying monozygotic twinning are poorly understood. The incidence of monozygotic twins is increased two- to fivefold in pregnancies conceived using assisted reproductive technology (ART). The predisposition to splitting may stem from specimen handling, growth media, or sperm DNA microinjection or may arise from intrinsic abnormalities associated with infertility (McNamara, 2016).

The outcome of the monozygotic twinning process depends on when division occurs. If zygotes divide within the first 72 hours after fertilization, two embryos, two amnions, and two chorions develop, and a diamnionic, dichorionic twin pregnancy evolves (Fig. 45-1). Two distinct placentas or a single, fused placenta may develop. If division occurs between the fourth and eighth day, a diamnionic, monochorionic twin pregnancy results. By approximately 8 days after fertilization, the chorion and the amnion have already differentiated, and division results in two embryos within a common amnionic sac, that is, a monoamnionic, monochorionic twin pregnancy. Conjoined twins result if twinning is initiated later.

FIGURE 45-1
Mechanism of monozygotic twinning. Black boxing and blue arrows in columns A, B, and C indicates timing of division. **A.** At 0 to 4 days postfertilization, an early conceptus may divide into two. Division at this early stage creates two chorions and two amnions (dichorionic, diamnionic). Placentas may be separate or fused. **B.** Division between 4 to 8 days leads to formation of a blastocyst with two separate embryoblasts (inner cell masses). Each embryoblast will form its own amnion within a shared chorion (monochorionic, diamnionic). **C.** Between 8 and 12 days, the amnion and amnionic cavity form above the germinal disc. Embryonic division leads to two embryos with a shared amnion and shared chorion (monochorionic, monoamnionic). **D.** Differing theories explain conjoined twin development. One describes an incomplete splitting of one embryo into two. The other describes fusion of a portion of one embryo from a monozygotic pair onto the other.



It has long been accepted that monochorionicity incontrovertibly indicated monozygosity. Rarely, however, monochorionic twins may in fact be dizygotic (Hackmon, 2009). Mechanisms for this are speculative, but in one review of 14 cases, nearly all had been conceived after ART procedures (Ekelund, 2008). McNamara and colleagues (2016) offer an excellent review of the mechanisms and evidence for both typical and atypical twinning.

Superfetation and Superfecundation

In *superfetation*, an interval as long as or longer than a menstrual cycle intervenes between fertilizations. Superfetation requires ovulation and fertilization during the course of an established pregnancy, which is theoretically possible until the uterine cavity is obliterated by fusion of the decidua capsularis to the decidua parietalis. Although known to occur in mares, superfetation is not known to occur spontaneously in humans. Lantieri and associates (2010) reported a case after ovarian hyperstimulation and intrauterine insemination in the presence of an undiagnosed tubal pregnancy. Most authorities believe that alleged cases of human superfetation result from markedly unequal growth and development of twin fetuses with the same gestational age.

Superfecundation refers to fertilization of two ova within the same menstrual cycle but not at the same coitus, nor necessarily by sperm from the same male. An instance of superfecundation or heteropaternity, documented by Harris (1982), is demonstrated in Figure 45-2. The mother was delivered of a black neonate whose blood type was A and a white neonate whose blood type was O. The blood type of the mother and her husband was O. More recent cases have been reported in the setting of paternity lawsuits (Girela, 1997). Given that superfecundation may also occur with ART, women should be advised to consider avoiding intercourse after embryo transfer (McNamara, 2016; Peigné, 2011).

FIGURE 45-2
An example of dizygotic twin boys as the consequence of superfecundation.

Factors Affecting Twinning

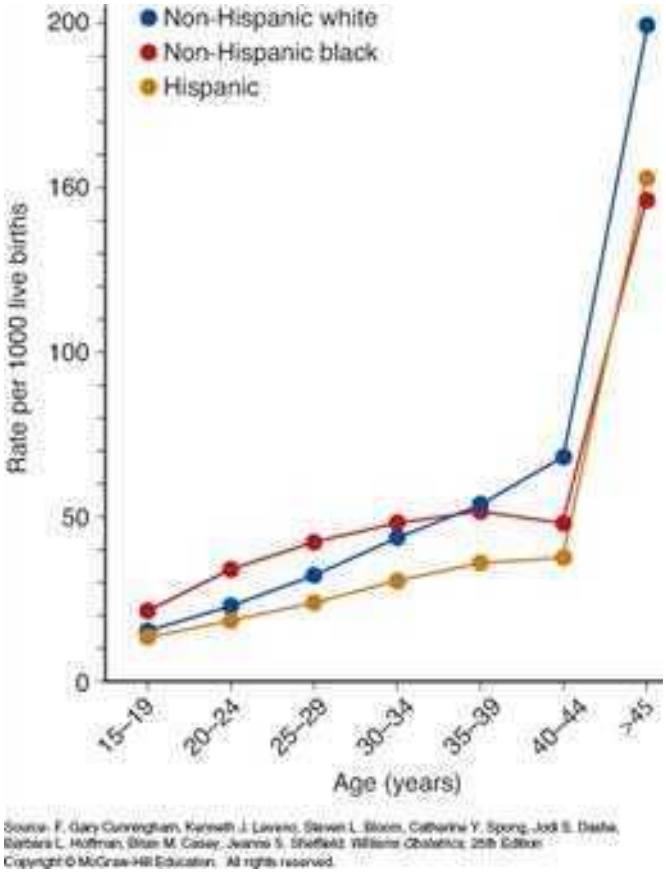
Dizygotic twinning is much more common than monozygotic splitting of a single oocyte, and its incidence is influenced by race, heredity, maternal age, parity, and, especially, fertility treatment. By contrast, the frequency of monozygotic twin births is relatively constant worldwide—approximately 1 set per 250 births, and this incidence is generally independent of demographic factors. One exception is that rates of zygotic splitting are increased following ART (Aston, 2008).

Demographics

Among different races and ethnic groups, the frequency of multifetal births varies significantly. In one analysis of more than 8 million births in the United States between 2004 and 2008, the rate of twinning was 3.5 percent in black women and 3 percent in whites (Abel, 2012). Hispanic, Asian, and Native American women had comparatively lower rates than white women. In one rural community in Nigeria, twinning occurred once in every 20 births (Knox, 1960)! These marked differences in twinning frequency may be the consequence of racial variations in levels of follicle-stimulating hormone—FSH (Nylander, 1973).

Maternal age is another important risk factor for multifetal pregnancies (Fig. 45-3). Dizygotic twinning frequency rises almost fourfold between the ages of 15 and 37 years (Painter, 2010). As such, there is a paradox of declining fertility but increasing twinning rates with advancing maternal age (Beemsterboer, 2006). Another explanation for the dramatic rise in twinning with advancing maternal age may be a higher use of ART in older women (Ananth, 2012). Paternal age has also been linked to twinning frequency, but its effect is felt to be small (Abel, 2012). Although twin pregnancy is associated with greater risks for most adverse perinatal outcomes, McLennan and associates (2017) did not find advanced maternal age to be an additional risk factor for fetal and infant death. From this population-based study of the United States, they concluded that women in their 30s may be counseled that their age is not a major additional risk factor for adverse obstetric outcomes in the setting of twin pregnancy.

FIGURE 45-3
Multifetal birth rates in the United States according to maternal age and race, 2015. (Data from Martin, 2017.)



Increasing parity independently raises the incidence of twinning in all populations studied. During a 30-year period, Antsaklis and coworkers (2013) noted a progressively increasing positive correlation between multiparity and twinning. However, they cautioned that greater use of ART may be partially contributory. In a two-year study from Nigeria, where such technology is not commonly available, Olusanya (2012) calculated the effects of multiparity compared with primiparity. They found an eightfold rise in multifetal gestation rates when parity was ≤4, and a 20-fold rise when parity was ≥5.

Heredity

As a determinant of twinning, the family history of the mother supersedes that of the father. One study of 4000 genealogical records showed that women who themselves were a dizygotic twin gave birth to twins at a rate of 1 set per 58 births (White, 1964). Women who were not a twin, but whose husbands were a dizygotic twin, gave birth to twins at a rate of 1 set per 116 pregnancies. Painter and associates (2010) performed genome-wide linkage analyses on more than 500 families of mothers of dizygotic twins and identified four potential linkage peaks. The highest peak was on the long arm of chromosome 6, and other suggestive peaks were on chromosomes 7, 9, and 16. That said, the contribution of these variants to the overall incidence of twinning is likely small (Hoekstra, 2008).

Nutrition

In animals, the litter size number grows in proportion to nutritional sufficiency. Evidence from various sources indicates that this occurs in humans as well. Nylander (1971) showed an increasing gradient in the twinning rate related to greater nutritional status as reflected by maternal size. Taller, heavier women had a twinning rate 25 to 30 percent greater than short, nutritionally deprived women. Likewise, Reddy and associates (2005) found an association of maternal weight and dizygotic twinning in the United States, in the absence of fertility drugs. Indeed, the influence of maternal weight as a factor for twinning will continue to rise in importance as the percentage of obese women in the United States continues to grow.

Evidence acquired during and after World War II suggested that twinning correlated more with nutrition than with body size. Widespread undernourishment in Europe during those years was associated with a marked fall in the dizygotic twinning rate (Bulmer, 1959). Several investigators have reported a greater prevalence of twinning among women who have taken supplementary folic acid (Ericson, 2001; Haggarty, 2006). Conversely, in a systematic review, Muggli and Halliday (2007) were unable to demonstrate a significant association. Analysis of twinning rate in Texas after folic acid fortification of cereal-grain products also failed to demonstrate an independent increase in twinning rates (Waller, 2003).

Pituitary Gonadotropin

The common factor linking race, age, weight, and fertility to multifetal gestation may be FSH levels (Benirschke, 1973). This theory is supported by the fact that greater fecundity and a higher rate of dizygotic twinning have been reported in women who conceive within 1 month after stopping oral contraceptives, but not during subsequent months (Rothman, 1977). This may be due to the sudden release of pituitary gonadotropin in amounts greater than usual during the first spontaneous cycle after stopping hormonal contraception. Indeed, the paradox of declining fertility but increasing twinning with advancing maternal age can be explained by an exaggerated pituitary release of FSH in response to decreased negative feedback from impending ovarian failure (Beemsterboer, 2006).

Infertility Therapy

Ovulation induction with FSH plus human chorionic gonadotropin (hCG) or clomiphene citrate remarkably enhances the likelihood of multiple concurrent ovulations. In their review of this practice, McClamrock and coworkers (2012) reported rates of twins and higher-order multifetal pregnancies as high as 28.6 percent and 9.3 percent, respectively. Rates this high remain a major concern. Two ongoing multicenter trials—Assessment of Multiple Gestations from Ovarian Stimulation (AMIGOS) and Pregnancy in Polycystic Ovary Syndrome II (PPCOSII)—are designed to provide guidance on achieving maximum pregnancy rates while minimizing multifetal gestation rates (Diamond, 2015; Legro, 2014).

In general with in vitro fertilization (IVF), the greater the number of embryos that are transferred, the greater the risk of twins and other multifetal gestations. In 2014, ART contributed to 1.6 percent of all newborns in the United States and to 18.3 percent of all neonates in multifetal gestations (Sunderam, 2017). The American Society for Reproductive Medicine (2017) recently revised their age-related guidelines regarding the number of cleavage-stage embryos or blastocysts to transfer during IVF. This effort aims to reduce the incidence of higher-order multifetal pregnancies. Based on these new recommendations, women younger than 35 years are encouraged to receive a single-embryo transfer, regardless of embryo stage. These practices have effectively lowered multifetal rates, and the rate of triplet or higher-order multifetal pregnancy has declined every year since 2009 (Kulkarni, 2013; Martin, 2017).

Sex Ratios in Multifetal Pregnancies

In humans, as the number of fetuses per pregnancy rises, the percentage of male conceptuses declines. Strandskov and coworkers (1946) found the percentage of males in 31 million singleton births in the United States was 51.6 percent. For twins, it was 50.9 percent; for triplets, 49.5 percent; and for quadruplets, 46.5 percent. Swedish birth data spanning 135 years reveals the number of males per 100 female newborns was 106 among singletons, 103 among twins, and 99 among triplets (Fellman, 2010). Females predominate even more in twins from late twinning events. For example, 68 percent of thoracopagus conjoined twins are female (Mutchinick, 2011). Two explanations have been offered. First, beginning in utero and extending throughout the life cycle, mortality rates are lower in females. Second, female zygotes have a greater tendency to divide.

Determining Zygosity

Twins of opposite sex are almost always dizygotic. In rare instances, due to somatic mutations or chromosome aberrations, the karyotype or phenotype of a monozygotic twin gestation can be different (Turpin, 1961). Most reported cases describe postzygotic loss of the Y chromosome in one 46,XY twin resulting in a phenotypically female twin with Turner syndrome (45,X). Zech and coworkers (2008) found a rare case of a 47,XXY zygote that underwent postzygotic loss of the X chromosome in some cells and loss of the Y chromosome in other cells. The phenotype of the resultant twins was one male and one female. Karyotype analyses revealed both to be 46,XX/46,XY genetic mosaics.

Determining Chorionicity

The risk for twin-specific complications varies in relation to both zygosity and chorionicity—the number of chorions. Shown in Table 45-2, the latter is the more important determinant. Specifically, perinatal mortality and neurological injury rates are greater in monochorionic diamnionic twins compared with dichorionic diamnionic pairs (Hack, 2008; Lee, 2008). In one retrospective analysis of more than 2000 twins, the risk of fetal demise in one or both monochorionic twin(s) was twice that in dichorionic multifetal gestations (McPherson, 2012). Moreover, the prospective risk of antepartum stillbirth is higher for monochorionic than for dichorionic twins at all preterm gestational ages. The highest risk is before 28 weeks' gestation (Glinianaia, 2011). In contrast, chorionicity differences do not significantly affect maternal outcomes (Carter, 2015).

TABLE 45-2

Overview of the Incidence of Twin Pregnancy Zygosity and Corresponding Twin-Specific Complications

	Rates of Twin-Specific Complications in Percent				
Type of Twinning	**Twins**	**Fetal-Growth Restriction**	**Preterm Delivery[a]**	**Placental Vascular Anastomosis**	**Perinatal Mortality**
Dizygotic	80	25	40	0	10–12
Monozygotic	20	40	50		15–18
Diamnionic/dichorionic	6–7	30	40	0	18–20
Diamnionic/monochorionic	13–14	50	60	100	30–40
Monoamnionic/monochorionic	<1	40	60–70	80–90	58–60
Conjoined	0.002 to 0.008	—	70–80	100	70–90

[a]Delivery before 37 weeks.

Data from Manning, 1995.

Sonographic Determination

This has become an integral tool to assist in multifetal pregnancy management. Indeed, the diagnosis and evaluation of a multifetal gestation is now considered a recognized indication for first-trimester sonography (Reddy, 2014). In addition, the North American Fetal Therapy Network (NAFTNet)—a consortium of 30 medical institutions in the United States and Canada—have provided recommendations for determination of chorionicity using sonography (Emery, 2015).

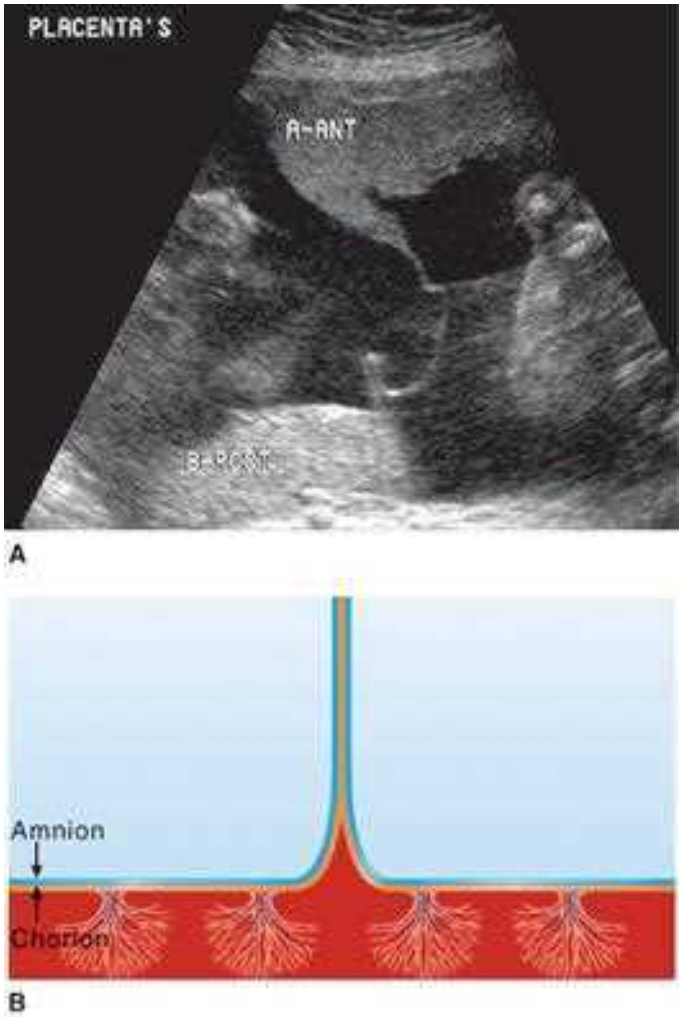
Sonographic features used to evaluate chorionicity vary according to gestational age. Accuracy is greatest in the first trimester and diminishes as gestational age advances. Namely, chorionicity can be determined sonographically with 98-percent accuracy in the first trimester but may be incorrect in up to 10 percent of second-trimester examinations (Emery, 2015; Lee, 2006). Moreover, for sonographic evaluations between 15 and 20 weeks' gestation, the odds of chorionicity misclassification rise by approximately 10 percent for each week of advancing gestational age in pregnancies compared with those completed before 14 weeks (Blumenfeld, 2014). Overall, chorionicity can be correctly determined with sonography before 24 weeks in approximately 95 percent of cases (Lee, 2006).

Early in the first trimester, the number of chorions equates to the number of gestational sacs. A thick band of chorion separating two gestational sacs signals a dichorionic pregnancy, whereas monochorionic twins have a single gestational sac. If the gestation is monochorionic diamnionic, it may be difficult to visualize the thin intervening amnion before 8 weeks' gestation (Emery, 2015). If the intervening membrane is difficult to visualize, the number of yolk sacs *usually* correlates with the number of amnions. However, the number of yolk sacs as a predictor of amnionicity may not always be accurate (Shen, 2006). Although uncommonly seen early, cord entanglement identifies a monoamnionic gestation. When chorionicity is uncertain, additional later sonographic examinations are performed.

After 10 to 14 weeks' gestation, sonographic assessment of chorionicity may be determined using four features. These are the number of placental masses, thickness of the membrane dividing the sacs, presence of an intervening membrane, and fetal gender (Emery, 2015). First, two separate placentas suggest dichorionicity. The converse is not necessarily true, such as cases with a single fused placental mass. Second, identification of a thick dividing membrane—generally ≥2 mm—supports a presumed diagnosis of dichorionicity. In a dichorionic pregnancy, this visualized membrane is composed of a total of four layers—two amnion and two chorion. Also, the *twin peak sign*—also called *lambda* or *delta sign*—is seen by examining the point of origin of the dividing membrane on the placental surface. The peak appears as a triangular projection of placental tissue extending a short distance between the layers of the dividing membrane (Fig. 45-4).

FIGURE 45-4

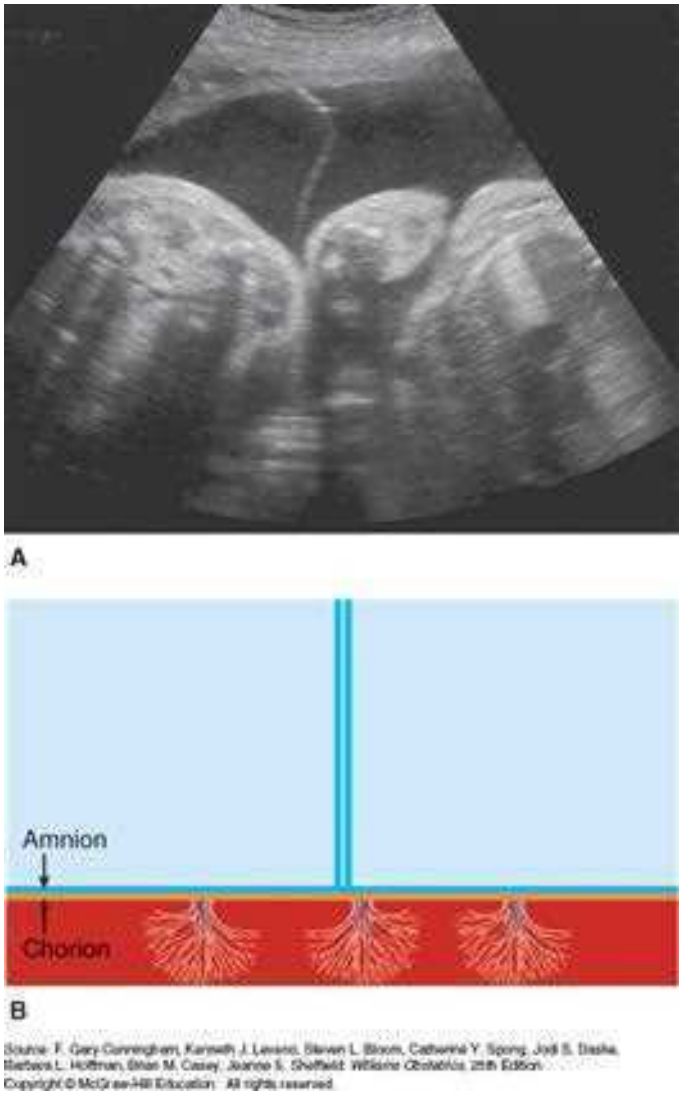
A. Sonographic image of the "twin-peak" sign, also termed the "lambda sign," in a 24-week gestation. At the top of this sonogram, tissue from the anterior placenta is seen extending downward between the amnion layers. This sign confirms dichorionic twinning. **B.** The "twin-peak" sign is seen at the bottom of this schematic diagram. The triangular portion of placenta insinuates between the amniochorion layers.



In contrast, monochorionic pregnancies have a dividing membrane that is so thin (generally <2 mm) that it may not be seen until the second trimester. The relationship between the membranes and placenta without apparent extension of placenta between the dividing membranes is called the *T sign* (Fig. 45-5). Evaluation of the dividing membrane can establish chorionicity in more than 99 percent of pregnancies in the first trimester (Miller, 2012). Lack of a dividing membrane signals a monochorionic monoamnionic gestation.

FIGURE 45-5

A. Sonographic image of the "T" sign in a monochorionic diamnionic gestation at 30 weeks. **B.** Schematic diagram of the "T" sign. Twins are separated only by a membrane created by the juxtaposed amnion of each twin. A "T" is formed at the point at which amnions meet the placenta.



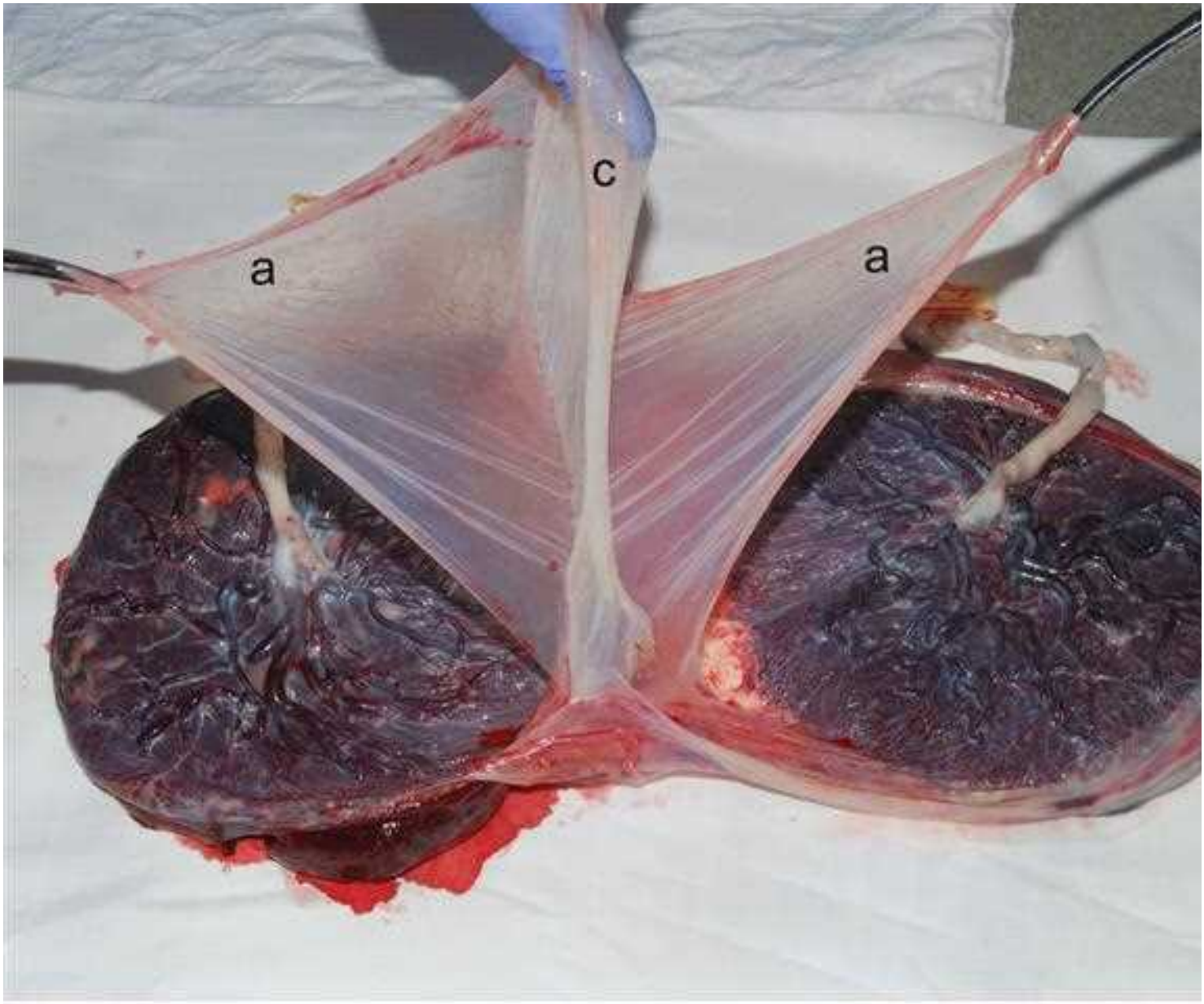
Last, twins with differing gender indicates a dichorionic (and dizygotic) gestation (Emery, 2015). A rare exception to this scenario would be a heterokaryotypic monochorionic gestation, described earlier (Sex Ratios in Multifetal Pregnancies). If both twins are the same gender, additional measures are necessary.

Placental Examination

A carefully performed visual examination of the placenta and membranes after delivery serves to establish zygosity and chorionicity promptly in approximately two thirds of cases. The following systematic examination is recommended. As the first neonate is delivered, one clamp is placed on a portion of its cord. Cord blood is generally not collected until after delivery of the other twin. As the second neonate is delivered, two clamps are placed on that cord, and so on as necessary. Alternatively, in higher-order deliveries, color-tagged clamps can be simpler. Until the delivery of the last fetus, each cord segment must remain clamped to prevent fetal hypovolemia and anemia caused by blood leaving the placenta via anastomoses and then through an unclamped cord. At this time, evidence is insufficient to recommend for or against delayed umbilical cord clamping in multifetal gestations (American College of Obstetricians and Gynecologists, 2017a). At Parkland Hospital, we currently do not perform delayed cord clamping in these pregnancies.

The placenta is carefully delivered to preserve the attachment of the amnion and chorion. With one common amnionic sac or with juxtaposed amnions not separated by chorion, the fetuses are monozygotic (see Fig. 45-1). If adjacent amnions are separated by chorion, the fetuses could be either dizygotic or monozygotic, but dizygosity is more common (Fig. 45-6). If the neonates are of the same sex, blood typing of cord blood samples may be helpful. Different blood types confirm dizygosity, although demonstrating the same blood type in each fetus does not confirm monozygosity. For definitive diagnosis, more complicated techniques such as DNA fingerprinting can be used. However, these tests are generally not performed at birth unless medical indications dictate a need.

FIGURE 45-6
Dichorionic diamnionic twin placenta. The membrane partition that separated twin fetuses is elevated and consists of chorion (***c***) between two amnions (***a***).



DIAGNOSIS OF MULTIFETAL GESTATION

Clinical Evaluation

During physical examination, accurate fundal height measurement, described in Chapter 9 (Subsequent Prenatal Visits), is essential. With multifetal pregnancies, uterine size is typically larger during the second trimester than expected for a singleton. Rouse and associates (1993) reported fundal heights in 336 well-dated twin pregnancies. Between 20 and 30 weeks' gestation, fundal heights averaged approximately 5 cm greater than expected for singletons of the same fetal age.

Diagnosing twins by palpation of fetal parts before the third trimester is difficult. Even late in pregnancy, this may be challenging, especially if one twin overlies the other, if the woman is obese, or if there is hydramnios. Palpating two fetal heads, often in different uterine quadrants, strongly supports a twin diagnosis. Late in the first trimester, two fetal heartbeats may be differentiated with Doppler ultrasonic equipment if their rates are clearly distinct from each other and from that of the mother.

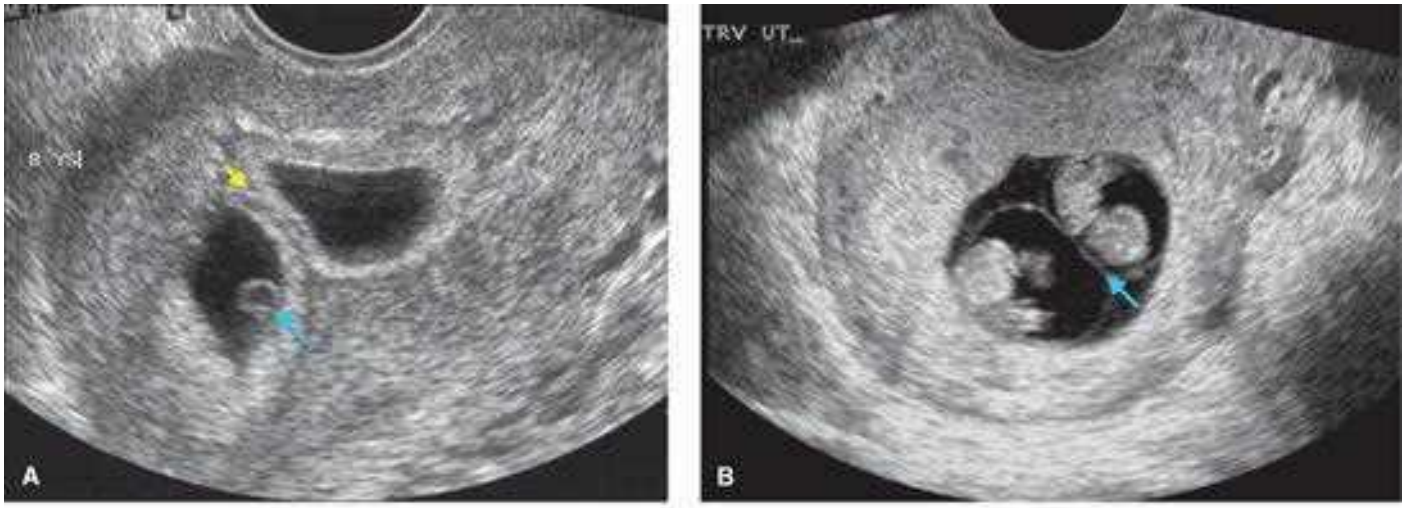
Overall, however, using clinical criteria alone to diagnose multifetal gestations is unreliable. For example, in the Routine Antenatal Diagnostic Imaging with Ultrasound (RADIUS) trial, for 37 percent of women who did not have a screening ultrasound examination, their twin pregnancies were not diagnosed until 26 weeks' gestation. And, in 13 percent of unscanned women, their multifetal gestations were only diagnosed during their admission for delivery (American College of Obstetricians and Gynecologists, 2016; LeFevre, 1993).

Sonography

Sonographic examination should detect practically all sets of twins. And, given the increased frequency of sonographic examinations during the first trimester, early detection of a twin pregnancy is common. Sonography can also be used to determine fetal number, estimated gestational age, chorionicity, and amnionicity. With careful examination, separate gestational sacs, if present, can be identified early in twin pregnancy (Fig. 45-7). Subsequently, each fetal head should be seen in two perpendicular planes so as not to mistake a cross section of the fetal trunk for a second fetal head. Ideally, two fetal heads or two abdomens should be seen in the same image plane to avoid scanning the same fetus twice and interpreting it as twins.

FIGURE 45-7

Sonograms of first-trimester twins. **A.** Dichorionic diamnionic twin pregnancy at 6 weeks' gestation. Note the thick dividing chorion (*yellow arrow*). One of the yolk sacs is indicated (*blue arrow*). **B.** Monochorionic diamnionic twin pregnancy at 8 weeks' gestation. Note the thin amnion encircling each embryo, resulting in a thin dividing membrane (*blue arrow*).



Higher-order multifetal gestations are more challenging to evaluate. Even in the first trimester, it can be difficult to identify the actual number of fetuses and their position. This determination is especially important if pregnancy reduction or selective termination is considered (Selective Reduction or Termination).

Other Diagnostic Aids

Abdominal radiography can be used if fetal number in a higher-order multifetal gestation is uncertain. However, radiographs generally have limited utility and may lead to an incorrect diagnosis if fetuses move during the exposure or if exposure time is inadequate. Additionally, fetal skeletons before 18 weeks' gestation are insufficiently radiopaque and may be poorly seen.

Although not typically used to diagnose multifetal pregnancy, magnetic resonance (MR) imaging may help delineate complications in monochorionic twins (Hu, 2006). In one review of 17 complicated twin gestations evaluated by both sonographic and MR imaging, the latter provided a more detailed assessment of twin pathology (Bekiesinska-Figatowska, 2013). This was particularly helpful in cases of conjoined twins.

No biochemical test reliably identifies multifetal gestations. Serum and urine levels of β-hCG and maternal serum levels of alpha-fetoprotein (MSAFP) are generally higher with twins compared with those in singletons. However, levels may vary considerably and overlap with those of singletons.

MATERNAL PHYSIOLOGICAL ADAPTATIONS

The various physiological burdens of pregnancy and the likelihood of serious maternal complications are typically greater with multifetal gestations than with a singleton pregnancy. This is considered, especially when counseling a woman whose health is compromised and in whom a multifetal gestation is recognized early. Similar consideration is given to the woman who is not pregnant but is considering infertility treatment.

Beginning in the first trimester, and temporarily associated with higher serum β-hCG levels, women with a multifetal gestation often have nausea and vomiting in excess of that with a singleton pregnancy. In women carrying more than one fetus, blood volume expansion is greater and averages 50 to 60 percent compared with 40 to 50 percent in those with a singleton (Pritchard, 1965). This augmented hypervolemia teleologically offsets blood loss with vaginal delivery of twins, which is twice that with a single fetus. Although red cell mass also accrues, it does so proportionately less in twin pregnancies. Combined with greater iron and folate requirements, this predisposes to anemia.

Women carrying twins also have a typical pattern of arterial blood pressure change. MacDonald-Wallis and coworkers (2012) analyzed serial blood pressures in more than 13,000 singleton and twin pregnancies. As early as 8 weeks' gestation, the diastolic blood pressure in women with twins was lower than that with singleton pregnancies but generally rose by a greater degree at term. An earlier study demonstrated that this rise was at least 15 mm Hg in 95 percent of women with twins compared with only 54 percent of women with a singleton (Campbell, 1986).

Hypervolemia along with decreased vascular resistance has an impressive effect on cardiac function. In one study of 119 women with a twin pregnancy, cardiac output rose another 20 percent above that in women with a singleton pregnancy (Kametas, 2003). Similarly, Kuleva and coworkers (2011) using serial

echocardiography found a greater increase in cardiac output in 20 women with uncomplicated twin pregnancies. Both studies found the augmented cardiac output was predominantly due to greater stroke volume rather than higher heart rate. Vascular resistance was significantly lower in twin gestations throughout pregnancy compared with singleton ones. In a study of 30 uncomplicated twin pregnancies, this same group of investigators using echocardiography later identified progressive diastolic dysfunction from the first to third trimester. The dysfunction subsequently normalized after delivery (Ghi, 2015).

Uterine growth in a multifetal gestation is substantively greater than in a singleton pregnancy. The uterus and its nonfetal contents may achieve a volume of 10 L or more and weigh in excess of 20 pounds. Especially with monozygotic twins, excessive amounts of amnionic fluid may rapidly accumulate. In these circumstances, maternal abdominal viscera and lungs can be appreciably compressed and displaced by the expanding uterus. As a result, the size and weight of the large uterus may preclude more than a sedentary existence for these women.

If hydramnios develops, maternal renal function can become seriously impaired, most likely as the consequence of obstructive uropathy (Quigley, 1977). With severe hydramnios, therapeutic amniocentesis may provide relief for the mother, may improve obstructive uropathy, and possibly may lower the preterm delivery risk that follows preterm labor or prematurely ruptured membranes. Unfortunately, hydramnios is often characterized by acute onset remote from term and by rapid reaccumulation despite amniocentesis.

PREGNANCY COMPLICATIONS

Spontaneous Abortion

Miscarriage is more likely with multifetal gestation. In one 16-year study, the spontaneous abortion rate per live birth in singleton pregnancies was 0.9 percent compared with 7.3 percent in multifetal ones (Joó, 2012). Also, twins achieved through ART are at greater risk for abortion compared with those conceived spontaneously (Szymusik, 2012).

In some cases, one fetus may be spontaneously lost rather than the entire gestation. As a result, the incidence of twins in the first trimester is much greater than the incidence of twins at birth. It has been estimated that 1 in *80 births* are multifetal, whereas 1 in *8 pregnancies* begin multifetal but are spontaneously reduced (Corsello, 2010). Sonography studies in the first trimester have shown that one twin is spontaneously reduced or "vanishes" before the second trimester in up to 10 to 40 percent of all twin pregnancies (Brady, 2013). The incidence is higher following ART conception. Also, monochorionic twins have a significantly greater risk of spontaneous reduction than dichorionic twins (Sperling, 2006). Undoubtedly, some threatened abortions are the result of death and resorption of one embryo from an unrecognized twin gestation.

Dickey and associates (2002) described spontaneous reduction in 709 multifetal pregnancies. Before 12 weeks, one or more embryos died in 36 percent of twin pregnancies, in 53 percent of triplet pregnancies, and in 65 percent of quadruplet pregnancies. Interestingly, ultimate pregnancy duration and birthweight were inversely related to the initial gestational sac number regardless of the final number of fetuses at delivery. This effect was most pronounced in twins who started as quadruplets. Chasen and coworkers (2006) reported that spontaneous reduction of an IVF twin pregnancy to a singleton pregnancy was associated with perinatal outcomes intermediate between those for IVF singleton and IVF twin pregnancies that did not undergo spontaneous reduction. Evidence for adverse immediate and long-term effects of twin spontaneous reduction on the remaining pregnancy is conflicting (McNamara, 2016).

Notably, spontaneous reduction of a twin gestation may affect prenatal screening results. In one study of ART-conceived gestations, Gjerris and colleagues (2009) compared 56 twin pregnancies with a single early demise and 897 singleton gestations. They found no differences in first-trimester serum marker concentrations as long as the embryonic loss was identified before 9 weeks' gestation. If diagnosed after 9 weeks, the serum markers were higher and less precise in gestations with an early demise of one twin than in the singleton gestations. With a vanishing twin, first-trimester maternal serum levels of the pregnancy associated plasma protein-A (PAPP-A) can be elevated. Second-trimester MSAFP and dimeric inhibin A levels can also be higher (Huang, 2015). This phenomenon may also affect noninvasive prenatal testing using cell-free DNA (cfDNA). In one report, this effect was thought to be responsible for 15 percent of the false-positive results from quantitative counting methods (Futch, 2013). The recent development of single nucleotide polymorphism technology for cfDNA testing appears to hold promise in better identifying these cases (Curnow, 2015). Regardless, the diagnosis of a spontaneously reduced abortus is ideally excluded to help avoid confusion with results from aneuploidy and neural-tube defect screening.

Congenital Malformations

As noted earlier, the incidence of congenital malformations is appreciably higher in multifetal gestations compared with that in singleton pregnancies. In one survey-based study, the congenital malformation rate was 406 per 10,000 twins compared with 238 per 10,000 singletons (Glinianaia, 2008). The malformation rate in monochorionic twins was almost twice that of dichorionic twin gestations. This increase has been attributed to the higher incidence of structural defects in monozygotic twins. Indeed, one large population-based study between 1998 and 2010 found that twins had a 73-percent greater risk of congenital heart disease than singletons. The risk was substantially higher among monochorionic twins (Best, 2015). But, from a 30-year European registry of multifetal births, structural anomaly rates rose steadily from 2.16 percent in 1987 to 3.26 percent in 2007 (Boyle, 2013). Yet, during this time, the proportion of dizygotic twins grew by 30 percent, whereas the proportion of monozygotic twins remained stable. This higher risk of congenital malformations in dizygotic twins over time correlated with increased availability of ART. An increase in rates of birth defects related to ART has been reported repeatedly (Boulet, 2016; Talauliker, 2012).

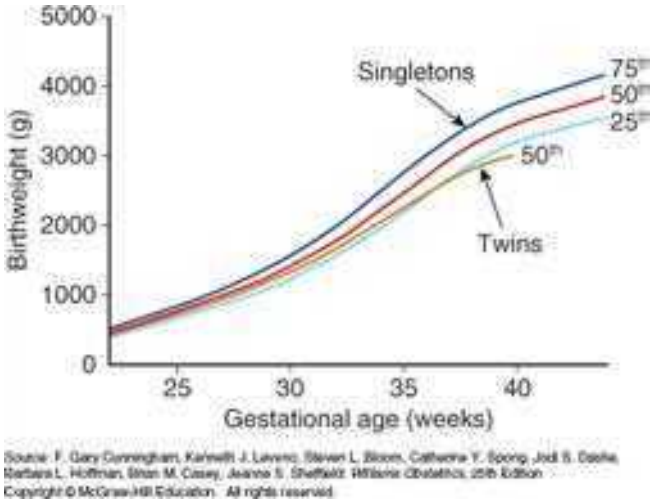
Low Birthweight

Multifetal gestations are more likely to be low birthweight than singleton pregnancies due to restricted fetal growth and preterm delivery. From 1988 to 2012 at Parkland Hospital, data were collected from 357,205 singleton neonates without malformations and from 3714 normal twins who were both liveborn. Birthweights in

twins closely paralleled those of singletons until 28 to 30 weeks' gestation. Thereafter, twin birthweights progressively lagged (Fig. 45-8). Beginning at 35 to 36 weeks' gestation, twin birthweights clearly diverge from those of singletons.

FIGURE 45-8

Birthweight percentiles (25th to 75th) for 357,205 singleton neonates compared with the 50th birthweight percentile for 3714 twins, Parkland Hospital 1988—2012. Infants with major malformations, pregnancies complicated by stillbirth, and twin gestations with >25 percent discordance were also excluded. (Data from Dr. Don McIntire.)



In general, the degree of growth restriction increases with fetal number. The caveat is that this assessment is based on growth curves established for singletons. Several authorities argue that fetal growth in twins is different from that of singleton pregnancies. And thus, abnormal growth should be diagnosed only when fetal size is less than expected for *multifetal gestation*. Accordingly, twin and triplet growth curves have been developed (Kim, 2010; Odibo, 2013; Vora, 2006). At Parkland, we use the standards of birthweight in twin gestations stratified by placental chorionicity for identification of suspected fetal-growth restriction (Ananth, 1998).

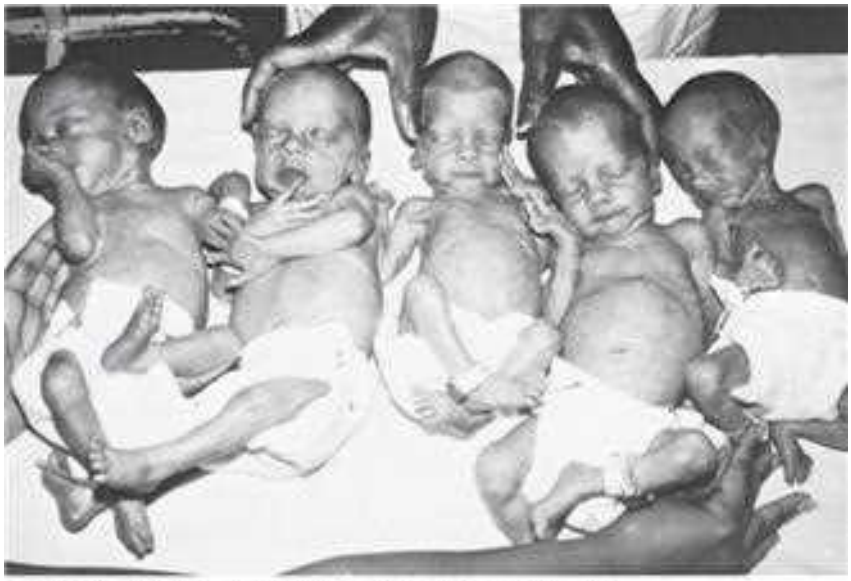
The degree of growth restriction in monozygotic twins is likely to be greater than that in dizygotic pairs (Fig. 45-9). With monochorionic embryos, allocation of blastomeres may not be equal, vascular anastomoses within the placenta may cause unequal distribution of nutrients and oxygen, and discordant structural anomalies resulting from the twinning event itself may affect growth. For example, the quintuplets shown in Figure 45-10 represent three dizygotic and two monozygotic fetuses. When delivered at 31 weeks, the three neonates from separate ova weighed 1420, 1530, and 1440 g, whereas the two derived from the same ovum weighed 990 and 860 g.

FIGURE 45-9

Marked growth discordance in monochorionic twins. (Used with permission from Dr. Laura Greer.)

FIGURE 45-10

Davis quintuplets at 3 weeks following delivery. The first, second, and fourth newborns from the left each arose from separate ova, whereas the third and fifth neonates are from the same ovum.



In the third trimester, the larger fetal mass leads to accelerated placental maturation and relative placental insufficiency. In dizygotic pregnancies, marked size discordancy usually results from unequal placentation, with one placental site receiving more perfusion than the other. Size differences may also reflect different genetic fetal-growth potentials. Discordancy can also result from fetal malformations, genetic syndromes, infection, or umbilical cord abnormalities such as velamentous insertion, marginal insertion, or vasa previa (Chap. 44, Accelerated Lung Maturation).

Hypertension

Pregnancy-related hypertensive disorders are more likely to develop with multifetal gestations. The exact incidence attributable to twin pregnancy is difficult to determine because these gestations are more likely to deliver preterm and before preeclampsia usually develops. Also, women with twin pregnancies are often older and multiparous, qualities associated with lower rates of preeclampsia (Francisco, 2017). The incidence of pregnancy-related hypertension in women with twins is 20 percent at Parkland Hospital. In their analysis of 513 twin pregnancies, Fox and coworkers (2014) identified 15 percent of parturients with preeclampsia. Another study compared 257 women with twins and gestational diabetes against 277 nondiabetic women carrying twins. These researchers found a twofold greater risk of preeclampsia in women diagnosed with gestational diabetes (Gonzalez, 2012). Conversely, no specific zygosity confers a greater rate of hypertensive disorder in twin pregnancies (Lučovnik, 2016). Finally, from the National Center for Health Statistics, Luke and associates (2008) analyzed 316,696 twin, 12,193 triplet, and 778 quadruplet pregnancies. These investigators noted that the risk for pregnancy-associated hypertension was significantly increased for triplets and quadruplets (11 and 12 percent, respectively) compared with that for twins (8 percent).

These data suggest that fetal number and placental mass are involved in preeclampsia pathogenesis. Women with twin pregnancies have levels of antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) that are twice that of singletons. Levels are seemingly related to greater placental mass rather than primary placental pathology (Bdolah, 2008; Maynard, 2008). Rana and coworkers (2012) measured antiangiogenic sFlt-1 and proangiogenic placental growth factor (PlGF) in 79 women with twins referred for evaluation of preeclampsia. In the 58 women identified with either gestational hypertension or preeclampsia, there was an incremental rise in sFlt-1 concentrations, decline in PlGF levels, and increase in sFlt-1/PlGF ratios compared with normotensive twin pregnancies. With multifetal gestation, hypertension not only develops more often but also tends to develop earlier and be more severe. In the analysis of angiogenic factors mentioned above, more than half of affected women presented before 34 weeks, and their sFlt-1/PlGF ratio rise was more striking (Rana, 2012). This relationship is discussed in Chapter 40 (Endothelial Cell Injury).

Preterm Birth

The duration of gestation shortens with accruing fetal number. More than five of every 10 twins and nine of 10 triplets born in the United States in 2015 were delivered preterm (Martin, 2017). Prematurity is sixfold and tenfold greater in twins and triplets, respectively (Giuffre, 2012). One review showed that approximately 60 percent of preterm births in twins are indicated, about a third result from spontaneous labor, and 10 percent follow prematurely ruptured membranes (Chauhan, 2010). In another analysis of almost 300,000 live births, the proportion of preterm birth associated with premature membrane rupture rose with gestational plurality from 13 percent with singletons to 20 percent with triplets or more (Pakrashi, 2013).

Although the causes of preterm delivery in twins and singletons may be different, neonatal outcome is generally the same at similar gestational ages (Kilpatrick, 1996; Ray, 2009; Salem, 2017). However, outcomes for preterm twins who are markedly discordant may not be comparable with those for singletons because whatever caused the discordance may have long-lasting effects (Yinon, 2005).

Long-Term Infant Development

Historically, twins have been considered cognitively delayed compared with singletons (Record, 1970; Ronalds, 2005). However, in cohort studies evaluating normal-birthweight term newborns, cognitive outcomes between twins and singletons are similar (Lorenz, 2012). Christensen and associates (2006) found similar national standardized test scores in the ninth grade in 3411 twins and 7796 singletons born between 1986 and 1988.

In contrast, among normal-birthweight neonates, the cerebral palsy risk is higher among twins and higher-order multiples. For example, the cerebral palsy rate has been reported to be 2.3 per 1000 in singletons, 12.6 per 1000 in twins, and 44.8 per 1000 in triplets (Giuffre, 2012). Greater risks of fetal-growth restriction, congenital anomalies, twin-twin transfusion syndrome, and fetal demise of a cotwin are suggested contributors to these differences (Lorenz, 2012).

UNIQUE FETAL COMPLICATIONS

Several unique complications arise in multifetal pregnancies. These are described in twins but can be found in higher-order multifetal gestations. Most fetal complications due to the twinning process itself are seen with monozygotic twins. Their pathogenesis is best understood after reviewing the possibilities shown in Figure 45-1.

Monoamnionic Twins

Only about 1 percent of all monozygotic twin gestations will share an amnionic sac, and approximately 1 in 20 monochorionic twin gestations are monoamnionic (Hall, 2003; Lewi, 2013). Diamnionic twins can become monoamnionic if the dividing membrane spontaneous or iatrogenically ruptures. Their morbidity and mortality rates then mirror those of monoamnionic twins.

Historical mortality rates in monoamnionic twins were reported to be as high as 70 percent. Contemporary outcomes are improved, yet the demise rate after viability remains elevated (Post, 2015). Of those fetuses alive before 16 weeks' gestation, less than half survive until the neonatal period. Fetal abnormalities and spontaneous miscarriage contribute to most losses (Prefumo, 2015). After 20 weeks, the perinatal mortality rate for monoamnionic twin pregnancies approximates 15 percent (Shub, 2015). A high fetal death rate is attributable to preterm birth, congenital anomalies, twin-twin transfusion syndrome, or cord entanglement.

Congenital anomaly rates in monoamnionic twins reach 18 to 28 percent (Post, 2015). Since concordance of anomalies is found in only approximately one quarter of cases, the finding of normal anatomy in one twin does not negate the need for a thorough evaluation in the second. Also, because of the higher risk of cardiac anomalies, fetal echocardiography is indicated in these pregnancies. Of note, monoamnionic twins are by definition monozygotic and thus presumed to be genetically identical. Consequently, either both or none of the fetuses have chromosomal abnormalities except in rare cases of discordance (Zwijnenburg, 2010). Indeed, the risk for Down syndrome in each fetus of the monozygotic pair is similar to or lower than the risk in maternal age-matched singletons (Sparks, 2016). The standard methods for Down syndrome screening in these pregnancies can be applied (Chap. 14, Traditional Aneuploidy Screening Tests).

The rate of twin-twin transfusion syndrome in monoamnionic twins is lower than the rate reported in monochorionic diamnionic pregnancies. This may be due to the near universal presence in monoamnionic twins of arterioarterial anastomoses, which are presumed to be protective (Hack, 2009b; Post, 2015). Nonetheless, twin-twin transfusion syndrome surveillance is recommended and described in Diagnosis.

Umbilical cords frequently entangle (Fig. 45-11). Morbid cord entanglement appears to occur early, and monoamnionic pregnancies that have successfully reached 30 to 32 weeks' gestation are at reduced risk. In one Dutch series, the incidence of intrauterine demise dropped from 15 percent after 20 weeks to 4 percent at gestational ages >32 weeks (Hack, 2009a). Although color-flow Doppler sonography is used to diagnose entanglement (Fig. 45-12), factors that lead to pathological umbilical vessel constriction are unknown. A consequence is that fetal death from cord entanglement is unpredictable. Unfortunately, monitoring for this is relatively ineffective. In one study, after analysis of more than 10,000 hours of fetal tracing from 17 sets of monoamnionic twins, Quinn and colleagues (2011) concluded that monitoring was physically possible in only 50 percent of cases. An abnormal fetal heart rate tracing prompted delivery in only six cases.

FIGURE 45-11

Monozygotic twins in a single amnionic sac. The smaller fetus apparently died first, and the second subsequently succumbed when umbilical cords entwined.

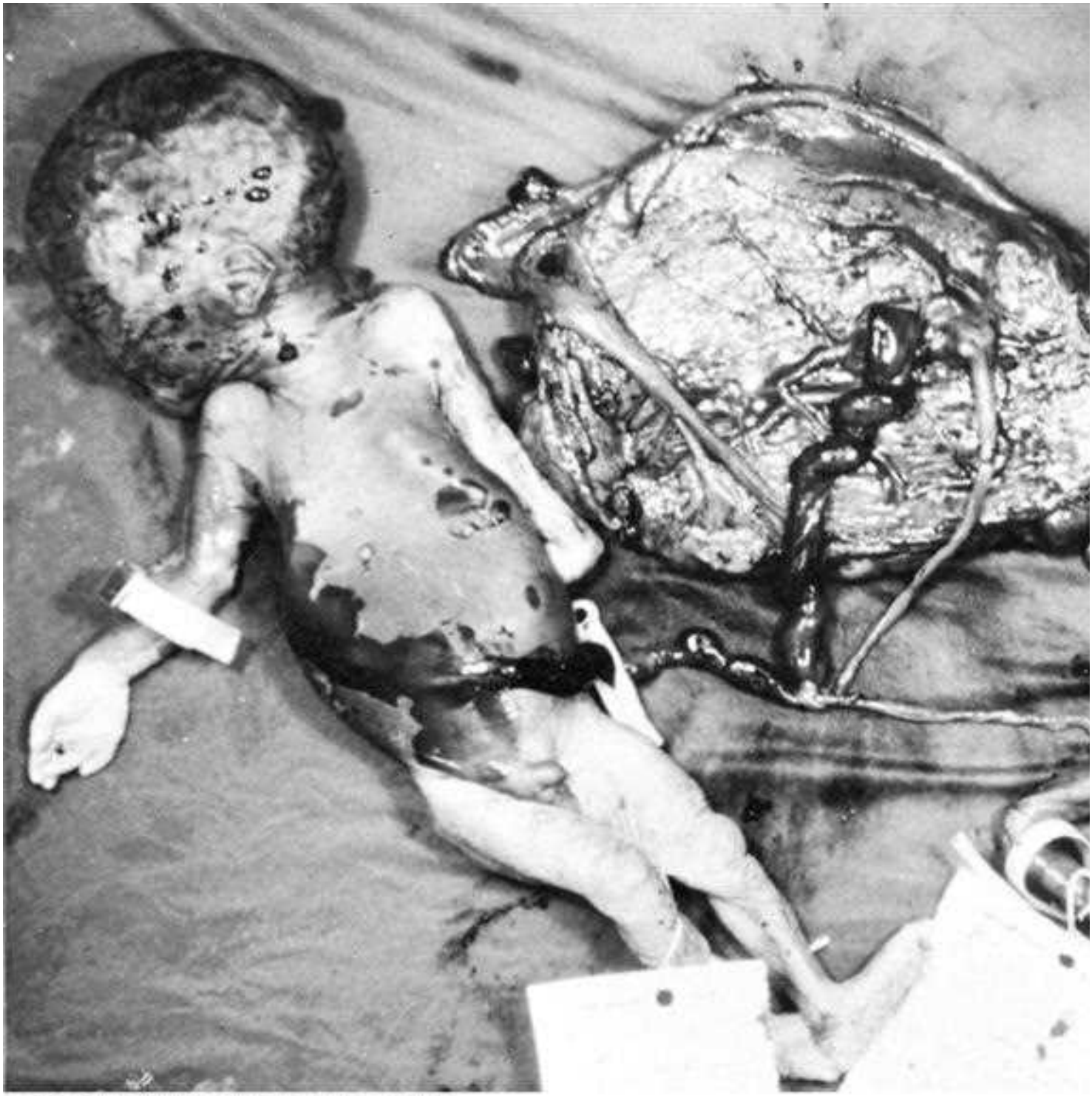
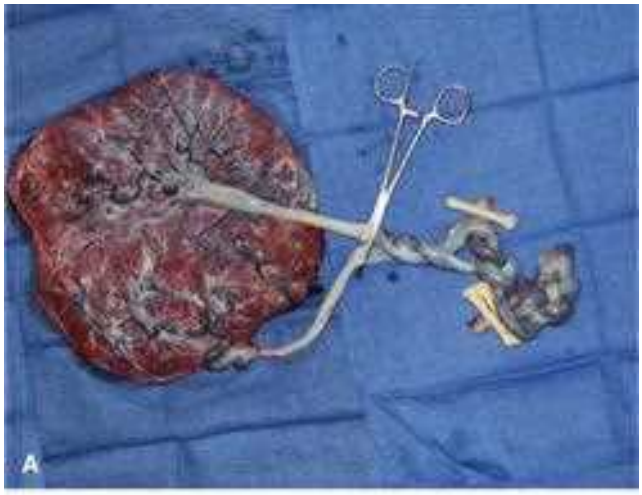
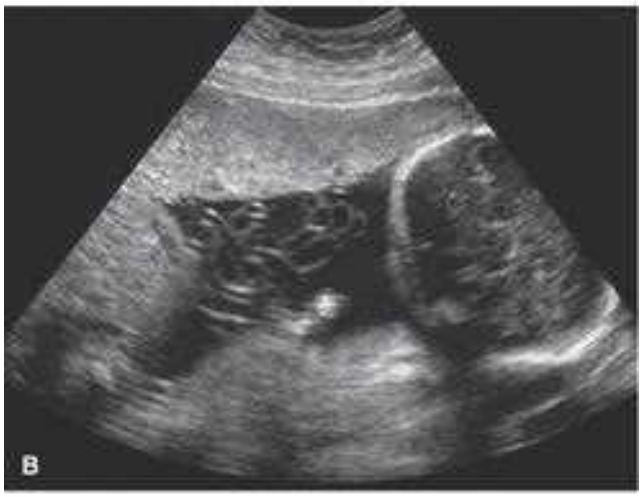
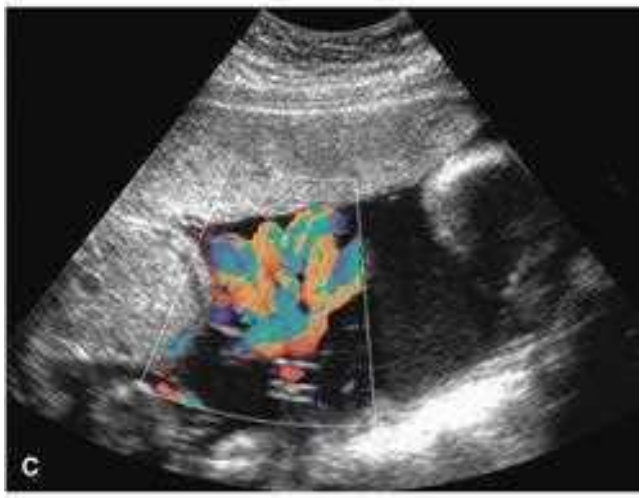


FIGURE 45-12

Monochorionic monoamnionic cord entanglement. **A.** Despite marked knotting of the cords, vigorous twins were delivered by cesarean. **B.** Preoperative sonogram of this pregnancy shows entwined cords. **C.** This finding is accentuated with application of color Doppler. (Used with permission from Dr. Julie Lo.)







One proposed management scheme is based on a study by Heyborne and coworkers (2005), who reported no stillbirths in 43 twin pregnancies of women admitted at 26 to 27 weeks' gestation for daily fetal surveillance. However, in 44 women managed as outpatients and admitted only for obstetrical indications, there were 13 stillbirths. Because of this report, women with monoamnionic twins are recommended to undergo 1 hour of daily fetal heart rate monitoring, either as an outpatient or inpatient, beginning at 26 to 28 weeks' gestation. With initial testing, a course of betamethasone is given to promote pulmonary maturation (Chap. 42, Corticosteroids for Fetal Lung Maturation). If fetal testing remains reassuring and no other intervening indications arise, cesarean delivery is performed at 32 to 34 weeks. A second course of betamethasone can be given before this (American College of Obstetricians and Gynecologists, 2016). This management scheme is used at Parkland Hospital and resulted in the successful 34-week delivery of the twins depicted in Figure 45-12.

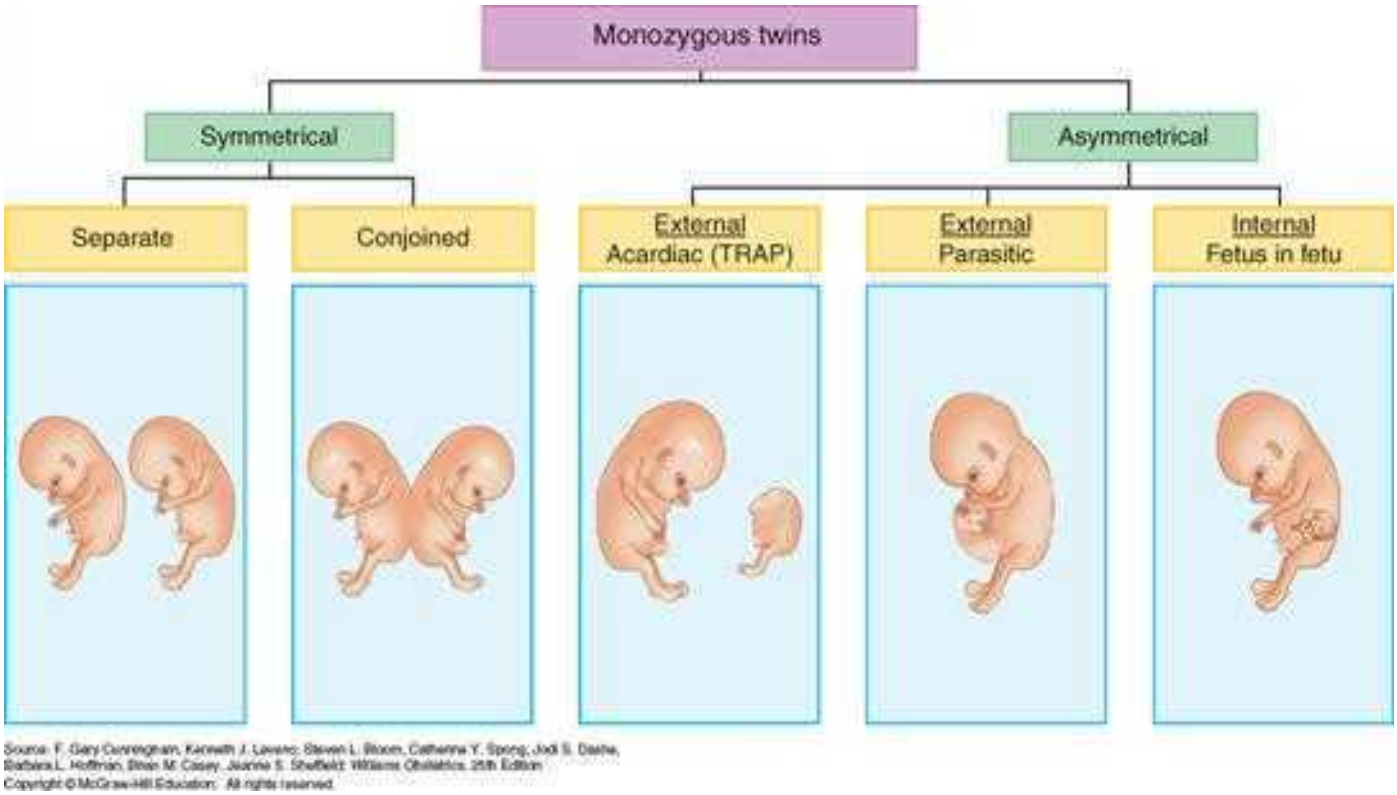
Unique and Aberrant Twinning

Of monoamnionic twins just described, one interesting subset derives from embryonic splitting on postfertilization day 9. These "mirror image twins" are genetically identical but have mirror image features such as handedness and hair whorls (Post, 2015).

More seriously, several aberrations in monozygotic twinning result in a spectrum of fetal malformations. These are traditionally ascribed to incomplete splitting of an embryo into two separate twins. However, it is possible that they may result from early secondary fusion of two separate embryos. These separated embryos are either symmetrical or asymmetrical, and the spectrum of anomalies is shown in Figure 45-13.

FIGURE 45-13

Possible outcomes of monozygotic twinning. The asymmetrical category contains twinning types in which one twin complement is substantially smaller and incompletely formed.

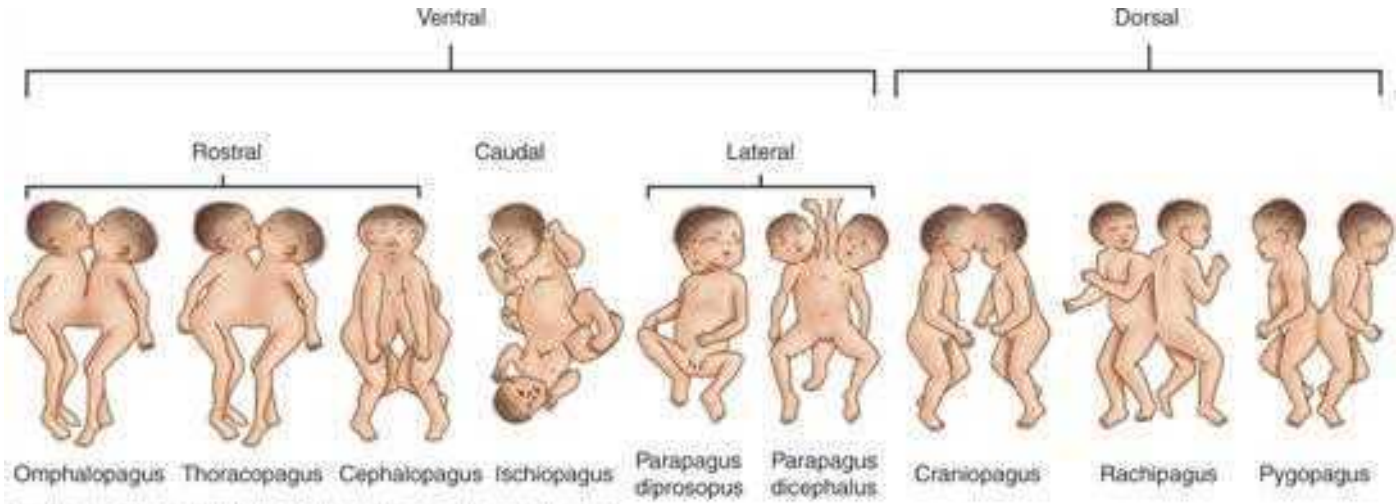


Conjoined Twins

In the United States, united or conjoined twins have been referred to as *Siamese twins*–after Chang and Eng Bunker of Siam (Thailand), who were displayed worldwide by P. T. Barnum. Joining of the twins may begin at either pole and produce characteristic forms depending on which body parts are joined or shared (Fig. 45-14). Of these, thoracopagus is the most common (Mutchinick, 2011). The frequency of conjoined twins is not well established. In Singapore, Tan and coworkers (1971) identified seven cases of conjoined twins among more than 400,000 deliveries—an incidence of 1 in 60,000.

FIGURE 45-14

Types of conjoined twins. (Modified with permission from Spencer R: Theoretical and analytical embryology of conjoined twins: part I: embryogenesis, Clin Anat. 2000;13(1):36–53.)



Conjoined twins can frequently be identified using sonography at midpregnancy (McHugh, 2006). This provides an opportunity for parents to decide whether to continue the pregnancy. As shown in Figure 45-15, identification of cases during the first trimester is also possible. During sonographic interrogation, fetal poles are closely associated and do not change relative position from one another. A targeted examination, including a careful evaluation of the organs involved, is necessary before counseling can be provided. As shown in Figure 45-16, MR imaging is a valuable adjunct to clarify shared organs. Compared with sonography, MR imaging can provide superior views, especially in later pregnancy when amnionic fluid is diminished and fetal crowding is greater (Hibbeln, 2012).

FIGURE 45-15
Sonogram of a conjoined twin pregnancy at 13 weeks' gestation. These thoracoomphalopagus twins have two heads but a shared chest and abdomen.

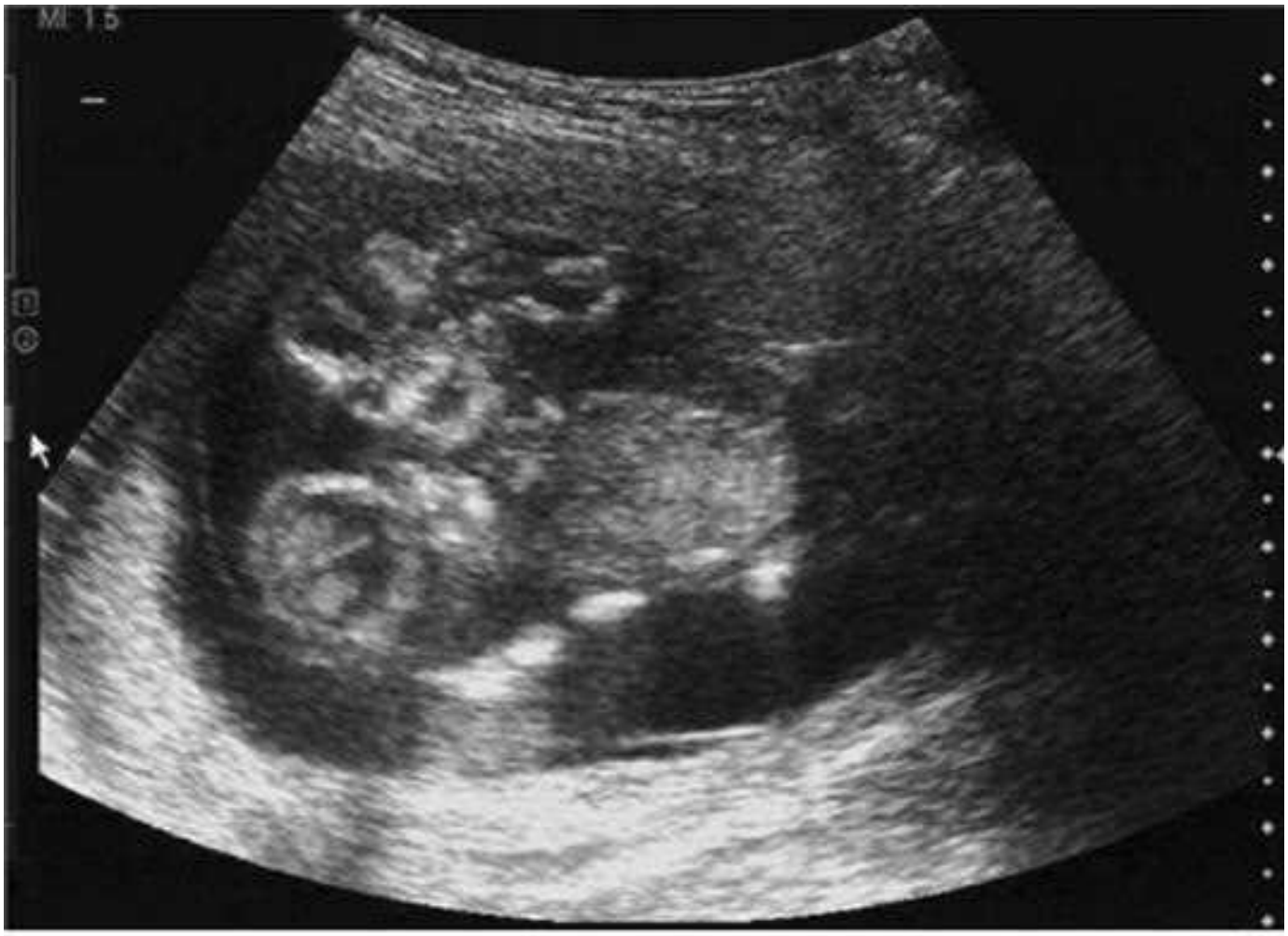
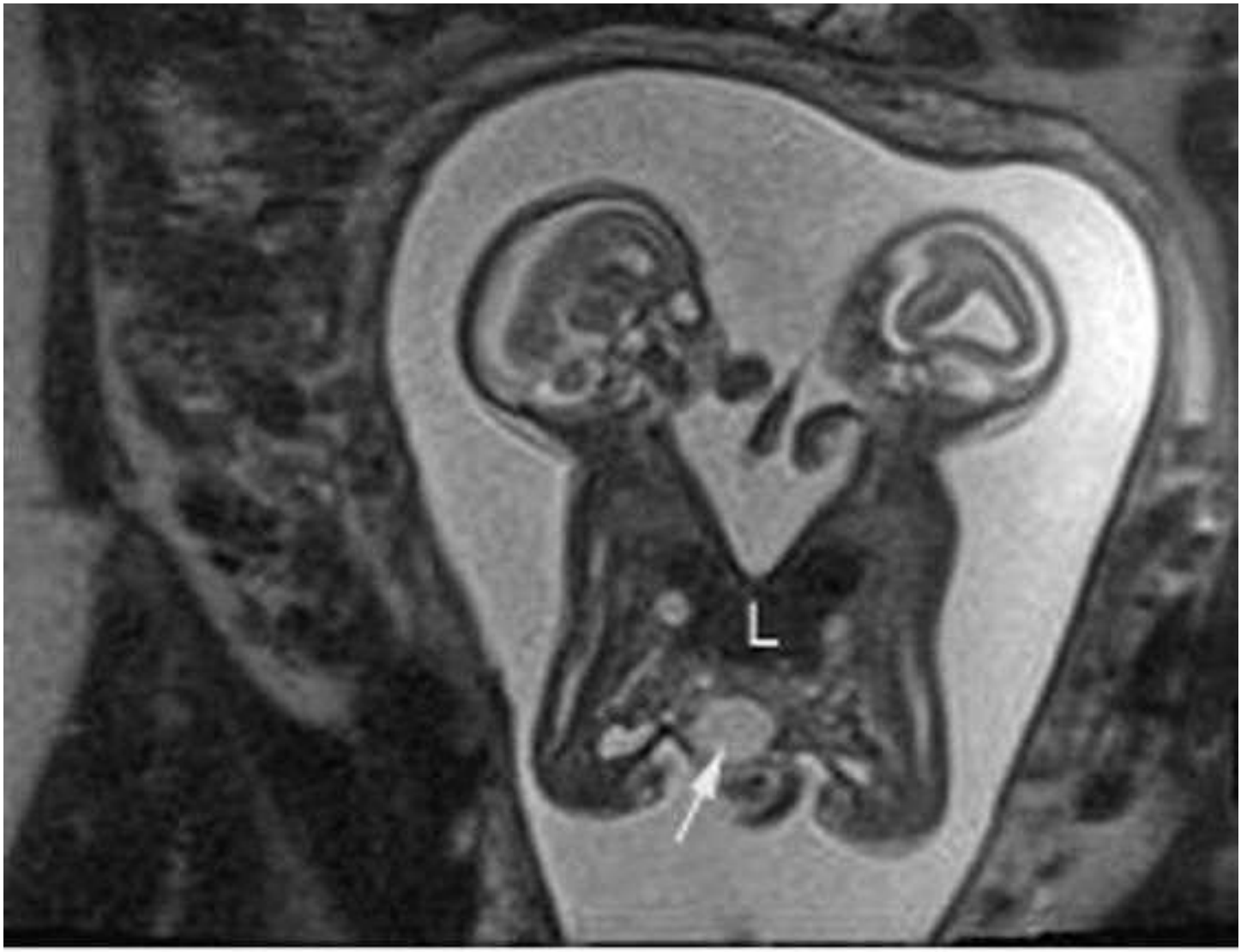


FIGURE 45-16
Magnetic resonance imaging of conjoined twins. This T2-weighted HASTE sagittal image demonstrates fusion from the level of the xiphoid process to just below the level of the umbilicus, that is, omphalopagus twins. Below the fused liver (*L*), there is a midline cystic mass (*arrow*) within the tissue connecting the twins. An omphalomesenteric cyst was favored given the location within the shared tissue. (Used with permission from Dr. April Bailey.)



Surgical separation of an almost completely joined twin pair may be successful if essential organs are not shared (O'Brien, 2015; Tannuri, 2013). Conjoined twins may have discordant structural anomalies that further complicate decisions about whether to continue the pregnancy. Consultation with a pediatric surgeon often assists parental decision making. A recent series in *Seminars in Pediatric Surgery* with a preface by Spitz (2015) provide an excellent reference regarding postnatal management.

Viable conjoined twins should be delivered by cesarean. For the purpose of pregnancy termination, however, vaginal delivery is possible because the union is most often pliable (Fig. 45-17). Still, dystocia is common, and if the fetuses are mature, vaginal delivery may be traumatic to the uterus or cervix.

FIGURE 45-17
Conjoined twins aborted at 17 weeks' gestation. (Used with permission from Dr. Jonathan Willms.)

External Parasitic Twins

This is a grossly defective fetus or merely fetal parts, attached externally to a relatively normal twin. A parasitic twin usually consists of externally attached supernumerary limbs, often with some viscera. Classically, however, a functional heart or brain is absent. Attachment mirrors those sites described earlier for conjoined twins (see Fig. 45-14). Parasites are believed to result from demise of the defective twin. Its surviving tissue attaches to and receives vascularity from the normal cotwin (Spencer, 2001). In one large epidemiological study, parasitic twins accounted for 4 percent of all conjoined twins and occurred more frequently in male fetuses (Mutchinick, 2011).

Fetus-in-Fetu

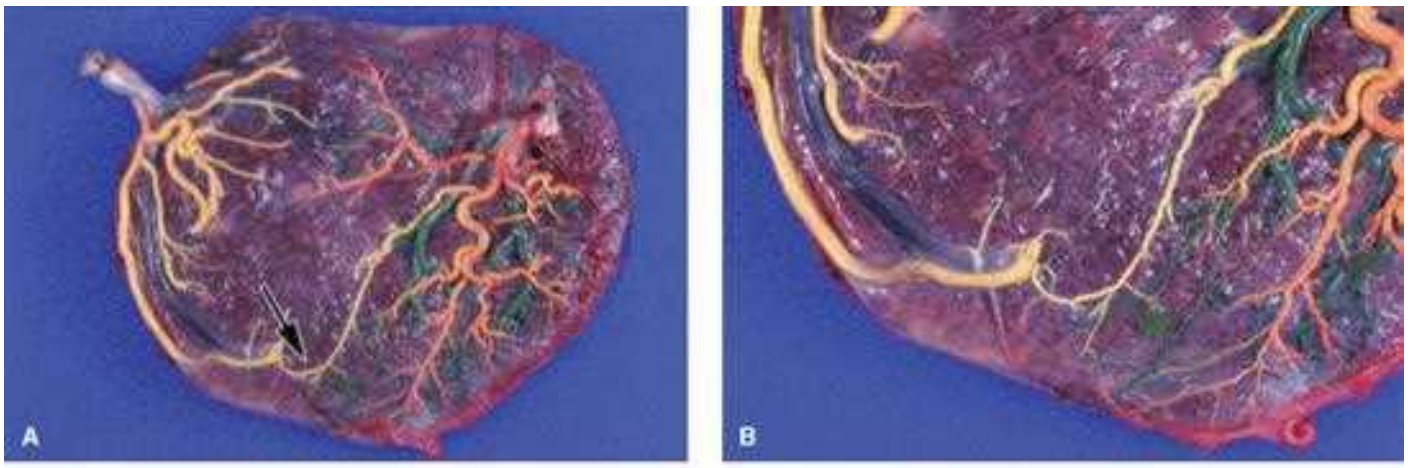
Early in development, one embryo may be enfolded within its twin. Normal development of this rare parasitic twin usually arrests in the first trimester. As a result, normal spatial arrangement of and presence of many organs is lost. Classically, vertebral or axial bones are found in the fetiform mass, whereas a heart and brain are absent. These masses are believed to represent a monozygotic, monochorionic diamnionic twin gestation and are typically supported by large parasitic vessels to the host (McNamara, 2016; Spencer, 2000). Malignant degeneration is rare (Kaufman, 2007).

Monochorionic Twins and Vascular Anastomoses

All monochorionic placentas likely share some anastomotic connections. And, with rare exceptions, anastomoses between twins are unique to monochorionic twin placentas. However, the number, size, and direction of these seemingly haphazard connections vary markedly (Fig. 45-18). In one analysis of more than 200 monochorionic placentas, the median number of anastomoses was 8, with an interquartile range of 4 to 14 (Zhao, 2013).

FIGURE 45-18

Shared placenta from pregnancy complicated by twin-twin transfusion syndrome. The following color code was applied for injection. Left twin: yellow = artery, blue = vein; right twin: red = artery, green = vein. **A.** Part of the arterial network of the right twin is filled with yellow dye, due to the presence of a small artery-to-artery anastomosis (*arrow*). **B.** Close-up of the lower portion of the placenta displays the yellow dye-filled anastomosis. (Reproduced with permission from De Paepe ME, DeKoninck P, Friedman RM: Vascular distribution patterns inmonochorionic twin placentas, Placenta. 2005 Jul;26(6):471–475.)



Artery-to-artery anastomoses are most frequent and are identified on the chorionic surface of the placenta in up to 75 percent of monochorionic twin placentas. Vein-to-vein and artery-to-vein communications are each found in approximately half. One vessel may have several connections, sometimes to both arteries and veins. In contrast to these superficial vascular connections on the surface of the chorion, deep artery-to-vein communications can extend through the capillary bed of a given villus (Fig. 45-19). These deep arteriovenous anastomoses create a common villous compartment or “third circulation” that has been identified in approximately half of monochorionic twin placentas.

FIGURE 45-19

Anastomoses between twins may be artery-to-vein (AV), artery-to-artery (AA), or vein-to-vein (VV). Schematic representation of an AV anastomosis in twin-twin transfusion syndrome that forms a “common villous district” or “third circulation” deep within the villous tissue. Blood from a donor twin may be transferred to a recipient twin through this shared circulation. This transfer leads to a growth-restricted discordant donor twin with markedly reduced amnionic fluid, causing it to be “stuck.”

Whether these anastomoses are dangerous to either twin depends on the degree to which they are hemodynamically balanced. In those with significant pressure or flow gradients, a shunt will develop between fetuses. This chronic fetofetal transfusion may result in several clinical syndromes that include *twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS),* and *acardiac twinning*.

Twin-Twin Transfusion Syndrome

In this syndrome, blood is transfused from a donor twin to its recipient sibling such that the donor may eventually become anemic and its growth may be restricted. In contrast, the recipient becomes polycythemic and may develop circulatory overload manifest as hydrops. Classically, the donor twin is pale, and its recipient sibling is plethoric. Similarly, one portion of the placenta often appears pale compared with the remainder. The recipient neonate may also have circulatory overload from heart failure and severe hypervolemia and hyperviscosity. Occlusive thrombosis is another concern. Finally, polycythemia in the recipient twin may lead to severe hyperbilirubinemia and kernicterus (Chap. 33, Polycythemia and Hyperviscosity). The prevalence of TTTS approximates 1 to 3 cases per 10,000 births (Society for Maternal-Fetal Medicine, 2013).

Chronic TTTS results from unidirectional flow through deep arteriovenous anastomoses. Deoxygenated blood from a *donor* placental artery is pumped into a cotyledon shared by the recipient (see Fig. 45-19). Once oxygen exchange is completed in the chorionic villus, the oxygenated blood leaves the cotyledon via a placental vein of the *recipient* twin. Unless compensated—typically through superficial arterioarterial anastomoses—this unidirectional flow leads to an imbalance in blood volumes (Lewi, 2013). Clinically important TTTS frequently is chronic and results from significant vascular volume differences between the twins. Even so, the pathogenesis is more complex than a net transfer of red blood cells from one twin to another. Indeed, in most monochorionic twin pregnancies with the syndrome, hemoglobin concentrations between the donor and recipient twin do not differ (Lewi, 2013).

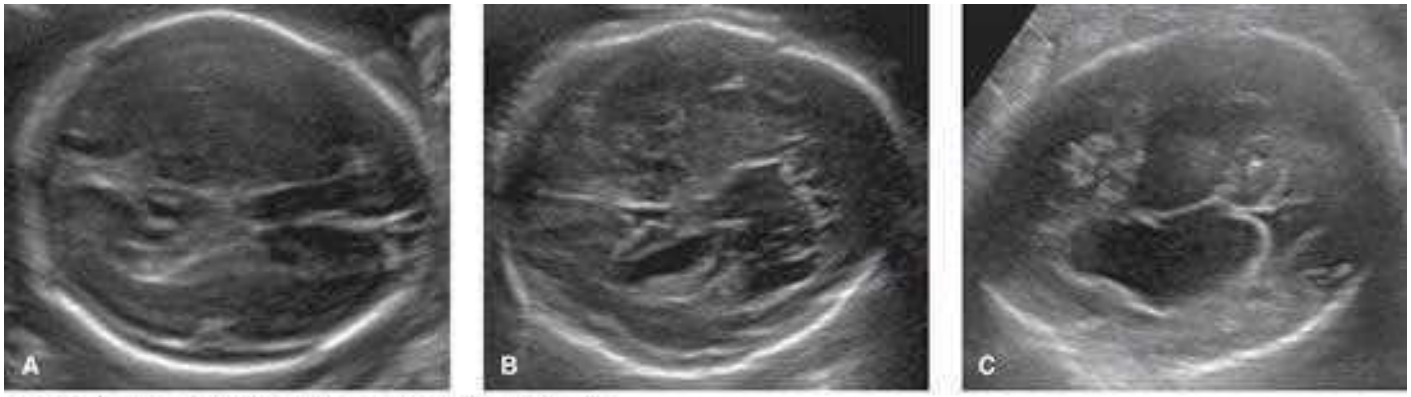
TTTS typically presents in midpregnancy when the donor fetus becomes oliguric from decreased renal perfusion (Society for Maternal-Fetal Medicine, 2013). This fetus develops oligohydramnios, and the recipient fetus develops severe hydramnios, presumably due to increased urine production. Virtual absence of amnionic fluid in the donor sac prevents fetal motion, giving rise to the descriptive term *stuck twin* or *polyhydramnios-oligohydramnios syndrome—"poly-oli."* This amnionic fluid imbalance is associated with growth restriction, contractures, and pulmonary hypoplasia in the donor twin, and premature rupture of the membranes and heart failure in the recipient.

Fetal Brain Damage

Cerebral palsy, microcephaly, porencephaly, and multicystic encephalomalacia are serious complications associated with placental vascular anastomoses in multifetal gestation. The exact pathogenesis of neurological damage is not fully understood but is likely caused by ischemic necrosis leading to cavitary brain lesions (Fig. 45-20). In the donor twin, ischemia results from hypotension, anemia, or both. In the recipient, ischemia develops from blood pressure instability and episodes of profound hypotension (Lopriore, 2011). Cerebral lesions may also be due to postnatal injury associated with preterm delivery (Chap. 34, Retinopathy of Prematurity). In one review of 315 liveborn fetuses from pregnancies with TTTS, cerebral abnormalities were found in 8 percent (Quarello, 2007).

FIGURE 45-20

These serial sonograms depict an interventricular hemorrhage with parenchymal extension and eventual porencephaly that developed following cotwin demise in a monochorionic pregnancy. From left to right, these images were obtained 1 week, 5 weeks, and 8 weeks following demise of the cotwin.



If one twin of an affected pregnancy dies, cerebral pathology in the survivor probably results from acute hypotension. A less likely cause is emboli of thromboplastic material originating from the dead fetus. Fusi and coworkers (1990, 1991) observed that with the death of one twin, acute twin-twin anastomotic transfusion from the high-pressure vessels of the living twin to the low-resistance vessels of the dead twin leads rapidly to hypovolemia and ischemic antenatal brain damage in the survivor. In one review of 343 twin pregnancies complicated by single fetal demise, the risk of neurodevelopmental morbidity in monochorionic twins was 26 percent compared with 2 percent in dichorionic twins (Hillman, 2011). This morbidity was related to the gestational age at the death of the cotwin. If the death occurred between 28 and 33 weeks' gestation, monochorionic twins had an almost eightfold risk of neurodevelopmental morbidity compared with dichorionic twins of the same gestational age. With fetal death after 34 weeks, the likelihood dramatically decreased—odds ratio 1.48.

The acuity of hypotension following the death of one twin with TTTS makes successful intervention for the survivor nearly impossible. Even with delivery immediately after a cotwin demise is recognized, the hypotension that occurs at the moment of death has likely already caused irreversible brain damage (Langer, 1997; Wada, 1998). As such, immediate delivery is not considered beneficial in the absence of another indication.

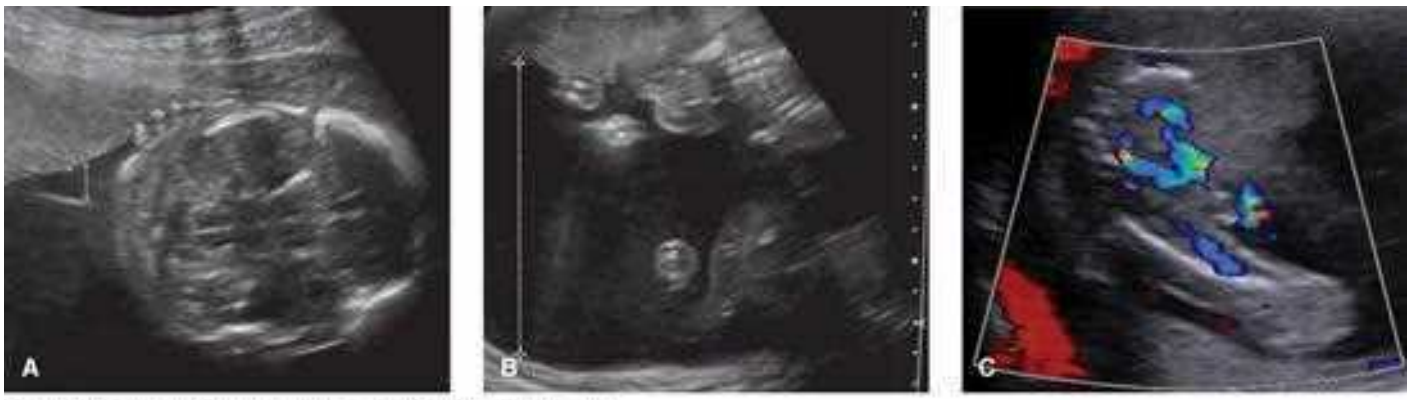
Diagnosis

The criteria used to diagnose and classify varying severities of TTTS have dramatically changed. Previously, weight discordancy and hemoglobin differences in monochorionic twins were calculated. However, in many cases, these are late findings. According to the Society for Maternal-Fetal Medicine (2013), TTTS is diagnosed based on two sonographic criteria. First, a monochorionic diamnionic pregnancy is identified. Second, hydramnios defined by a largest vertical pocket >8 cm in one sac and oligohydramnios defined by a largest vertical pocket <2 cm in the other twin is found. Only 15 percent of pregnancies complicated by lesser degrees of fluid imbalance progress to TTTS (Huber, 2006). Although growth discordance or growth restriction may be found with TTTS, these per se are not considered diagnostic criteria.

Organizations that include the American College of Obstetricians and Gynecologists (2016), Society for Maternal–Fetal Medicine (2013), and North American Fetal Therapy Network (Emery, 2015) recommend sonography surveillance of pregnancies at risk for TTTS. To aid earlier identification of amnionic fluid abnormalities and other complications of monochorionic twins, these examinations begin at approximately 16 weeks' gestation, and subsequent studies are considered every 2 weeks. Once identified, TTTS is typically classified by the Quintero (1999) staging system (Fig. 45-21):

FIGURE 45-21

A. Sonogram of stage I TTTS at 19 weeks' gestation. Oligohydramnios in the donor twin sac causes the membrane to essentially wrap around the "stuck twin" and suspend it from the anterior uterine wall. **B.** In this same pregnancy, hydramnios is seen in the recipient twin sac. The measured pocket exceeds 10 cm. **C.** Stage II TTTS in a donor twin at 17 weeks' gestation. Color Doppler highlights the arteries that outline the fetal bladder, which contains no urine.



Stage I—discordant amnionic fluid volumes as described in the earlier paragraph, but urine is still visible sonographically within the bladder of the donor twin

Stage II—criteria of stage I, but urine is not visible within the donor bladder

Stage III—criteria of stage II and abnormal Doppler studies of the umbilical artery, ductus venosus, or umbilical vein

Stage IV—ascites or frank hydrops in either twin

Stage V—demise of either fetus.

In addition to these criteria, evidence suggests that cardiac function of the recipient twin correlates with fetal outcome (Crombleholme, 2007). Although fetal echocardiographic findings are not part of the Quintero staging system, many centers routinely perform fetal echocardiography for TTTS. Theoretically, earlier diagnosis of cardiomyopathy in the recipient twin may identify pregnancies that would benefit from early intervention. One system for evaluating cardiac function—the *myocardial performance index (MPI)* or *Tei index*—is a Doppler index of ventricular function calculated for each ventricle (Michelfelder, 2007). Although scoring systems that include assessment of cardiac function have been developed, their usefulness to predict outcomes remains controversial (Society for Maternal-Fetal Medicine, 2013).

Management and Prognosis

The prognosis for multifetal gestations complicated by TTTS is related to Quintero stage and gestational age at presentation. More than three fourths of stage I cases have been reported to remain stable or regress without intervention. Conversely, outcomes in those identified at stage III or higher are much worse, and the perinatal loss rate is 70 to 100 percent without intervention (Society for Maternal-Fetal Medicine, 2013). At Parkland Hospital, among expectantly managed pregnancies with TTTS, most had early disease at diagnosis, and 50 percent of stage I cases progressed (Duryea, 2016).

Several therapies are available for TTTS and include amnioreduction, laser ablation of vascular placental anastomoses, selective feticide, and septostomy. Described further in Chapter 11 (Oligohydramnios), amnioreduction describes needle drainage of excess amnionic fluid. Septostomy is intentionally creating a hole in the dividing amnionic membrane but has largely been abandoned as treatment (Society for Maternal-Fetal Medicine, 2013). Comparative data from randomized trials for some of these other techniques are discussed below.

The Eurofetus trial included 142 women with severe TTTS diagnosed before 26 weeks. Participants were randomly assigned to laser ablation of vascular anastomoses or to serial amnioreduction (Senat, 2004). A higher survival rate to age 6 months for at least one twin was found in pregnancies undergoing laser ablation–76 versus 51 percent, respectively. Moreover, analyses of randomized studies confirm better neonatal outcomes with laser therapy compared with selective amnioreduction (Roberts, 2008; Rossi, 2008, 2009). In contrast, Crombleholme and associates (2007), in a randomized trial of 42 women, found equivalent rates of 30-day survival of one or both twins treated with either amnioreduction or selective fetoscopic laser ablation–75 versus 65 percent, respectively. Furthermore, evaluation of twins from the Eurofetus trial through 6 years of age did not demonstrate an additional survival benefit beyond 6 months or improved neurological outcomes in those treated with laser (Salomon, 2010). At this time, laser ablation of anastomoses is preferred for severe TTTS (stages II–IV). Optimal therapy for stage I disease is controversial.

After laser therapy, close ongoing surveillance is necessary. Robyr and colleagues (2006) reported that a fourth of 101 pregnancies treated with laser required additional invasive therapy because of either recurrent TTTS, or middle cerebral artery (MCA) Doppler evidence of anemia or polycythemia. Recently, in a comparison of selective laser ablation of individual anastomoses versus ablation of the entire surface of the chorionic plate along the vascular equator, Baschat and coworkers (2013) found that equatorial photocoagulation reduced the likelihood of recurrence.

Selective fetal reduction has generally been considered if severe amnionic fluid and growth disturbances develop before 20 weeks. In such cases, both fetuses typically will die without intervention. Any substance injected into one twin may affect the other twin because of shared circulations. Thus, for the fetus chosen for reduction, feticidal techniques include methods that occlude the umbilical vein or umbilical cord of using radiofrequency ablation, fetoscopic ligation, or coagulation with laser, monopolar, or bipolar energy (Challis, 1999; Chang, 2009; Parra-Cordero, 2016). Even after these procedures, however, the risks to the remaining fetus are still appreciable (Rossi, 2009). This topic is further discussed in Selective Reduction or Termination.

Twin Anemia–Polycythemia Sequence

This form of chronic fetofetal transfusion, referred to as TAPS, is characterized by significant hemoglobin differences between donor and recipient twins. However, TAPS lacks the discrepancies in amnionic fluid volumes typical of TTTS (Slaghekke, 2010). It is diagnosed antenatally by MCA peak systolic velocity (PSV) >1.5 multiples of the median (MoM) in the donor and <1.0 MoM in the recipient twin (Society for Maternal-Fetal Medicine, 2013). The spontaneous form of TAPS reportedly complicates 3 to 5 percent of monochorionic pregnancies, and it occurs in up to 13 percent of pregnancies after laser photocoagulation of the placenta. *Spontaneous* TAPS usually occurs after 26 weeks' gestation, and *iatrogenic* TAPS develops within 5 weeks of a procedure (Lewi, 2013). Although a staging system has been proposed by Slaghekke and colleagues (2010), further studies are necessary to better elucidate the natural history of TAPS and its management. In brief, evidence of fetal compromise or greater differences in MCA PSV between twins raise the stage.

Twin Reversed-Arterial-Perfusion Sequence

Also known as an *acardiac twin*, this is a rare but serious complication of monochorionic multifetal gestation. An estimated incidence is 1 case in 35,000 births. In the classic twin reversed-arterial-perfusion (TRAP) sequence, there is a normally formed donor twin that shows features of heart failure and a recipient twin that lacks a heart (acardius) and other structures. In one theory, the TRAP sequence is caused by a large artery-to-artery placental shunt, often also accompanied by a vein-to-vein shunt (Fig. 45-22). Within the single, shared placenta, arterial perfusion pressure of the donor twin exceeds that in the recipient twin, who thus receives reverse blood flow containing deoxygenated arterial blood from its cotwin (Lewi, 2013). This "used" arterial blood reaches the recipient twin through its umbilical arteries and preferentially goes to its iliac vessels. Thus, only the lower body is perfused, and therefore disrupted growth and development of the upper body results. In these cases, failed head growth is called *acardius acephalus*; a partially developed head with identifiable limbs is called *acardius myelacephalus*; and failure of any recognizable structure to form is *acardius amorphous,* which is shown in Figure 45-23 (Faye-Petersen, 2006). Because of this vascular connection, the normal donor

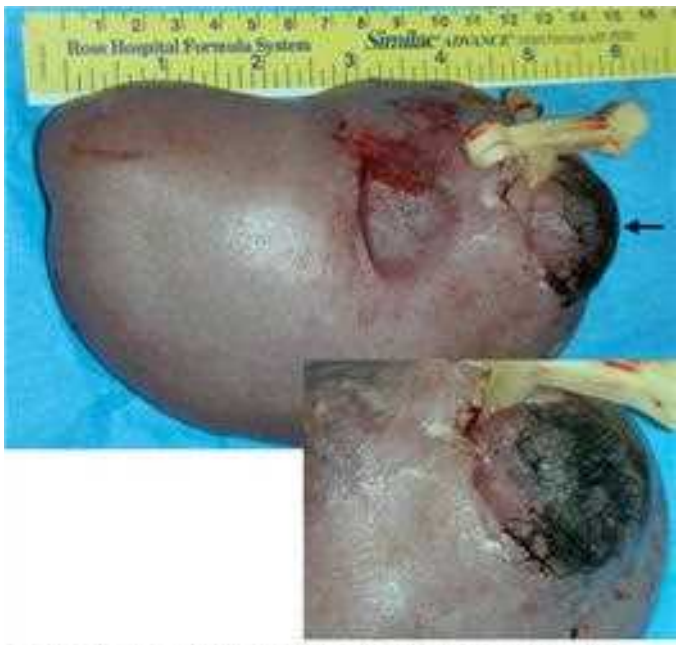
twin must not only support its own circulation but also pump blood through the underdeveloped acardiac recipient. This may lead to cardiomegaly and high-output heart failure in the normal twin (Fox, 2007).

FIGURE 45-22

Twin reversed-arterial-perfusion sequence. In the TRAP sequence, there is usually a normally formed donor twin that has features of heart failure, and a recipient twin that lacks a heart. It has been hypothesized that the TRAP sequence is caused by a large artery-to-artery placental shunt, often also accompanied by a vein-to-vein shunt. Within the single, shared placenta, perfusion pressure of the donor twin overpowers that in the recipient twin, who thus receives reverse blood flow from its twin sibling. The "used" arterial blood that reaches the recipient twin preferentially goes to its iliac vessels and thus perfuses only the lower body. This disrupts growth and development of the upper body.

FIGURE 45-23

Photograph of an acardiac twin weighing 475 grams. The underdeveloped head is indicated by the black arrow, and its details are shown in the inset. A yellow clamp is seen on its umbilical cord. Its viable donor cotwin was delivered vaginally at 36 weeks and weighed 2325 grams. (Used with permission from Dr. Michael D. Hnat.)



In the past, the mortality rate among the pump twins exceeded 50 percent. This stemmed largely from complications of prematurity or from a prolonged high-output state leading to cardiac failure (Dashe, 2001). Risk appears to be directly related to size of the acardiac twin. One sonographic method to estimate acardiac twin size uses the volume of an ellipse: length × width × height ×π/6. When the acardiac twin volume is <50 percent of that of the pump twin, expectant management may be reasonable given the inherent risks of fetal intervention (Chap. 15, Radiofrequency Ablation)(Jelin, 2010). When the volume of the acardiac twin is large, however,

treatment has generally been offered. Radiofrequency ablation (RFA) is the preferred modality of therapy, and contemporary reports now suggest improved perinatal outcomes. The North American Fetal Therapy Network reviewed their experiences with 98 cases from 1998 to 2008 in which RFA of the umbilical cord was performed (Lee, 2013). Median gestational age at delivery was 37 weeks, and 80 percent of neonates survived (Lee, 2013). The average gestational age at the time of the RFA was 20 weeks, and the estimated acardius-to-pump twin volume on average was 90 percent. Major complications were prematurely ruptured membranes and preterm birth.

Interestingly, TRAP sequences can also occur within monoamnionic pregnancies. The perinatal outcomes of such pregnancies appear to be worse than that of monochorionic diamnionic cases. Sugibayashi and associates (2016) in a review of 40 cases recently reported that pump twin survival following RFA was 88 percent in monochorionic diamnionic pregnancies but only 67 percent in monoamnionic pregnancies.

Hydatidiform Mole with Coexisting Normal Fetus

This unique gestation contains one normal fetus, and its cotwin is a complete molar pregnancy. Reported prevalence rates range from 1 in 22,000 to 1 in 100,000 pregnancies (Dolapcioglu, 2009). It must be differentiated from a partial molar pregnancy, in which an anomalous singleton fetus—usually triploid—is accompanied by molar tissue (Fig. 20-4). At times, a twin pregnancy may occur with a normal twin in one sac and a partial mole in the other sac (McNamara, 2016).

Diagnosis is usually made in the first half of pregnancy. Sonographically, a normal-appearing twin is accompanied by its cotwin, which is a large placenta containing multiple small anechoic cysts (Fig. 20-4). Often, these pregnancies are terminated, but pregnancy continuation is increasingly adopted. First, the pregnancy prognosis is not as poor as previously thought, and live birth rates range between 20 and 40 percent (Dolapcioglu, 2009; McNamara, 2016). Second, the risk of persistent trophoblastic disease is similar whether the pregnancy is terminated or not (Massardier, 2009; Sebire, 2002). That said, given the limited number of cases, robust data for firm recommendations are lacking. Importantly, complications of expectant management include vaginal bleeding, hyperemesis gravidarum, thyrotoxicosis, and early-onset preeclampsia (McNamara, 2016). Many of these complications result in preterm birth with its attendant adverse perinatal sequelae as well as perinatal loss. Logically, close surveillance is needed for those continuing the pregnancy.

DISCORDANT GROWTH OF TWIN FETUSES

Fetal size inequality develops in approximately 15 percent of twin gestations and may reflect pathological growth restriction in one fetus (Lewi, 2013; Miller, 2012). Generally, as the weight difference within a twin pair rises, the perinatal mortality rate increases proportionately. If it develops, restricted growth of one twin fetus, often termed *selective fetal-growth restriction*, usually develops late in the second and early third trimester. Earlier discordancy indicates higher risk for fetal demise in the smaller twin. Specifically, when discordant growth is identified before 20 weeks, fetal death occurs in approximately 20 percent of the growth-restricted fetuses (Lewi, 2013).

Etiopathogenesis

The cause of birthweight inequality in twin fetuses is often unclear, but the etiology in monochorionic twins likely differs from that in dichorionic twins. Because the single placenta is not always equally shared in monochorionic twins, these twins have greater rates of discordant growth outside of TTTS than dichorionic twins. Discordancy in monochorionic twins is usually attributed to placental vascular anastomoses that cause hemodynamic imbalance between the twins. Reduced pressure and perfusion of the donor twin can cause diminished placental and fetal growth. Even so, unequal placental sharing is probably the most important determinant of discordant growth in monochorionic twins (Lewi, 2013). Occasionally, monochorionic twins are discordant in size because they are discordant for structural anomalies.

Discordancy in dichorionic twins may result from various factors. Dizygotic fetuses may have different genetic growth potential, especially if they are of opposite genders. Second, because the placentas are separate and require more implantation space, one placenta might have a suboptimal implantation site. Bagchi and associates (2006) observed that the incidence of severe discordancy is twice as great in triplets as it is in twins. This finding lends credence to the view that in utero crowding is a factor in multifetal growth restriction. Placental pathology may play a role as well. In one study of 668 twin placentas, a strong relationship between histological placental abnormalities and birthweight discordancy was observed in dichorionic, but not monochorionic, twin pregnancies (Kent, 2012).

Diagnosis

Size discordancy between twins can be determined sonographically. That said, differences in crown-rump length are not reliable predictors for birthweight discordance (Miller, 2012). Thus, most begin surveillance for discordancy after the first trimester. One common method uses sonographic fetal biometry to compute an estimated weight for each twin (Chap. 10, Gestational Age Assessment). The weight of the smaller twin is then compared with that of the larger twin. Thus, percent discordancy is calculated as the weight of the larger twin minus the weight of the smaller twin, then divided by the weight of the larger twin. Alternatively, given that abdominal circumference (AC) reflects fetal nutrition, some use the sonographic AC value of each twin.

With these methods, some diagnose selective fetal-growth restriction if the AC measurements differ more than 20 mm or if the estimated fetal weight difference is 20 percent or more. That said, several different weight disparities between twins have been used to define discordancy. Accumulated data suggest that weight discordancy greater than 25 to 30 percent most accurately predicts an adverse perinatal outcome. At Parkland, Hollier and coworkers (1999) retrospectively evaluated 1370 delivered twin pairs and stratified twin weight discordancy in 5-percent increments within a range of 15 to 40 percent. They found that the incidence of respiratory distress syndrome, intraventricular hemorrhage, seizures, periventricular leukomalacia, sepsis, and necrotizing enterocolitis rose directly with the degree of weight discordancy. Rates of these conditions grew substantially if discordancy exceeded 25 percent. The relative risk of fetal death increased significantly to 5.6 if discordancy was more than 30 percent and rose to 18.9 if it was greater than 40 percent.

Management

Serial Sonography

Sonographic monitoring of twin growth has become a mainstay in management. Monochorionic twins are generally monitored more frequently. This is because their risk of death is higher—3.6 percent versus 1.1 percent—and the risk of neurological damage in the surviving twin is substantial compared with those risks in dichorionic twins (Hillman, 2011; Lee, 2008). Thorson and colleagues (2011) retrospectively analyzed 108 monochorionic twin pregnancies and found that a sonographic evaluation interval >2 weeks was associated with a higher Quintero stage at the time of TTTS diagnosis. These findings have led some to recommend serial sonographic examination every 2 weeks in monochorionic twins (Simpson, 2013; Society for Maternal-Fetal Medicine, 2013). However, there have been no randomized trials of the optimal frequency of sonographic surveillance in monochorionic twin pregnancies. At Parkland Hospital, monochorionic twins undergo sonographic evaluation to assess interval growth every 4 weeks. In addition, a specific ultrasound examination to search for TTTS is completed at each intervening 2-week mark between these sonograms.

For dichorionic pregnancies, a recent report suggests that sonographic evaluation every 2 weeks would identify more abnormalities prompting delivery (Corcoran, 2015). It has yet to be determined if this practice would improve perinatal outcomes. At our institution, dichorionic twins are sonographically evaluated every 6 weeks.

Fetal Surveillance

Depending on the degree of discordancy and the gestational age, fetal surveillance may be indicated, especially if one or both fetuses exhibit restricted growth. Nonstress testing, biophysical profile, and umbilical artery Doppler assessment have all been recommended in the management of twins. However, none has been assessed in appropriately sized prospective trials (Miller, 2012).

If discordancy is identified in a monochorionic twin pregnancy, umbilical artery Doppler studies in the smaller fetus may help guide management (Gratacós, 2007). Namely, investigators have correlated umbilical artery Doppler results with placental findings and with the degree of selective fetal-growth restriction to predict fetal outcome (Gratacós, 2012). These correlations have yielded categories of selective fetal-growth restriction. Type I is characterized by positive end-diastolic flow, a smaller degree of weight discordance, and a relatively benign clinical course. Type II displays persistently absent end-diastolic flow in the smaller twin and carries a high risk of deterioration and demise. Type III is intermittently absent or reversed end-diastolic flow. Because of large artery-to-artery anastomoses associated with the placentas in this category, type III is associated with a lower risk of deterioration than type II. In all evaluated cases, unequally shared placenta was noted to some degree.

With uncomplicated dichorionic multifetal gestations, use of antepartum surveillance has not improved perinatal outcomes. In sum, the American College of Obstetricians and Gynecologists (2016) recommends that antepartum testing be performed in multifetal gestations for indications similar to those for singleton fetuses (Chap. 17, Fetal Movements).

At Parkland, all women with twin discordancy ≥25 percent undergo daily monitoring as an inpatient. Data are limited to establish the optimal timing of delivery of twins for size discordancy alone. For those at advanced gestational ages, delivery can be pursued.

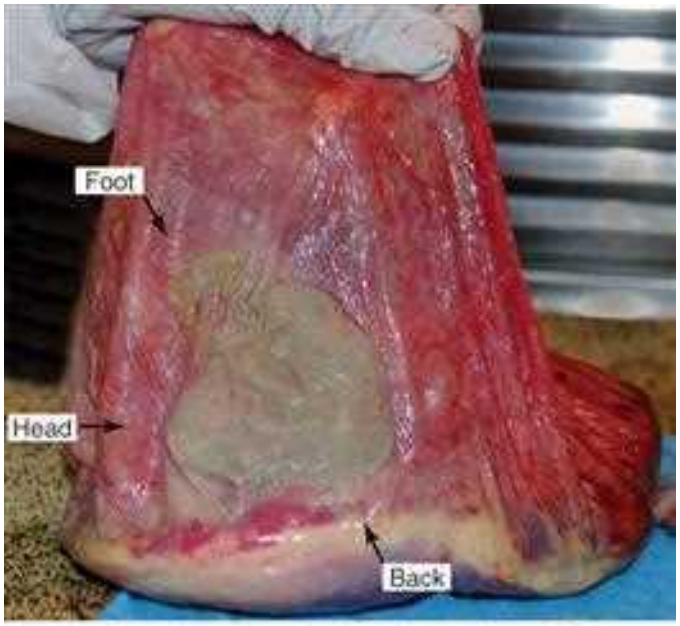
FETAL DEMISE

Death of One Fetus

At any time during multifetal pregnancy, one or more fetuses may die, either simultaneously or sequentially. Causes and incidence of fetal death are related to zygosity, chorionicity, and growth concordance.

In some pregnancies, one fetus dies remote from term, but pregnancy continues with one or more live fetuses. When this occurs early in pregnancy, it may manifest as a vanishing twin, discussed in Pregnancy Complications. In a slightly more advanced gestation, fetal death may go undetected until delivery. In this case, delivery of a normal newborn is followed by expulsion of a dead fetus that is barely identifiable. It may be compressed appreciably–*fetus compressus,* or it may be flattened remarkably through desiccation—*fetus papyraceus* (Fig. 45-24).

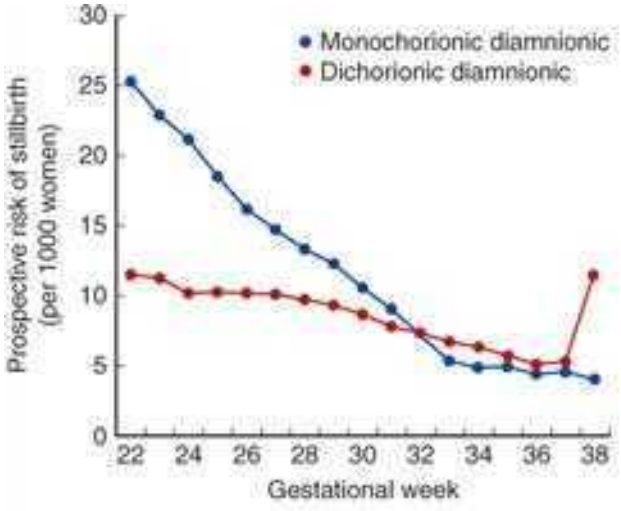
FIGURE 45-24
This fetus papyraceus is a tan ovoid mass compressed against the fetal membranes. Anatomical parts can be identified as marked. Demise of this twin had been noted during sonographic examination performed at 17 weeks' gestation. Its viable cotwin delivered at 40 weeks. (Used with permission from Dr. Michael V. Zaretsky.)



As shown in Figure 45-25, the risk of stillbirth is related to gestational age in all twins but is much higher for monochorionic twin pregnancies before 32 weeks' gestation. In a review of 9822 twin pregnancies, Morikawa and associates (2012) reported that 2.5 percent of monochorionic diamnionic twins greater than 22 weeks had a death of one or both twins. This compared with 1.2 percent of dichorionic twins. In this same review, women with monochorionic diamnionic twins who lost one twin were 16 times more likely to experience death of the cotwin than women with dichorionic twins who lost one twin. Other investigations have found similar trends (Danon, 2013; Hillman, 2011; Mahony, 2011).

FIGURE 45-25

Prospective risk of stillbirth among women who reached a given gestational week (per 1000 women). (Reproduced with permission from Morikawa M, Yamada T, Yamada T, et al: Prospective risk of stillbirth: monochorionic diamniotic twins vs dichorionic twins, J Perinat Med. 2012 Jan 10;40(3):245–249.)



Other factors that affect the prognosis for the surviving twin include gestational age at the time of the demise and duration between the demise and delivery of the surviving twin. With a vanishing twin, the risk of death after the first trimester is not increased for the survivor. However, when a fetus dies in the second trimester or later, the effect of gestational age at the time of death and the mortality risk to the cotwin are less clear. In an analysis by Hillman and colleagues (2011), cotwin demise rates were unaffected regardless of whether the first death occurred at 13 to 27 weeks' gestation or at 28 to 34 weeks. In cases with the death of one twin after the first trimester, however, the odds of spontaneous and iatrogenic preterm delivery of the remaining living twin were increased (Hillman, 2011). Preterm birth was five times more likely in monochorionic twin gestations complicated by demise of one twin between 28 and 33 weeks' gestation. If the fetus died after 34 weeks, preterm delivery rates were similar.

The neurological prognosis for a surviving cotwin depends almost exclusively on chorionicity. In their comprehensive review, Ong and coworkers (2006) found an 18-percent rate of neurological abnormality in twins with monochorionic placentation compared with only 1 percent in those with dichorionic placentation. In another review, in twin pregnancies complicated by a single fetal demise before 34 weeks, a fivefold higher risk of neurodevelopmental morbidity was identified in monochorionic twins compared with dichorionic twins. If the one fetus died after 34 weeks, the likelihood of neurological deficits was essentially the same between monochorionic and dichorionic twin pregnancies (Hillman, 2011).

Later in gestation, the death of one of multiple fetuses could theoretically trigger coagulation defects in the mother. Only a few cases of maternal coagulopathy after a single fetal death in a twin pregnancy have been reported. This is probably because the surviving twin is usually delivered within a few weeks of the demise (Eddib, 2006). That said, we have observed transient, spontaneously corrected consumptive coagulopathy in multifetal gestations in which one fetus died and was retained in utero along with its surviving twin. The plasma fibrinogen concentration initially decreased but then increased spontaneously, and the level of serum fibrinogen-fibrin degradation products increased initially but then returned to normal levels. At delivery, the portions of the placenta that supplied the living fetus appeared normal. In contrast, the part that had once provided for the dead fetus was the site of massive fibrin deposition.

Management

Decisions should be based on gestational age, the cause of death, and the risk to the surviving fetus. First-trimester losses require no additional surveillance for this specific indication. If the loss occurs after the first trimester, the risk of death or damage to the survivor is largely limited to monochorionic twin gestations. Morbidity in the monochorionic twin survivor is almost always due to vascular anastomoses, which often cause the demise of one twin followed by sudden hypotension in the other (Twin-Twin Transfusion Syndrome). For this reason, if one fetus of a monochorionic twin gestation dies after the first trimester but before viability, pregnancy termination can be considered (Blickstein, 2013). Occasionally, death of one but not all fetuses results from a maternal complication such as diabetic ketoacidosis or severe preeclampsia with abruption. Pregnancy management is based on the diagnosis and the status of both the mother and surviving fetus. If the death of one dichorionic twin is due to a discordant congenital anomaly in the first trimester, it should not affect the surviving twin.

Single fetal death during the late second and early third trimesters presents the greatest risk to the surviving twin. Although the risks of subsequent death or neurological damage to the survivor are comparatively higher for monochorionic twins at this gestational age, the risk of preterm birth is equally increased in mono- and dichorionic twins (Ong, 2006). Delivery generally occurs within 3 weeks of diagnosis of fetal demise, thus antenatal corticosteroids for survivor lung maturity should be considered (Blickstein, 2013). Regardless, unless the intrauterine environment is hostile, the goal is to prolong the preterm pregnancy.

Timing of elective delivery after conservative management of a late second- or early third-trimester single fetal death is debatable. Dichorionic twins can probably be safely delivered at term. Monochorionic twin gestations are more difficult to manage and are often delivered between 34 and 37 weeks' gestation (Blickstein, 2013). In cases of single fetal death at term, especially when the etiology is unclear, most opt for delivery instead of expectant management. The American College of Obstetricians and Gynecologists (2016) also endorse an individualized approach to such cases.

Impending Death of One Fetus

During antepartum surveillance tests of well-being, abnormal results in one twin, but not the other, pose a particular dilemma. Delivery may be the best option for the compromised fetus yet may result in death from immaturity of the cotwin. If fetal lung maturity is confirmed, salvage of both the healthy fetus and its jeopardized sibling is possible. Unfortunately, ideal management if twins are immature is problematic but should be based on the chances of intact survival for both fetuses. Often the compromised fetus is severely growth restricted or anomalous. Thus, performing amniocentesis for fetal chromosomal analysis in women of advanced maternal age carrying twin pregnancies is advantageous, even for those who would continue their pregnancies regardless of the diagnosis. Chromosomal abnormality identification in one fetus allows rational decisions regarding interventions.

PRENATAL CARE

With prenatal management of multifetal pregnancy, primary goals aim to prevent or interdict complications as they develop. A major imperative is to prevent preterm delivery of markedly immature neonates. At Parkland Hospital, women with multifetal gestations are seen every 2 weeks beginning at 22 weeks' gestation. A digital cervical examination is performed at each visit to screen for cervical shortening or dilation. Identification of other unique complications discussed earlier may also lead to interventions including admission or early delivery.

Diet

Along with more frequent prenatal visits, the maternal diet should provide additional requirements for calories, protein, minerals, vitamins, and essential fatty acids. The Institute of Medicine (2009) recommends a 37- to 54-lb weight gain for women with twins and a normal BMI. In their review, Goodnight and Newman (2009) endorse supplementation of micronutrients such as calcium, magnesium, zinc, and vitamins C, D, and E. This is based on upper intake levels from the Food and Nutrition Board of the Institute of Medicine. The daily recommended augmented caloric intake for women with twins is 40 to 45 kcal/kg/d. Diets contain 20 percent protein, 40 percent carbohydrate, and 40 percent fat divided into three meals and three snacks daily.

Sonography

As noted earlier (Fetal Demise), serial sonographic examinations are usually performed throughout the third trimester to search for abnormal fetal growth and assess amnionic fluid volume. Associated oligohydramnios may indicate uteroplacental pathology and should prompt further evaluation of fetal well-being. That said, quantifying amnionic fluid volume in multifetal gestation is sometimes difficult. Some measure the deepest vertical pocket in each sac or assess the fluid subjectively. Magann and coworkers (2000) compared subjective assessment and several objective methods of assessing amnionic fluid volume in 23 sets of twins. They found all methods to be equally poor in predicting abnormal volumes in diamnionic twins. At Parkland Hospital, the single deepest vertical pocket is measured in each sac. A measurement <2 cm is considered oligohydramnios, and a measurement >8 cm is considered hydramnios (Duryea, 2017; Hernandez, 2012).

Antepartum Fetal Surveillance

Of surveillance methods, the nonstress test or biophysical profile is often selected for twin or higher-order multifetal gestations. Because of the complex complications associated with these gestations and the potential technical difficulties in differentiating fetuses during antepartum testing, the usefulness of these methods appears limited. According to DeVoe (2008), the few exclusive studies of nonstress testing in twins suggest that the method performs the same as in singleton pregnancies.

Elliott and Finberg (1995) used the biophysical profile as the primary method for monitoring higher-order multifetal gestations. They reported that four of 24 monitored pregnancies had a poor outcome despite reassuring biophysical profile scores. Although biophysical testing is commonly performed in multifetal gestations, there are insufficient data to determine its efficacy (DeVoe, 2008).

Similar findings have been reported with the addition of umbilical artery Doppler velocimetry in twins with concordant growth. For example, when umbilical artery Doppler velocimetry was added to management compared with fetal testing based on fetal-growth parameters alone in the absence of growth discordance, perinatal outcomes were not improved (Giles, 2003). Likewise, Hack and associates (2008) investigated the utility of umbilical artery Doppler velocimetry in 67 uncomplicated monochorionic twin gestations and did not find differences in mortality rates using pulsatility indices of the umbilical artery.

All testing schemes have high false-positive rates in singletons, and data suggest that testing in multifetal gestations performs no better. In cases of abnormal testing in one twin and normal results in another, iatrogenic preterm delivery remains a major concern. Options are similar to those described in the management of impending fetal death (Prenatal Care).

PRETERM BIRTH

Preterm labor is common in multifetal pregnancies and may complicate up to 50 percent of twin, 75 percent of triplet, and 90 percent of quadruplet pregnancies (Elliott, 2007). Similar to singleton preterm labor, intraamnionic infection is documented in approximately one third of twin pregnancy cases (Oh, 2017).

In twins, the proportion of preterm births varies widely from 40 to 70 percent (Giuffre, 2012). For example, black women have disparately higher risks for preterm delivery (Grant, 2017).

Prediction of Preterm Birth

A major goal of multifetal prenatal care is accurate prediction of women likely to experience preterm delivery. Within the past decade, cervical length has been shown to be a potent predictor of preterm labor and delivery. To and associates (2006) sonographically measured cervical length in 1163 twin pregnancies at 22 to 24 weeks' gestation. Rates of preterm delivery before 32 weeks were 66 percent in those with cervical lengths of 10 mm; 24 percent for lengths of 20 mm; and only 1 percent for 40 mm. In one review, Conde-Agudelo and coworkers (2010) concluded that a cervical length <20 mm was most accurate for predicting birth before 34 weeks, with a specificity of 97 percent and positive likelihood ratio of 9.0. Kindinger and colleagues (2016) noted that prediction depended on both cervical length and gestational age at ascertainment. One study compared serial cervical length measurements with a single midgestation measurement. These authors found that multiple assessments were more accurate to determine the risk of preterm twin birth in asymptomatic women (Melamed, 2016a). In another study, a change in cervical length ≥0.2 cm identified pregnancies at risk for delivery before 35 weeks (Moroz, 2017). Interestingly, a closed internal os by digital examination was found to be as predictive of postponed delivery as was the combination of a normal sonographically measured cervical length and negative fetal fibronectin test result (McMahon, 2002). Unfortunately, cervical length assessment in twin pregnancies has not been associated with improved outcomes (Gordon, 2016).

Prevention of Preterm Birth

Several schemes have been evaluated to prevent preterm labor and delivery. In recent years, some have been shown to decrease the risk of preterm delivery, but only in subgroups of singleton pregnancies. In general, most have been disappointingly ineffective for both singleton and multifetal pregnancies (American College of Obstetricians and Gynecologists, 2016).

Bed Rest

The bulk of evidence suggests that routine hospitalization does not prolong multifetal pregnancy. In one metaanalysis, the practice did not reduce the risk of preterm birth or perinatal mortality (Crowther, 2010). At Parkland Hospital, elective hospitalization was compared with outpatient management, and no advantages were found (Andrews, 1991). Importantly, however, almost half of women managed as outpatients required admission for specific indications such as hypertension or threatened preterm delivery.

Limited physical activity, early work leave, more frequent health-care visits and sonographic examinations, and structured maternal education regarding preterm delivery risks have been advocated to reduce preterm birth rates in women with multiple fetuses. However, little evidence suggests that these measures substantially change outcome.

Prophylactic Tocolysis

This has not been studied extensively in multifetal pregnancies. In one review of prophylactic oral beta-mimetic therapy that included 374 twin pregnancies, treatment did not reduce the rate of twins delivering before 37 or before 34 weeks' gestation (Yamasmit, 2015). In light of the Food and Drug Administration warning against the use of oral terbutaline because of maternal side effects, the prophylactic use of beta-mimetic drugs in multifetal gestations seems unwarranted.

Intramuscular Progesterone Therapy

Although somewhat effective in reducing recurrent preterm birth in women with a singleton pregnancy, weekly injections of 17 alpha-hydroxyprogesterone caproate (17-OHP-C) are not effective for multifetal gestations (Caritis, 2009; Rouse, 2007). These results were corroborated in a randomized trial of 240 twin pregnancies (Combs, 2011). Moreover, women carrying twins and having a cervical length <36 mm (25th percentile) did not benefit despite their greater risk for preterm birth (Durnwald, 2010). Senat and colleagues (2013) assigned 165 asymptomatic women with twins and a cervical length <25 mm to 17-OHP-C and also found no reduction in delivery rate before 37 weeks. Last, in an evaluation of plasma drug concentrations, higher concentrations of 17-OHP-C were associated with *earlier* gestational age at delivery (Caritis, 2012). The authors concluded that 17-OHP-C may adversely lower the gestational age at delivery in women with twin gestations. In sum, administration of intramuscular 17-OHP-C to women with twin pregnancies, even to those with a shortened cervix, does not lower the preterm birth risk.

Vaginal Progesterone Therapy

Micronized progesterone administered vaginally to women with twins to prevent preterm birth has provided conflicting results. Cetingoz and coworkers (2011) gave 100 mg of micronized progesterone intravaginally daily from 24 to 34 weeks' gestation. This practice reduced rates of delivery before 37 weeks from 79 to 51 percent in 67 women with twins. In contrast, several studies have failed to demonstrate any preterm birth rate reduction in women receiving various formulations of vaginal progesterone. In the Prevention of Preterm Delivery in Twin Gestations (PREDICT) trial, 677 women with twins were randomly assigned to receive prophylactic, 200-mg progesterone pessaries or placebo pessaries (Rode, 2011). Progesterone failed to reduce delivery rates before 34 weeks. In a subgroup analysis that included only women with a short cervix or a history of prior preterm birth, also no benefit was found (Klein, 2011). Norman and colleagues (2009) also noted no lower rates of delivery before 34 weeks with progesterone gel treatment.

Romero and colleagues (2017) performed a metaanalysis of individual patient data for 303 women with twin gestation and a short cervix randomized to receive either vaginal progesterone or no treatment. They reported a significantly reduced risk of preterm birth before 30 weeks' gestation and improved composite perinatal outcomes in the treated women. Currently at Parkland Hospital, management of women with multifetal gestations does not typically include progesterone in any formulation.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is currently enrolling patients into a randomized, placebo-controlled trial to further evaluate the use of micronized vaginal progesterone or the Arabin pessary, describe subsequently (PROSPECT, 2015). The primary outcome is delivery prior to 35 weeks or fetal loss.

Cervical Cerclage

Prophylactic cerclage does not improve perinatal outcome in women with multifetal pregnancies. Studies have included women who were not specially selected but also those who were selected because of a shortened cervix that was identified sonographically (Houlihan, 2016; Newman, 2002; Rebarber, 2005). Indeed, in the latter group, cerclage may actually worsen outcomes (Berghella, 2005; Roman, 2013).

Rescue cerclage in women with a second-trimester twin gestation and a dilated cervix may be beneficial. Roman and coworkers (2016) reported a retrospective cohort study in which women undergoing rescue cerclage had significantly better neonatal outcomes than those without cerclage.

Pessary

A vaginal pessary that encircles and theoretically compresses the cervix, alters the inclination of the cervical canal, and relieves direct pressure on the internal cervical os has been proposed as an alternative to cerclage. One of the most popular is the silicone Arabin pessary. In a study of its use in women with a short cervix between 18 and 22 weeks' gestation, a subgroup analysis of 23 women with twins showed a significant reduction in the delivery rate before 32 weeks compared with the rate in 23 control pregnancies (Arabin, 2003). In another randomized trial, women treated with a cervical pessary had significantly fewer births before 34 weeks (Goya, 2016).

Other studies have been less favorable. In the randomized Pessaries in Multiple Pregnancy as a Prevention of Preterm Birth (ProTWIN) trial, 813 unselected women with twins received either the Arabin pessary between 12 and 20 weeks or no treatment (Liem, 2013). The pessary failed to reduce preterm birth overall but did decrease delivery rates before 32 weeks—29 versus 14 percent—in a subset of women with a cervical length <38 mm. Similar results were reported from a randomized multicenter trial with a total of 1180 twin pregnancies (Nicolaides, 2016). A smaller randomized study using a *Bioteque cup pessary* showed no difference in outcomes (Berghella, 2017). At this time, pessary use is not recommended by the American College of Obstetricians and Gynecologists (2016). As noted above, results from the ongoing PROSPECT trial are anticipated to provide more data.

Treatment of Preterm Labor

Although many advocate their use, therapy with tocolytic agents to forestall preterm labor in multifetal pregnancy does not result in measurably improved neonatal outcomes (Chauhan, 2010; Gyetvai, 1999). Another caveat is that tocolytic therapy in women with a multifetal pregnancy entails higher risks than in singleton pregnancy. This stems in part from augmented pregnancy-induced hypervolemia, which raises cardiac demands and increases the susceptibility to iatrogenic pulmonary edema (Chap. 47, Acute Pulmonary Edema). Gabriel and colleagues (1994) compared outcomes of 26 twin and six triplet pregnancies with those of 51 singletons—all treated with a beta-mimetic drug for preterm labor. Women with a multifetal gestation had significantly more cardiovascular complications—43 versus 4 percent—including three gravidas with pulmonary edema. In a retrospective analysis, Derbent and coworkers (2011) evaluated nifedipine tocolysis in 58 singleton and 32 twin pregnancies. These authors reported higher incidences of side effects such as maternal tachycardia in women with twins—19 versus 9 percent.

Glucocorticoids for Lung Maturation

Administration of corticosteroids to stimulate fetal lung maturation has not been well studied in multifetal gestation. However, these drugs logically should be as beneficial for multiples as they are for singletons (Roberts, 2006). In a large retrospective study evaluating betamethasone therapy efficacy in preterm twin versus preterm singleton pregnancies, no differences in neonatal morbidity between the two groups were identified (Melamed, 2016b). Gyamfi and associates (2010) evaluated betamethasone concentrations in women receiving weekly antenatal corticosteroids and found no differences in levels between twins and singletons. Conversely, another study found lower cord/maternal ratios of dexamethasone in twin versus singleton pregnancies (Kim, 2017). These treatments are discussed in Chapter 42 (Corticosteroids for Fetal Lung Maturation). At this time, guidelines for the use of these agents do not differ from those for singleton gestations (American College of Obstetricians and Gynecologists, 2016).

Preterm Premature Membrane Rupture

The frequency of preterm premature rupture of membranes (PPROM) rises with increasing plurality. In a population-based study of more than 290,000 live births, the proportion of preterm birth complicated by premature rupture was 13.2 percent in singletons (Pakrashi, 2013). This rate compared with rates of 17, 20, 20, and 100 percent in twins, triplets, quadruplets, and even higher-order multiples, respectively. Multifetal gestations with PPROM are managed expectantly similar to singleton pregnancies (Chap. 42, Intentional Delivery). Ehsanipoor and colleagues (2012) compared outcomes of 41 twin and 82 singleton pregnancies, both with ruptured membranes between 24 and 32 weeks. They found the median number of days to subsequent delivery was overall shorter for twins—3.6 days compared with 6.2 days for singletons. This latency difference was significant in pregnancies after 30 weeks—1.7 days and 6.9 days. Importantly, latency beyond 7 days approximated 40 percent in both groups.

Delayed Delivery of Second Twin

Infrequently, after preterm birth of the presenting fetus, it may be advantageous for undelivered fetus(es) to remain in utero. Trivedi and Gillett (1998) reviewed 45 case reports of asynchronous birth in multifetal gestations. Although reported outcomes may reflect bias, pregnancies with a surviving retained twin or triplet continued for an average of 49 days. No advantage was gained by management with tocolytics, prophylactic antimicrobials, or cerclage. In their 10-year experience, Roman and associates (2010) reported a median latency of 16 days in 13 twin and five triplet pregnancies with delivery of the first fetus between 20 and 25 weeks' gestation. Survival of the firstborn neonate was 16 percent. Although 54 percent of the retained fetuses survived, only 37 percent of survivors did so without major morbidity. Livingston and coworkers (2004) described 14 pregnancies in which an active attempt was made to delay delivery of 19 fetuses after delivery of the first neonate. Only one fetus survived without major sequelae, and one mother developed sepsis syndrome with shock. Arabin and van Eyck (2009) reported better outcomes in a few of the 93 twin and 34 triplet pregnancies that qualified for delayed delivery in their center during a 17-year period.

If asynchronous birth is attempted, there must be careful evaluation for infection, abruption, and congenital anomalies. The mother must be thoroughly counseled, particularly regarding the potential for serious, life-threatening infection. The range of gestational age in which the benefits outweigh the risks for delayed delivery is likely narrow. Avoidance of delivery from 23 to 26 weeks would seem most beneficial. In our experience, good candidates for delayed delivery are rare.

LABOR AND DELIVERY

Preparations

A litany of complications may be encountered during labor and delivery of multiple fetuses. In addition to preterm birth, rates of uterine contractile dysfunction, abnormal fetal presentation, umbilical cord prolapse, placenta previa, placental abruption, emergent operative delivery, and postpartum hemorrhage from uterine atony are higher. All of these must be anticipated, and thus certain precautions and special arrangements are prudent. These should include the following.

1. An appropriately trained obstetrical attendant should remain with the mother throughout labor. Continuous electronic monitoring is preferable. If membranes are ruptured and the cervix dilated, the presenting fetus is monitored internally.
2. An intravenous infusion system capable of delivering fluid rapidly is established. In the absence of hemorrhage, lactated Ringer or an aqueous dextrose solution is infused at a rate of 60 to 125 mL/hr.
3. Blood for transfusion is readily available if needed.
4. An obstetrician skilled in intrauterine identification of fetal parts and in intrauterine manipulation of a fetus should be present.
5. A sonography machine is readily available to evaluate the presentation and position of the fetuses during labor and to image the remaining fetus(es) after delivery of the first.
6. An anesthesia team is immediately available in the event that emergent cesarean delivery is necessary or that intrauterine manipulation is required for vaginal delivery.
7. For each fetus, at least one attendant who is skilled in resuscitation and care of newborns and who has been appropriately informed of the case should be immediately available.
8. The delivery area should provide adequate space for the nursing, obstetrical, anesthesia, and pediatric team members to work effectively. Equipment must be on site to provide emergent anesthesia, operative intervention, and maternal and neonatal resuscitation.

Timing of Delivery

Several factors affect this timing and include gestational age, fetal growth, lung maturity, and presence of maternal complications. As measured by determination of the lecithin-sphingomyelin ratio, pulmonary maturation is usually synchronous in twins (Leveno, 1984). Moreover, although this ratio usually does not exceed 2.0 until 36 weeks in singleton pregnancies, it often exceeds this value by approximately 32 weeks in multifetal pregnancies. Similar increased values of surfactant have been noted in twins after 31 weeks' gestation (McElrath, 2000). In a comparison of respiratory morbidity in 100 twins and 241 singleton newborns delivered by cesarean before labor, Ghi and associates (2013) found less neonatal respiratory morbidity in twins, especially those delivered <37 weeks' gestation. In some cases, however, pulmonary function may be markedly different, and the smallest, most stressed twin fetus is typically more mature.

At the other end of the spectrum, Bennett and Dunn (1969) suggested that a twin pregnancy of 40 weeks or more should be considered postterm. Twin stillborn neonates delivered at 40 weeks or beyond commonly had features similar to those of postmature singletons (Chap. 43, Incidence). From an analysis of almost 300,000 twin births, at and beyond 39 weeks, the risk of subsequent stillbirth was greater than the risk of neonatal mortality (Kahn, 2003).

From their guidelines, the American College of Obstetricians and Gynecologists (2016) recommends delivery at 38 weeks for uncomplicated dichorionic twin pregnancies. Women with uncomplicated monochorionic diamnionic twin pregnancies can undergo delivery between 34 and $37^{6/7}$ weeks. And, for women with monoamnionic twin pregnancies, delivery is recommended at 32 to 34 weeks. At Parkland Hospital, we generally follow these recommendations but do not routinely deliver monochorionic diamnionic twin pregnancies before 37 weeks unless another obstetrical indication develops.

Evaluation of Fetal Presentation

In addition to the standard preparations for the conduct of labor and delivery discussed in Chapter 22, there are special considerations for women with a multifetal pregnancy. First, the positions and presentations of fetuses are best confirmed sonographically. Although any possible combination of positions may be encountered, those most common at admission for delivery are cephalic-cephalic, cephalic-breech, and cephalic-transverse. At Parkland Hospital between 2008 and 2013, 71 percent of twin pregnancies had a cephalic presentation of the first fetus at the time of admission to labor and delivery. Importantly, with perhaps the exception of cephalic–cephalic presentations, these are all unstable before and during labor and delivery. Accordingly, compound, face, brow, and footling breech presentations are relatively common, and even more so if fetuses are small, amnionic fluid is excessive, or maternal parity is high. Cord prolapse is also frequent in these circumstances.

After this initial evaluation, if active labor is confirmed, then a decision is made to attempt vaginal delivery or to proceed with cesarean delivery. The latter is usually chosen because of fetal presentations. In general, cephalic presentation of the first fetus in a laboring woman with twins may be considered for vaginal delivery (American College of Obstetricians and Gynecologists, 2016). The proportion of women undergoing an attempted vaginal delivery varies greatly depending on the skills of the delivering physician (de Castro, 2016; Easter, 2017; Schmitz, 2017). Still, the cesarean delivery rate is high. For example, of the 547 women with the first twin presenting cephalic who were admitted to Parkland Hospital during 5 years, only 32 percent were delivered spontaneously. And, the overall cesarean delivery rate in twin pregnancies during those years was 77 percent. Notably, 5 percent of cesareans performed were for emergent delivery of the second twin following vaginal delivery of the first twin. The desire to avoid this obstetrical dilemma has contributed to the rising cesarean delivery rate in twin pregnancies across the United States (Antsaklis, 2013).

Labor Induction or Stimulation

After a comparison of 891 twins with more than 100,000 singleton pregnancies included in the Consortium of Safe Labor, Leftwich and colleagues (2013) concluded that active labor progressed more slowly in both nulliparas and multiparas with twins. Provided women with twins meet all criteria for oxytocin administration, it may be used as described in Chapter 26 (Oxytocin). Wolfe and associates (2013) evaluated the success of labor induction and concluded that oxytocin alone or in combination with cervical ripening can safely be used in twin gestations. Taylor and coworkers (2012) reported similar results. Conversely, Razavi and colleagues (2017) found that maternal morbidity was increased with labor induction. In an analysis of twin births in the United States, induction rates of twin pregnancies have decreased from a maximum of 13.8 percent in 1999 to 9.9 percent in 2008 (Lee, 2011). Generally, at Parkland Hospital we do not induce or augment labor in women with a multifetal gestation. In suitable candidates with a strong desire for vaginal birth, amniotomy induction has been one option.

Analgesia and Anesthesia

During labor and delivery of multiple fetuses, decisions regarding analgesia and anesthesia may be complicated by problems imposed by preterm labor, preeclampsia, desultory labor, need for intrauterine manipulation, and postpartum uterine atony and hemorrhage.

Labor epidural analgesia is ideal because it provides excellent pain relief and can be rapidly extended cephalad if internal podalic version or cesarean delivery is required. If general anesthesia becomes necessary for intrauterine manipulation, uterine relaxation can be accomplished rapidly with one of the halogenated inhalation agents discussed in Chapter 25 (Inhalational Anesthetics). Some clinicians use intravenous or sublingual nitroglycerin or intravenous terbutaline to achieve uterine relaxation yet avoid the risks associated with general anesthetics. These agents are usually best administered by the anesthesia team.

Delivery Route

Regardless of fetal presentation during labor, obstetricians must be ready to deal with any change of fetal position during delivery. This is especially true following delivery of the first twin. Importantly, related to delivery method, second twins at term have worse composite neonatal outcomes compared with outcomes of their cotwin regardless of delivery method (Muleba, 2005; Smith, 2007; Thorngren-Jerneck, 2001).

Cephalic-Cephalic Presentation

If the first twin presents cephalic, delivery can usually be accomplished spontaneously or with forceps. According to D'Alton (2010), there is general consensus that a trial of labor is reasonable in women with cephalic-cephalic twins. From their review, Hogle and associates (2003) found that planned cesarean delivery does not improve neonatal outcome when both twins are cephalic. The randomized trial by Barrett and coworkers (2013) affirms this conclusion.

Cephalic-Noncephalic Presentation

The optimal delivery route for cephalic–noncephalic twin pairs remains controversial. Patient selection is crucial, and options include cesarean delivery of both twins, or less commonly, vaginal delivery with intrapartum external cephalic version of the second twin. Longer intertwin delivery time has been shown in some studies to be associated with poorer second twin outcome (Edris, 2006; Stein, 2008). Thus, breech extraction may be preferable to version. Least desirable, vaginal delivery of the first but cesarean delivery of the second twin may be required due to intrapartum complications such as umbilical cord prolapse, placental abruption, contracting cervix, or fetal distress. Most but not all studies report the worst composite fetal outcomes for this scenario (Alexander, 2008; Rossi, 2011; Wen, 2004).

Several reports attest to the safety of vaginal delivery of second noncephalic twins whose birthweight is >1500g. A French multicenter study of 5915 twin pregnancies illustrates this (Schmitz, 2017). Of these, 25 percent had a planned cesarean delivery. The other 75 percent with a first twin cephalic and gestational age >32 weeks had a planned trial of vaginal delivery, which was successful in 80 percent. Interestingly, perinatal mortality and morbidity rates were significantly higher in the planned cesarean delivery group delivered <37 weeks—5.2 versus 3.0 percent, respectively. Fox and colleagues (2014) reported outcomes in 287 diamnionic twin pregnancies, of which 130 underwent a planned vaginal delivery. Only 15 percent of the planned vaginal delivery group underwent a cesarean delivery. Perinatal outcomes were similar in both groups. These two studies included only those fetuses with estimated weights >1500 g. Notably, comparable or even better fetal outcomes with vaginal delivery have been reported with neonates weighing <1500 g compared with those weighing >1500 g (Caukwell, 2002; Davidson, 1992).

Other investigators advocate cesarean delivery for both members of a cephalic-noncephalic twin pair (Armson, 2006; Hoffmann, 2012). Yang and coworkers (2005a,b) studied 15,185 cephalic-noncephalic twin pairs. The risks of asphyxia-related neonatal deaths and morbidity were higher in the group in which both twins were delivered vaginally compared with the group in which both twins underwent cesarean delivery.

To add insight into the clinical complexities just discussed, a randomized trial was designed by the Twin Birth Study Collaborative Group from Canada. The study results described by Barrett and associates (2013) included 2804 women carrying a presumed diamnionic twin pregnancy with the first fetus presenting cephalic. Women were randomly assigned between 32 and 38 weeks' gestation to planned cesarean or vaginal delivery. The time from randomization to delivery—12.4 versus 13.3 days, the mean gestational age at delivery—36.7 versus 36.8 weeks, and use of regional analgesia—92 versus 87 percent, were similar in both groups. Salient maternal and perinatal outcomes are shown in Table 45-3. No significant differences in outcomes were noted between the two groups of women. Although risks to mother or fetuses with planned vaginal delivery in these circumstances were not increased, Greene (2013) posited that this trial would have only modest effects on the cesarean delivery rate of women with twins.

TABLE 45-3

Maternal and Perinatal Outcomes of Women with a Twin Pregnancy Randomized to Planned Cesarean versus Vaginal Delivery

Outcome	Planned Cesarean Delivery	Planned Vaginal Delivery	*p* value
Maternal (No.)	1393	1393	
Cesarean delivery	89.9%	39.6%	
Before labor	53.8%	14.1%	
Serious morbidity	7.3%	8.5%	0.29
Death (No.)	1	1	
Hemorrhage	6.0%	7.8%	
Blood transfusion	4.7%	5.4%	
Thromboembolism	0.4%	0.1%	
Perinatal (No.)	2783	2782	
Primary composite outcome	2.2%	1.9%	0.49
Perinatal mortality	9 per 1000	6 per 1000	
Serious morbidity	1.3%	1.3%	
Possible encephalopathy[a]	0.5%	0.4%	
Intubation	1.0%	0.6%	

[a]Includes coma; stupor; hyperalert, drowsy or lethargic; or ≥2 seizures.

Data from Barrett, 2013.

Breech Presentation of First Twin

Problems with the first twin presenting as a breech are similar to those encountered with a singleton breech fetus. Thus, major difficulties may develop in the following settings. First, the fetus may be large, and the aftercoming head is larger than the birth canal. Second, the fetal body can be small, and delivery of the extremities and trunk through an inadequately effaced and dilated cervix causes the relatively larger head to become trapped above the cervix. This is more likely when there is significant disproportion between the head and body. Examples are preterm or growth-restricted fetuses or those with macrocephaly from hydrocephaly. Last, umbilical cord prolapse is an ever-present risk.

If these problems are anticipated or identified, cesarean delivery is often preferred with a viable-sized fetus. But even without these problems, many obstetricians perform cesarean delivery if the first twin presents as breech. This is despite data that support the safety of vaginal delivery. Specifically, Blickstein and associates (2000) reported experiences from 13 European centers with 613 twin pairs and the first twin presenting breech. Vaginal delivery was attempted in 373 of these cases and was successful in 64 percent. Cesarean delivery of the second twin was done in 2.4 percent. There was no difference in the rate of 5-minute Apgar scores <7 or of mortality in breech-presenting first twins who weighed at least 1500 g. Details of techniques for delivery of a breech presentation are described in Chapter 28 (Partial Breech Extraction).

Twin fetuses may become locked together during delivery if the first presents breech and the second cephalic. As the breech of the first twin descends through the birth canal, the chin locks between the neck and chin of the second cephalic-presenting cotwin. This phenomenon is rare, and Cohen and coworkers (1965) described it only once in 817 twin gestations. Cesarean delivery should be considered when the potential for locking is identified.

Vaginal Delivery of the Second Twin

Following delivery of the first twin, the presenting part of the second twin, its size, and its relationship to the birth canal should be quickly and carefully ascertained by combined abdominal, vaginal, and at times, intrauterine examination. Sonography is a valuable aid. If the fetal head or the breech is fixed in the birth canal, moderate fundal pressure is applied and membranes are ruptured. Immediately afterward, digital examination of the cervix is repeated to exclude cord prolapse. Labor is allowed to resume. If contractions do not begin within approximately 10 minutes, dilute oxytocin may be used to stimulate contractions.

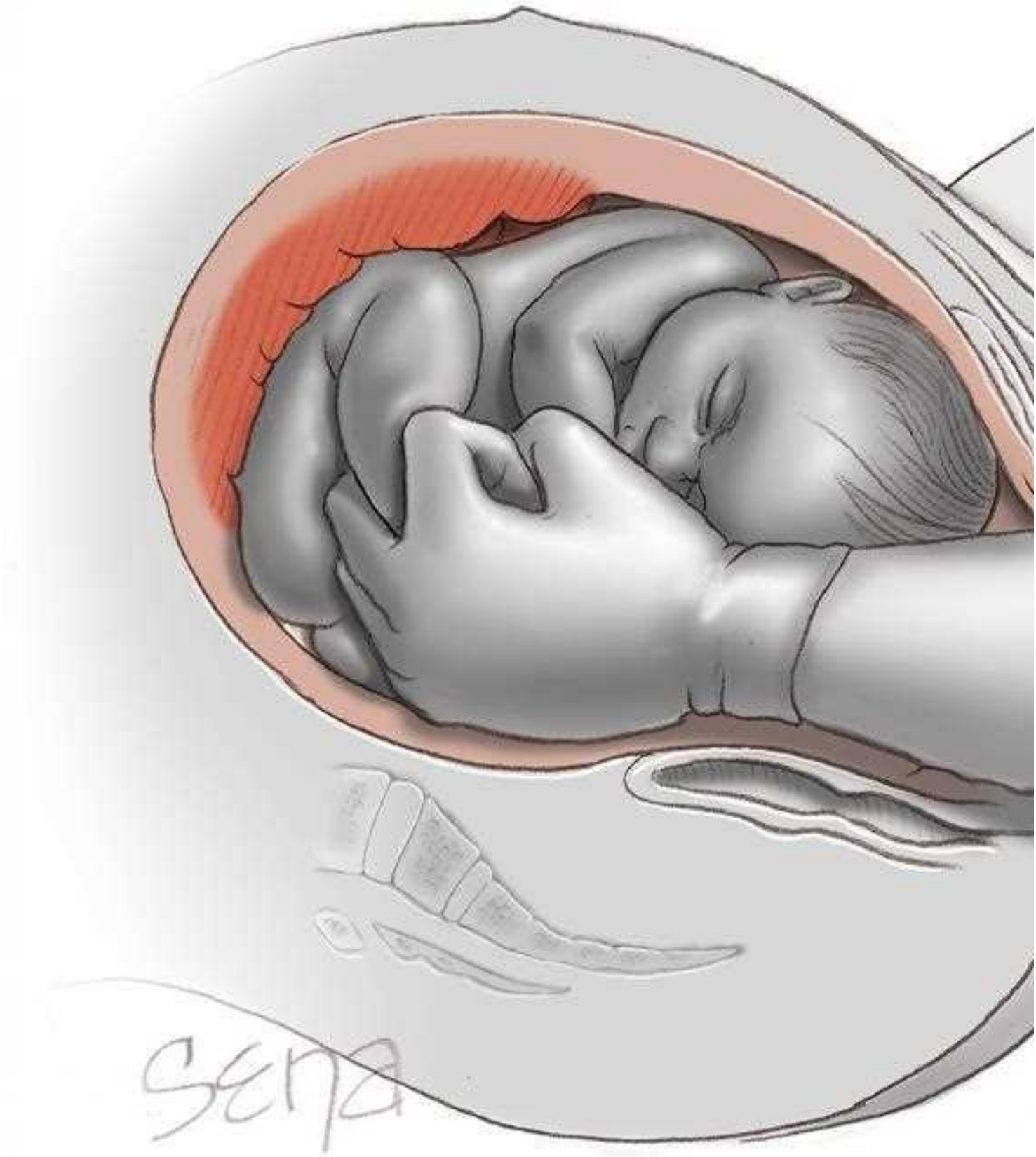
In the past, the safest interval between delivery of the first and second twins was frequently cited as <30 minutes. Rayburn and colleagues (1984) and others have shown that if continuous fetal monitoring is used, a good outcome is usually achieved even if this interval is longer. A direct correlation between worsening umbilical cord blood gas values and increasing time between delivery of first and second twins has been shown (Leung, 2002; Stein, 2008). From review of 239 twin gestations, Gourheux and associates (2007) determined that mean umbilical arterial pH was significantly lower after the delivery interval exceeded 15 minutes. In a study of more than 175,000 twin pairs, Cheng and colleagues (2017) reached similar conclusions for maternal and perinatal morbidity.

If the occiput or breech presents immediately over the pelvic inlet, but is not fixed in the birth canal, the presenting part can often be guided into the pelvis by one hand in the vagina, while a second hand on the uterine fundus exerts moderate pressure caudally. A presenting shoulder may be gently converted into a cephalic presentation. Alternatively, with abdominal manipulation, an assistant can guide the presenting part into the pelvis. Sonography can aid guidance and allow heart rate monitoring. Intrapartum external version of a noncephalic second twin has also been described.

If the occiput or breech is not over the pelvic inlet and cannot be so positioned by gentle pressure or if appreciable uterine bleeding develops, delivery of the second twin can be problematic. To obtain a favorable outcome, an obstetrician skilled in intrauterine fetal manipulation and anesthesia personnel skilled in providing anesthesia to effectively relax the uterus for vaginal delivery of a noncephalic second twin are essential (American College of Obstetricians and Gynecologists, 2016). To take maximum advantage of the dilated cervix before the uterus contracts and the cervix retracts, delay should be avoided. Prompt cesarean delivery of the second fetus is preferred if no one present is skilled in the performance of internal podalic version or if anesthesia that will provide effective uterine relaxation is not immediately available.

With internal podalic version, a fetus is turned to a breech presentation using the hand placed into the uterus (Fig. 45-26). The obstetrician grasps the fetal feet to then effect delivery by breech extraction (Chap. 28, Total Breech Extraction). As mentioned earlier, Fox and associates (2010) described a strict protocol for management of the delivery of the second twin, which included internal podalic version. They reported that none of the 110 women who delivered the first twin vaginally underwent a cesarean delivery for the second twin. Chauhan and coworkers (1995) compared outcomes of 23 second twins delivered by internal podalic version and breech extraction with those of 21 who underwent external cephalic version. Breech extraction was considered superior to external version because less fetal distress developed. Additional information and illustrations of this procedure are found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition (Yeomans, 2017).

FIGURE 45-26
Internal podalic version. Upward pressure on the head by an abdominal hand is applied as downward traction is exerted on the feet.



Vaginal Birth after Cesarean Delivery

Any attempt to deliver twins vaginally in a woman who has previously undergone one or more cesarean deliveries should be carefully considered. Some studies support the safety of attempting a vaginal birth after cesarean delivery (VBAC) for selected women with twins (Cahill, 2005; Ford, 2006; Varner, 2005). According to the American College of Obstetricians and Gynecologists (2017c), no evidence currently suggests an increased risk of uterine rupture, and women with twins and one

previous cesarean delivery with a low transverse incision may be considered candidates for trial of labor. At Parkland Hospital, we recommend repeat cesarean delivery.

Cesarean Delivery for Multifetal Gestation

Several unusual intraoperative problems can arise during cesarean delivery of twins or higher-order multiples. Supine hypotension is common, and thus gravidas are positioned in a left lateral tilt to deflect uterine weight off the aorta (Chap. 4, Renin, Angiotensin II, and Plasma Volume). A low transverse hysterotomy is preferable if the incision can be made large enough to allow atraumatic delivery of both fetuses. Piper forceps can be used if the second twin is presenting breech (Fig. 28-11). In some cases, a vertical hysterotomy beginning as low as possible in the lower uterine segment may be advantageous. For example, if a fetus is transverse with its back down and the arms are inadvertently delivered first, it is much easier and safer to extend a vertical uterine incision upward than to extend a transverse incision laterally or to make a "T" incision vertically.

Triplet or Higher-Order Gestation

Fetal heart rate monitoring during labor with triplet pregnancies is challenging. A scalp electrode can be attached to the presenting fetus, but it is difficult to ensure that the other two fetuses are each being monitored separately. With vaginal delivery, the first neonate is usually born with little or no manipulation. Subsequent fetuses, however, are delivered according to the presenting part. This often requires complicated obstetrical maneuvers such as total breech extraction with or without internal podalic version or even cesarean delivery. Associated with malposition of fetuses is an increased incidence of cord prolapse. Moreover, reduced placental perfusion and hemorrhage from separating placentas are more likely during delivery.

For all these reasons, many clinicians believe that pregnancies complicated by three or more fetuses should undergo cesarean delivery (American College of Obstetricians and Gynecologists, 2016). Vaginal delivery is reserved for those circumstances in which survival is not expected because fetuses are markedly immature or maternal complications make cesarean delivery hazardous to the mother. Others believe that vaginal delivery is safe under certain circumstances. Grobman and associates (1998) and Alran and coworkers (2004) reported vaginal delivery completion rates of 88 and 84 percent, respectively, in women carrying triplets who underwent a trial of labor. Neonatal outcomes did not differ from those of a matched group of triplet pregnancies undergoing elective cesarean delivery. Conversely, in one review of more than 7000 triplet pregnancies, vaginal delivery was associated with a higher perinatal mortality rate (Vintzeleos, 2005). Lappen and coworkers (2016) reported similar results from the database of the Consortium on Safe Labor. They recommended prelabor cesarean delivery for triplets. Importantly, the overall cesarean delivery rate among triplets was 95 percent.

SELECTIVE REDUCTION OR TERMINATION

In some cases of higher-order multifetal gestation, reduction of the fetal number to two or three improves survival of the remaining fetuses. Selective reduction implies early pregnancy intervention, whereas selective termination is performed later. The procedure should be performed by an operator skilled and experienced in sonographically guided procedures.

Selective Reduction

Reduction of a selected fetus or fetuses in a multichorionic multifetal gestation may be chosen as a therapeutic intervention to enhance survival of the remaining fetuses (American College of Obstetricians and Gynecologists, 2017b). One metaanalysis of nonrandomized prospective studies indicates that pregnancy reduction to twins compared with expectant management is associated with lower rates of maternal complications, preterm birth, and neonatal death (Dodd, 2004, 2012).

Pregnancy reduction can be performed transcervically, transvaginally, or transabdominally, but the transabdominal route is usually easiest. Transabdominal fetal reductions are typically performed between 10 and 13 weeks' gestation. This gestational age is chosen because most spontaneous abortions have already occurred, the remaining fetuses are large enough to be evaluated sonographically, the amount of devitalized fetal tissue remaining after the procedure is small, and the risk of aborting the entire pregnancy as a result of the procedure is low. The smallest fetuses and any anomalous fetuses are chosen for reduction. Potassium chloride is then injected under sonographic guidance into the heart or thorax of each selected fetus. Care is used to avoid entry or traverse the sacs of fetuses selected for retention.

Evans and associates (2005) analyzed more than 1000 pregnancies from 1995 to 1998. The pregnancy loss rate varied from a low of 4.5 percent for triplets that were reduced to twins. The loss rate rose with each addition to the starting number of fetuses and peaked at 15 percent for six or more fetuses. Operator skill and experience are believed responsible for the low and declining rates of pregnancy loss.

Selective Termination

With the identification of multiple fetuses discordant for structural or genetic abnormalities, three options are available: abortion of all fetuses, selective termination of the abnormal fetus, or pregnancy continuation. Because anomalies are typically not discovered until the second trimester, selective termination is performed later in gestation than selective reduction and entails greater risk. This procedure is therefore usually not performed unless the anomaly is severe but not lethal. In some cases, termination is considered because the abnormal fetus may jeopardize the normal one.

Prerequisites to selective termination include a precise diagnosis for the anomalous fetus and absolute certainty of fetal location. Unless a special procedure such as umbilical cord interruption is used, selective termination should be performed only in multichorionic multifetal gestations to avoid damaging the surviving fetuses (Lewi, 2006). Roman and coworkers (2010) compared 40 cases of bipolar umbilical cord coagulation with 20 cases of radiofrequency ablation for treatment of complicated monochorionic multifetal gestations at midpregnancy. They found similar survival rates of 87 and 88 percent, and a median gestational age >36 weeks

at delivery in both. Prefumo and colleagues (2013) reported their preliminary experience with microwave ablation of the umbilical cord for selective termination in two monochorionic twin pregnancies. One pregnancy aborted within 7 days, and the other resulted in a term singleton delivered at 39 weeks' gestation.

Evans and coworkers (1999) have provided the most comprehensive results to date on second-trimester selective termination for fetal abnormalities. A total of 402 cases were analyzed from eight centers worldwide. Included were 345 twin, 39 triplet, and 18 quadruplet pregnancies. Selective termination using potassium chloride resulted in delivery of a viable neonate or neonates in more than 90 percent of cases, with a mean age of 35.7 weeks at delivery. The entire pregnancy was lost in 7 percent of pregnancies reduced to singletons and in 13 percent of those reduced to twins. The gestational age at the time of the procedure did not appear to affect the pregnancy loss rate.

Before selective termination or reduction, a discussion should include the morbidity and mortality rates expected if the pregnancy is continued; the morbidity and mortality rates expected with surviving twins or triplets; and the risks of the procedure itself (American College of Obstetricians and Gynecologists, 2017b). Specific risks of selective termination or reduction are: (1) abortion of the remaining fetuses; (2) abortion or retention of the wrong fetus(es); (3) damage without death to a fetus; (4) preterm labor; (5) discordant or growth-restricted fetuses; and (6) maternal complications. The last includes potential infection, hemorrhage, or disseminated intravascular coagulopathy because of retained products of conception. The final decision to continue the pregnancy without intervention, to terminate the entire pregnancy, or to elect selective termination is solely the patient's (Chervenak, 2013).

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CHAPTER 46: General Considerations and Maternal Evaluation

As a rule, all diseases which subject the organism to a considerable strain are much more serious when occurring in a pregnant woman.

—J. Whitridge Williams (1903)

INTRODUCTION

As reviewed by Williams in 1903, pregnant women are susceptible to any medical and surgical disorder that can affect childbearing-aged women. Some of these, especially those that are chronic, more often precede pregnancy. But, they can acutely complicate an otherwise normal pregnancy. Of estimates, one managed-care population had an overall antenatal hospitalization rate of 10.1 per 100 deliveries (Gazmararian, 2002). Approximately one third was for nonobstetrical conditions that included renal, pulmonary, and infectious diseases. In another study from the 2002 Nationwide Inpatient Sample, the injury hospitalization rate was 4.1 women per 1000 deliveries (Kuo, 2007). Last, approximately 1 in every 635 pregnant women will undergo a nonobstetrical surgical procedure (Corneille, 2010; Kizer, 2011).

Obstetricians should have a working knowledge of the wide-ranging medical disorders common to childbearing-aged women. Many of these are within the purview of the general obstetrician. Other disorders, however, will warrant consultation, and still others require a multidisciplinary team. The latter may include maternal-fetal medicine specialists, hospitalists, internists and medical subspecialists, surgeons, anesthesiologists, and numerous other disciplines (Levine, 2016). The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (2014, 2017b) has redefined aspects of maternal care and proposed required levels of specialized care.

It should be axiomatic that a woman must never be penalized because she is pregnant. To ensure this, several questions should be addressed:

What management would be recommended if the woman were not pregnant?

If the proposed management is different because the woman is pregnant, can this be justified?

What are the risks versus benefits to the mother and her fetus, and are they counter to each other?

Can an individualized management plan be devised that balances benefits versus risks of any alterations?

Such an approach allows individualized care for women with most medical and surgical disorders complicating pregnancy.

MATERNAL PHYSIOLOGY AND LABORATORY VALUES

Pregnancy induces physiological changes in virtually all organ systems. In turn, results of numerous laboratory tests are altered, and some values would, in the nonpregnant woman, be considered abnormal. Conversely, some may appear to be within a normal range but are decidedly abnormal for the gravida. These changes may amplify or obfuscate evaluation of coexisting conditions. The wide range of pregnancy effects on normal physiology and laboratory values are discussed in the chapters that follow in this section and are listed in the Appendix (Serum and Blood Constituents).

MEDICATIONS AND SURGERIES

Pregnancy Outcomes

Fortunately, most medications needed to treat frequently encountered illnesses complicating pregnancy can be given with relative safety. That said, notable exceptions are considered in Chapter 12 and throughout this text.

Regarding surgery, the risk of an adverse pregnancy outcome is not appreciably increased in most women who undergo an uncomplicated operative procedure. With complications, however, risks likely are increased. For example, perforative appendicitis with feculent peritonitis has significant maternal and perinatal morbidity and mortality rates even if surgical and anesthetic techniques are flawless. Conversely, procedure-related complications may adversely affect outcomes. For example, a woman who has uncomplicated removal of an inflamed appendix may suffer aspiration of acidic gastric contents during tracheal intubation or extubation. Still, compared with nonpregnant women undergoing similar procedures, pregnant women do not appear to have excessive complications (Silvestri, 2011). In a study of the American College of Surgeons' National Surgical Quality Improvement Program, outcomes in pregnant women were compared with matched nonpregnant controls (Moore, 2015). The investigators reported similar outcomes in the two cohorts, each with 2539 patients. In a smaller study, however, women undergoing nonobstetrical surgery after 23 weeks' gestation had a high rate of subsequent preterm delivery (Baldwin, 2015).

The most extensive data regarding anesthetic and surgical risks for the gravida and her fetus are from the Swedish Birth Registry and described by Mazze and Källén (1989). The effects on pregnancy outcomes of 5405 nonobstetrical surgical procedures performed in 720,000 pregnant women from 1973 to 1981 were analyzed. For approximately half of these procedures, general anesthesia was used and commonly involved nitrous oxide supplemented by another inhalation agent or

intravenous medications. These procedures were performed in 41 percent of women in the first trimester, 35 percent in the second, and 24 percent in the third. Overall, 25 percent were abdominal operations, and 20 percent were gynecological or urological procedures. Laparoscopy was the most frequently performed operation, and appendectomy was the most common second-trimester procedure.

Perinatal Morbidity

Excessive perinatal morbidity associated with nonobstetrical surgery is attributable in many cases to the disease itself rather than to adverse effects of surgery and anesthesia. The Swedish Birth Registry again provides valuable data (Table 46-1). Importantly, the incidences of congenital malformations or of stillbirths were not significantly different from those of nonexposed control newborns. However, incidences of low birthweight, preterm birth, and neonatal death in infants born to women who had undergone surgery were significantly greater. Increased neonatal death rates were largely due to preterm birth. In two other studies, the preterm delivery rate in women undergoing nonobstetrical surgery was also elevated (Baldwin, 2015; Hong, 2006).

TABLE 46-1

Birth Outcomes in 5405 Pregnant Women Undergoing Nonobstetrical Surgery

Outcome	Rate	*p* value[a]
Major malformation	1.9%	NS
Stillbirth	7 per 1000	NS
Neonatal death by 7 days	10.5 per 1000	<0.05
Preterm <37 wk	7.5%	<0.05
Birthweight <1500 g	1.2%	<0.05
Birthweight <2500 g	6.6%	<0.05

[a]Compared with 720,000 pregnancies in women without surgery.

NS = not significant.

Data from Mazze, 1989.

Rates of fetal abnormalities with maternal surgery in early pregnancy do not appear increased. Källén and Mazze (1990) scrutinized 572 operations performed at 4 to 5 weeks' gestation and reported a nonsignificant relationship with elevated neural-tube defect rates. In a similar study from a Hungarian database, Czeizel and colleagues (1998) found no evidence that anesthetic agents were teratogenic.

LAPAROSCOPIC SURGERY

Laparoscopy has become the most common first-trimester procedure used for diagnosis and management of several surgical disorders. In 2017, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) updated its recommendations concerning laparoscopy use in pregnant women (Table 46-2).

TABLE 46-2

Some Guidelines from the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) for Laparoscopic Surgery in Pregnant Women

Indications—same as for nonpregnant women
Adnexal mass excision
Investigation of acute abdominal processes
Appendectomy, cholecystectomy, nephrectomy, adrenalectomy, splenectomy
Technique
Position: lateral recumbent
Entry: open technique, careful Veress needle, or optical trocar; fundal height may alter insertion site selection
Trocars: direct visualization for placement; fundal height may alter insertion site selection
CO_2 insufflation pressures: 10–15 mm Hg
Monitoring: capnography intraoperatively, FHR assessment pre- and postoperatively
Perioperative pneumatic compression devices and early postoperative ambulation

CO_2 = carbon dioxide; FHR = fetal heart rate.

Data from Pearl, 2017.

Information regarding surgical approach selection in pregnancy comes from the American College of Surgeons database (Silvestri, 2011). During the 5-year period ending in 2009, almost 1300 pregnant women were studied who had undergone either appendectomy or cholecystectomy. Open appendectomy was performed in 36 percent of 857 gravidas compared with only 17 percent of those not pregnant. Of those undergoing cholecystectomy, an open procedure was used in 10 percent of 436 pregnant women compared with 5 percent of nonpregnant women. No randomized trials compare laparoscopic with open surgery, however, most reviews report equally satisfactory outcomes (Bunyavejchevin, 2013; Cox, 2015; Fatum, 2001). The most frequently performed procedures were cholecystectomy, adnexal surgery, and appendectomy. For adnexal mass surgery in pregnancy, laparoscopy is preferred, and several studies confirm its relative safety (Daykan, 2016; Hoover, 2011; Webb, 2015). At first, 26 to 28 weeks became the upper gestational-age limit recommended, but as experience has accrued, many now describe laparoscopic surgery performed in the third trimester (Kizer, 2011). In one report of 59 gravidas undergoing laparoscopic cholecystectomy or appendectomy, a third were >26 weeks' gestation (Rollins, 2004). No serious adverse sequelae are linked to these procedures. In addition, laparoscopic splenectomy, adrenalectomy, and nephrectomy have also been described in pregnant women (Asizare, 2014; Dong, 2014; Gernsheimer, 2007; Miller, 2012; Stroup, 2007).

Hemodynamic Effects

Abdominal insufflation for laparoscopy causes hemodynamic changes that are summarized in Table 46-3. Reedy and associates (1995) studied baboons at the human equivalent of 22 to 26 weeks' gestation. No substantive physiological changes were found with insufflation pressures of 10 mm Hg, but 20 mm Hg caused significant maternal cardiovascular and respiratory changes after 20 minutes. These included increased respiratory rate, respiratory acidosis, diminished cardiac output, and increased pulmonary artery and capillary wedge pressures.

TABLE 46-3

Physiological Effects of CO_2 Insufflation of the Peritoneal Cavity

System	Effects[a]	Mechanisms	Possible Maternal-Fetal Effects
Respiratory	Increased PCO_2; decreased pH	CO_2 absorption	Hypercarbia, acidosis
Cardiovascular	Increased: heart rate; systemic vascular resistance; pulmonary, central venous, and mean arterial pressures	Hypercarbia and increased intraabdominal pressure	Uteroplacental hypoperfusion— possible fetal hypoxia, acidosis, and hypoperfusion[b]
	Decreased cardiac output	Decreased venous return	
Blood flow	Decreased splanchnic flow with hypoperfusion of liver, kidneys, and gastrointestinal organs	Increased intraabdominal pressure	As above
	Decreased venous return from lower extremities	Increased intraabdominal pressure	As above
	Increased cerebral blood flow	Hypercarbia possibly from shunting due to splanchnic tamponade	Increased CSF pressure[b]

[a]Effects intensified when insufflation pressure >20 mm Hg in baboons (Reedy, 1995).

[b]Data primarily from animal studies.

CO_2 =carbon dioxide; CSF = cerebrospinal fluid; PCO_2 = partial pressure of CO_2.

Data from O'Rourke, 2006; Reynolds, 2003.

In women, cardiorespiratory changes are generally not severe if insufflation pressures are kept below 15 mm Hg. With noninvasive hemodynamic monitoring in women at midpregnancy, the cardiac index decreased 26 percent by 5 minutes of insufflation and 21 percent by 15 minutes (Steinbrook, 2001). Despite this, mean arterial pressures, systemic vascular resistance, and heart rate did not change significantly.

Obesity

Laparoscopic surgery frequently is ideal for the obese woman (Sisodia, 2015). However, some outcomes may be adversely affected in obese gravidas compared with normal-weight patients. Of these, higher conversion rates to laparotomy, longer operating times, and longer hospitalizations have been reported. Also, adequate ventilation is more difficult, and greater pneumoperitoneal pressures are needed to create suitable operating space. There is anatomical distortion of the abdominal wall with displaced landmarks. Finally, the risk of developing hernias at port sites is greater.

Perinatal Outcomes

Because precise effects of laparoscopy in the human fetus are unknown, animal studies are informative. In early studies of pregnant ewes, various investigators reported that uteroplacental blood flow declines when intraperitoneal insufflation pressure exceeded 15 mm Hg (Barnard, 1995; Hunter, 1995). This was the result of decreased perfusion pressure and increased placental vessel resistance (see Table 46-3). The previously cited baboon studies by Reedy and coworkers (1995) produced similar findings.

Perinatal outcomes in women are limited to observational studies. Reedy and colleagues (1997) used the updated Swedish Birth Registry database to analyze a 20-year period with more than 2 million deliveries. Of 2181 laparoscopic procedures, most were performed during the first trimester. Perinatal outcomes for these women were compared with those of all women in the database and those undergoing open surgical procedures. These investigators confirmed the earlier findings of an increased risk of low birthweight, preterm delivery, and fetal-growth restriction. Differences were not found, however, in outcomes of women undergoing laparoscopy versus laparotomy. An observational study of 262 women undergoing surgery for an adnexal mass noted similar findings (Koo, 2012).

Technique

The following description is an overview of laparoscopic techniques in pregnancy. For a detailed description refer to Chapter 15 in *Cunningham and Gilstrap's Operative Obstetrics, 3rd edition* (Kho, 2016).

Preparation for laparoscopy differs little from that used for laparotomy. Bowel cleansing is not needed but may aid visualization and manipulations by emptying the large intestine. Nasogastric or orogastric decompression reduces the risk of stomach trocar puncture and aspiration. Aortocaval compression is avoided by a left-lateral tilt. Positioning of the lower extremities in boot-type stirrups maintains access to the vagina for fetal sonographic assessment or *manual* uterine displacement. Intrauterine manipulators are logically avoided.

Most reports describe the use of general anesthesia after tracheal intubation with monitoring of end-tidal carbon dioxide— $EtCO_2$ (Hong, 2006; Ribic-Pucelj, 2007). With controlled ventilation, $EtCO_2$ is maintained at 30 to 35 mm Hg.

Beyond the first trimester, technical modifications of standard pelvic laparoscopic entry are required to avoid uterine puncture or laceration (Fig. 46-1). Many recommend open entry techniques to avoid perforations of the uterus, pelvic vessels, and adnexa (Kizer, 2011; Koo, 2012). The abdomen is incised at or above the umbilicus, and the peritoneal cavity entered under direct visualization (Fig. 46-2). At this point, the cannula is then connected to the insufflation system, and a 12-mm Hg pneumoperitoneum is created. The initial insufflation should be conducted slowly to allow for prompt assessment and reversal of any untoward pressure-related effects. Gas leakage around the cannula is managed by tightening the surrounding skin with a towel clamp. Insertion of secondary trocars into the abdomen is most safely performed under direct laparoscopic viewing. Single-port surgery has also been described (Dursun, 2013).

FIGURE 46-1

Pregnant uterus at 10, 20, and 36 weeks' gestation depicting distortion of other intraperitoneal organs. (From Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics 3rd ed, New York McGraw-Hill Education, 2017.)

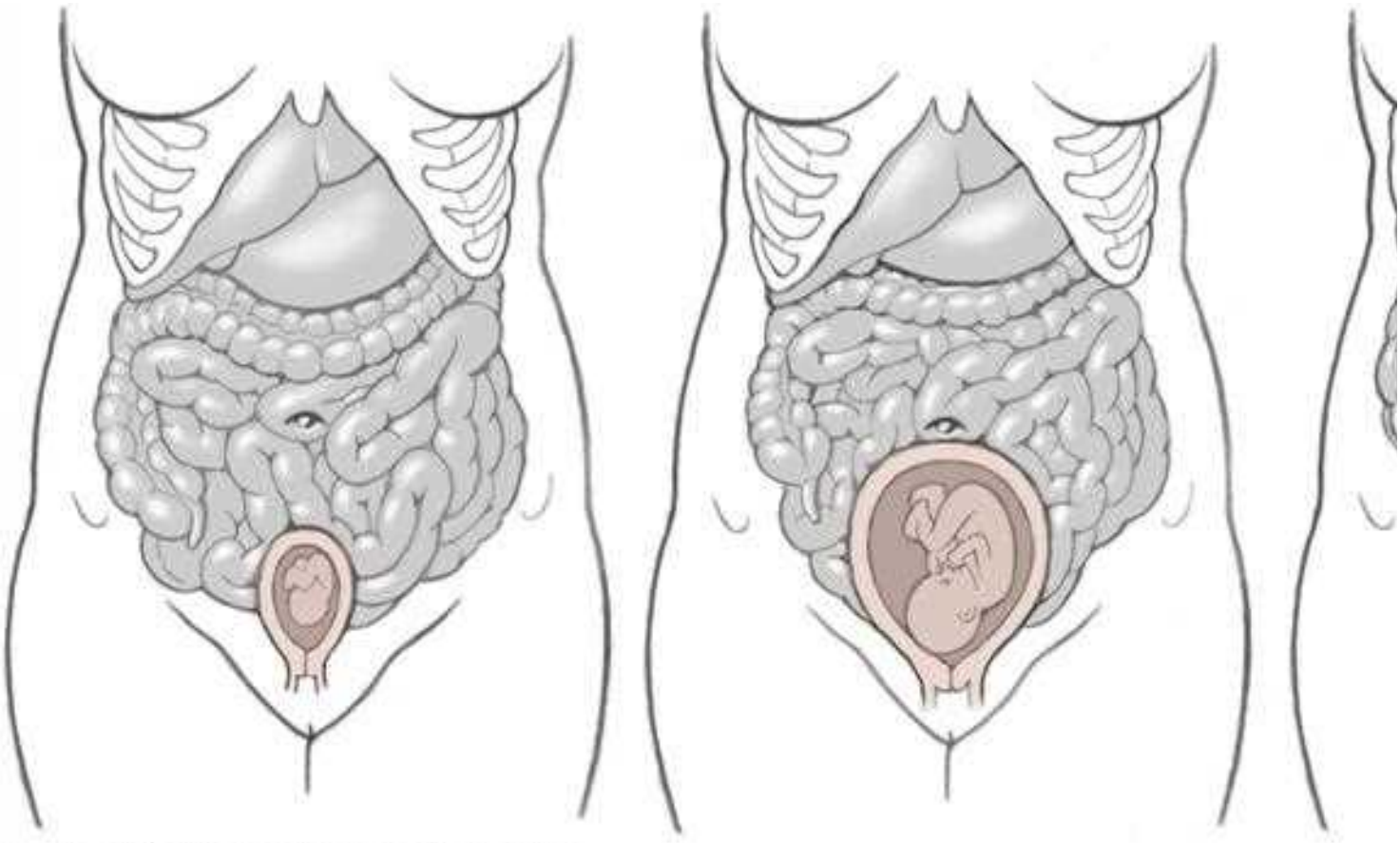
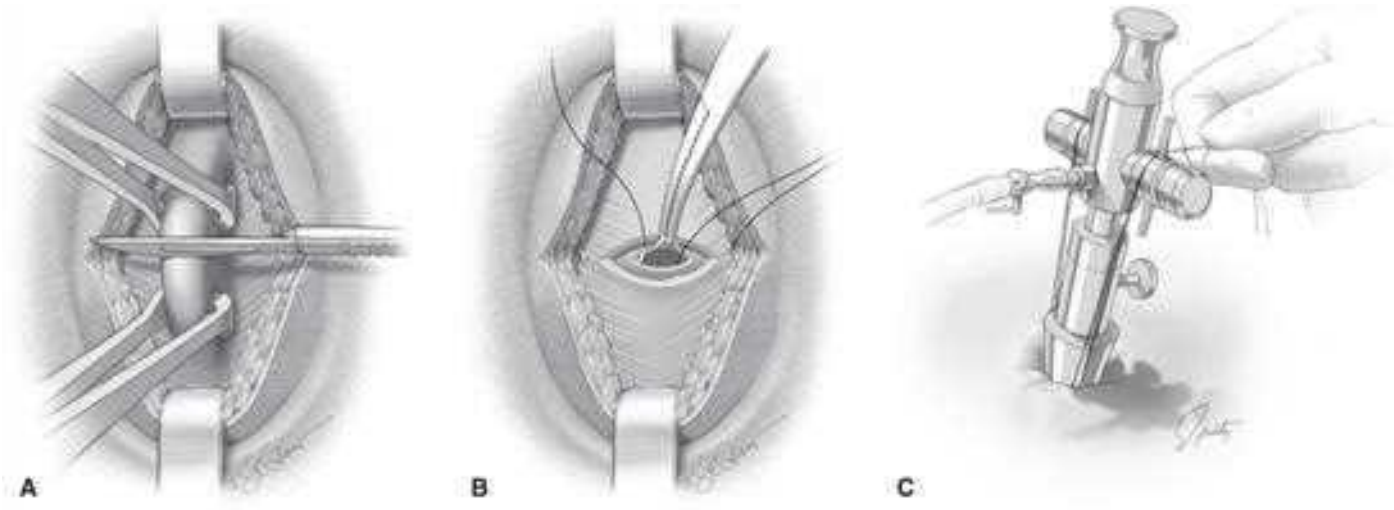


FIGURE 46-2

Open entry technique for laparoscopic instrument placement. **A.** Fascia grasped with two Allis clamps and elevated prior to sharp incision. **B.** Two fascial stitches incorporate the peritoneum and fascia. **C.** These fascial sutures are wrapped around holders of the Hasson cannula to anchor it in place. (From Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics 3rd ed, New York McGraw-Hill Education, 2017.)



In more advanced pregnancies, direct entry through a left upper quadrant port in the midclavicular line, 2 cm beneath the costal margin, may better avoid the fundus (Donkervoort, 2011; Stepp, 2004). Known as *Palmer point*, this entry site is also used in gynecological laparoscopy because visceroparietal adhesions infrequently form here (Vilos, 2007).

Gasless laparoscopy is a less commonly selected alternative approach that uses a rod with intraabdominal fan-blade-shaped retractors. When opened, these allow the abdominal wall to be lifted upward. It avoids the typical laparoscopic cardiovascular changes because the pneumoperitoneum is created by retraction rather than insufflation (Phupong, 2007).

Complications

Risks inherent to any abdominal endoscopic procedure are probably increased slightly during pregnancy. The obvious unique complication is perforation of the pregnant uterus with either a trocar or Veress needle (Azevedo, 2009; Kizer, 2011; Mala, 2014). That said, reported complications are infrequent (Fatum, 2001; Koo, 2012). One Cochrane database review noted a need for randomized trials to deduce comparative benefits and risks of laparoscopy versus laparotomy during pregnancy (Bunyavejchevin, 2013). Pragmatically, this seems unfeasible, and common sense should dictate the approach.

RADIOGRAPHY

Imaging modalities are used as adjuncts for diagnosis and therapy during pregnancy. Options include sonography, radiography, and magnetic resonance (MR) imaging. Of these, radiography is the most problematic. Inevitably, some radiographic procedures are performed before recognition of early pregnancy, usually because of trauma or serious illness. Fortunately, most diagnostic radiographic procedures are associated with minimal fetal risks. As with drugs and medications, however, these procedures may lead to litigation if pregnancy outcome is adverse. And, x-ray exposure may lead to a needless therapeutic abortion because of patient or physician anxiety.

Since 2007, the American College of Radiology (ACR) has addressed the growing concern of radiation dose in all fields of medicine (Amis, 2007). Some of its goals were to limit exposure through radiation safety practices and promote lifelong accumulated records of exposures in any given patient. Task Force recommendations included additional considerations for special radiosensitive populations, such as children and pregnant and potentially pregnant women. At our institutions, special recommendations are made for gravidas. Radiation exposure values and duration are recorded and monitored in high-exposure areas such as computed tomography (CT) and fluoroscopy.

Ionizing Radiation

The term *radiation* literally refers to energy transmission and thus is often applied not only to x-rays, but also to microwaves, ultrasound, diathermy, and radio waves. Of these, x-rays and gamma rays have short wavelengths with very high energy and are ionizing radiation forms. The other four energy forms have rather long wavelengths and low energy (Brent, 1999b, 2009).

Ionizing radiation refers to waves or particles-*photons*-of significant energy that can change the structure of molecules such as those in DNA or that can create free radical or ions capable of secondarily damaging tissue (Hall, 1991; National Research Council, 1990). Methods of measuring the effects of x-rays are summarized in Table 46-4. The standard terms used are *exposure* (in air), *dose* (to tissue), and *relative effective dose* (to tissue). In the range of energies for diagnostic x-rays, the dose is now expressed in grays (Gy), and the relative effective dose is expressed in sieverts (Sv). These can be used interchangeably. For consistency, all doses discussed subsequently are expressed in contemporaneously used units of gray (1 Gy = 100 rad) or sievert (1 Sv = 100 rem). To convert, 1 Sv = 100 rem = 100 rad.

TABLE 46-4

Some Measures of Ionizing Radiation

Exposure	Number of ions produced by x-rays per kg of air Unit: roentgen (R)
Dose	Amount of energy deposited per kg of tissue Modern unit: gray (Gy) (1 Gy = 100 rad) Traditional unit: rad
Relative effective dose	Amount of energy deposited per kg of tissue normalized for biological effectiveness Modern unit: sievert (Sv) (1 Sv = 100 rem) Traditional unit: rem

As noted, the biological effects of x-rays are caused by an electrochemical reaction that can damage tissue. According to Brent (1999a, 2009), x- and gamma-radiation at high doses can create two types of biological effects and reproductive risks in the fetus. These are *deterministic effects* and *stochastic effects*, which are both described in the next sections.

Deterministic Effects

One potential harmful effect of radiation exposure is deterministic, which may result in abortion, growth restriction, congenital malformations, microcephaly, or mental retardation. These deterministic effects are threshold effects, and the threshold level is the *NOAEL—No Observed Adverse Effect Level* (Brent, 2009). Although controversial, the NOAEL concept supports that there is no risk below a threshold dose (0.05 Gy or 5 rad). It also suggests that the threshold for gross fetal malformations is more likely to be 0.2 Gy (20 rad).

The harmful deterministic effects of ionizing radiation have been extensively studied for cell damage with resultant disordered embryogenesis. These have been assessed in animal models, as well as in Japanese atomic bomb survivors and the Oxford Survey of Childhood Cancers (Sorahan, 1995). Additional sources have confirmed prior observations and provided more information (Groen, 2012). One is a 2003 International Commission on Radiological Protection publication that describes biological fetal effects from prenatal irradiation. Another is the Biological Effects of Ionizing Radiation—BEIR VII Phase 2 report of the National Research Council (2006), which discusses health risks from exposure to low levels of ionizing radiation.

Animal Studies

In the mouse model, the lethality risk is highest during the preimplantation period—up to 10 days postconception (Kanter, 2014). This is likely due to blastomere destruction caused by chromosomal damage (Hall, 1991). During organogenesis, high-dose radiation—1 Gy or 100 rad—is more likely to cause malformations and growth restriction and less likely to have lethal effects in the mouse. Studies of brain development suggest effects on neuronal development and a window of cortical sensitivity in early and midfetal periods. That said, acute low-dose ionizing radiation appears to have no deleterious effects (Howell, 2013).

Human Data

Data on adverse human effects of high-dose ionizing radiation mostly derive from the atomic bomb survivors of Hiroshima and Nagasaki (Greskovich, 2000; Otake, 1987). The International Commission on Radiological Protection (2003) confirmed initial studies showing that the increased risk of severe mental retardation was greatest between 8 and 15 weeks' gestation. There may be a lower-threshold dose of 0.3 Gy (30 rad), which is a range similar to the window of cortical sensitivity in the mouse model discussed earlier. The mean decrease in intelligence quotient (IQ) scores was 25 points per Gy or 100 rad. There appears to be linear dose response, but it is not clear whether there is a threshold dose. Most estimates err on the conservative side by assuming a linear nonthreshold hypothesis. In a study of fetuses exposed to low radiation doses, Choi and colleagues (2012) did not find an increased risk for congenital anomalies.

Finally, an increased risk of mental retardation in humans <8 weeks' or >25 weeks' gestation has not been documented, even with doses exceeding 0.5 Gy or 50 rad (International Commission on Radiological Protection, 2003). Reports have described high-dose radiation used to treat women for malignancy, menorrhagia, and uterine myomas. Dekaban (1968) described 22 infants with microcephaly, mental retardation, or both following exposure in the first half of pregnancy to an estimated 2.5 Gy or 250 rad.

Summary of Fetal Radiation Exposure

From 8 to 15 weeks, the fetus is most susceptible to radiation-induced mental retardation. It has not been resolved whether this is a threshold or nonthreshold linear function of dose. The Committee on Biological Effects (1990) estimates the risk of severe mental retardation to be as low as 4 percent for 0.1 Gy (10 rad) and as high as 60 percent for 1.5 Gy (150 rad). But recall that these doses are 2 to 100 times higher than those considered maximal from diagnostic radiation. Importantly, cumulative doses from multiple procedures may reach the harmful range, especially at 8 to 15 weeks' gestation. At 16 to 25 weeks, the risk is less. And again, there is no proven risk before 8 weeks or after 25 weeks. Importantly, embryofetal risks from low-dose diagnostic radiation appear to be minimal. Current evidence suggests that risks for malformations, growth restriction, or abortion are not increased from a radiation dose of less than 0.05 Gy (5 rad). Indeed, Brent (2009) concluded that gross congenital malformations would not be increased with exposure to less than 0.2 Gy (20 rad). Because diagnostic x-rays seldom exceed 0.1 Gy (10 rad), Strzelczyk and associates (2007) concluded that these procedures are unlikely to cause deterministic effects. As emphasized by Groen and coworkers (2012), 0.1 Gy is the radiation equivalent to that from more than 1000 chest x-rays!

Stochastic Effects

These effects refer to random, presumably unpredictable oncogenic or mutagenic effects of radiation exposure. Stochastic effects concern associations between fetal diagnostic radiation exposure and increased risk of childhood cancers or genetic diseases. According to Doll and Wakeford (1997), as well as the National Research Council (2006) BEIR VII Phase 2 report, excess cancers can result from in utero exposure to doses as low as 0.01 Sv or 1 rad. Stated another way by Hurwitz and colleagues (2006), the estimated risk of childhood cancer following fetal exposure to 0.03 Gy or 3 rad doubles the background risk of 1 in 600 to that of 2 in 600.

In one report, in utero radiation exposure was determined for 10 solid cancers in adults from age 17 to 45 years. There was a dose-response relationship as previously noted at the 0.1 Sv or 10 rem threshold. These cancers likely are associated with a complex series of interactions between DNA and ionizing radiation. They also make it more problematic to predict cancer risk from low-dose radiation of less than 0.1 Sv or 10 rem. Importantly, below doses of 0.1 to 0.2 Sv, there is no convincing evidence of a carcinogenic effect (Brent, 2009, 2014; Preston, 2008; Strzelczyk, 2007).

X-Ray Dosimetry

Estimates of dose to the uterus and embryo for various frequently used radiographic examinations are summarized in Table 46-5. Imaging of maternal body parts farthest from the uterus results in a very small dose of radiation scatter to the embryo or fetus. The size of the woman, radiographic technique, and equipment performance are other variables (Wagner, 1997). Thus, data in the table serve only as guidelines. When the radiation dose for a specific individual is required, a medical physicist should be consulted. Brent (2009) recommends consulting the Health Physics Society website (www.hps.org) to view some examples of questions and answers posed by patients exposed to radiation.

TABLE 46-5

Dose to the Uterus for Common Radiologic Procedures

Study	View	Dose[a] per View (mGy)	No. Films[b]	Dose (mGy)
Skull[c]	AP, PA, Lat	<0.0001	4.1	<0.0005
Chest	AP, PA[c], Lat[d]	<0.0001–0.0008	1.5	0.0002–0.0007
Mammogram[d]	CC, Lat	<0.0003–0.0005	4.0	0.0007–0.002
Lumbosacral spine[e]	AP, Lat	1.14–2.2	3.4	1.76–3.6
Abdomen[e]	AP		1.0	0.8–1.63
Intravenous pyelogram[e]	3 views		5.5	6.9–14
Hip[b] (single)	AP	0.7–1.4		
	Lat	0.18–0.51	2.0	1–2

[a]Calculated for x-ray beams with half-value layers ranging from 2 to 4 mm aluminum equivalent using the methodology of Rosenstein, 1988.

[b]Based on data and methods reported by Laws, 1978.

[c]Entrance exposure data from Conway, 1989.

[d]Estimates based on compilation of above data.

[e]Based on NEXT data reported in National Council on Radiation Protection and Measurements, 1989.

AP = anterior-posterior; CC = cranial-caudal; Lat = lateral; PA = posterior-anterior.

Therapeutic Radiation

The Radiation Therapy Committee Task Group of the American Association of Physics in Medicine (Stovall, 1995) emphasizes careful individualization of radiotherapy for the pregnant woman (Chap. 63, Cancer Therapy in Pregnancy). For example, in some cases, shielding of the fetus and other safeguards can be employed (Fenig, 2001; Nuyttens, 2002). In other instances, the fetus will be exposed to dangerous radiation doses, and a carefully designed plan must be improvised (Prado, 2000). Examples include models that estimate the fetal dose given during maternal brain radiotherapy or tangential breast irradiation (Mazonakis, 1999, 2003). The harmful effects of radiotherapy on future fertility and pregnancy outcomes were reviewed by Wo and Viswanathan (2009) and others and are detailed in Chapter 63 (Reproductive Tract Neoplasms).

Diagnostic Radiation

Radiographs

To estimate fetal risk, approximate x-ray dosimetry must be known. According to the American College of Radiology, no single diagnostic procedure results in a radiation dose significant enough to threaten embryo-fetal well-being (Hall, 1991).

For standard radiographs, dosimetry is presented in Table 46-5. In pregnancy, the AP-view chest radiograph is the most commonly used study, and fetal exposure is exceptionally small—0.0007 Gy or 70 mrad. With one abdominal radiograph, because the embryo or fetus is directly in the x-ray beam, the dose is higher—0.001 Gy or 100 mrad. The standard intravenous pyelogram may exceed 0.005 Gy or 500 mrad because of several exposures. The one-shot pyelogram described in Chapter 53 (Nephrolithiasis) is useful when urolithiasis or other causes of obstruction are unproven by sonography but still suspected. Most "trauma series," such as radiographs of an extremity, skull, or rib series, deliver low doses because of the fetal distance from the target area (Shakerian, 2015).

Fluoroscopy and Angiography

Dosimetry calculations are much more difficult with these procedures because of variations in the number of radiographs obtained, total fluoroscopy time, and fluoroscopy time in which the fetus is in the radiation field. As shown in Table 46-6, the range is variable. The Food and Drug Administration (FDA) limits the exposure rate for conventional fluoroscopy such as barium studies, however, special-purpose systems such as angiography units have the potential for much higher exposure.

TABLE 46-6

Estimated X-Ray Doses to the Uterus/Embryo from Common Fluoroscopic Procedures

Procedure	Dose to Uterus (mGy)	Fluoroscopic Exposure in Seconds (SD)
Cerebral angiography[a]	<0.1	—
Cardiac angiography[b,c]	0.65	223 (± 118)
Single-vessel PTCA[b,c]	0.60	1023 (± 952)
Double-vessel PTCA[b,c]	0.90	1186 (± 593)
Upper gastrointestinal series[d]	0.56	136
Barium swallow[b,e]	0.06	192
Barium enema[b,f,g]	20–40	289–311

[a] Wagner, 1997.

[b] Calculations based on data of Gorson, 1984.

[c] Finci, 1987.

[d] Suleiman, 1991.

[e] Based on female data from Rowley, 1987.

[f] Assumes embryo in radiation field for entire examination.

[g] Bednarek, 1983.

PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

Angiography and vascular embolization may occasionally be necessary for trauma and for serious maternal disorders, especially renal disease (Wortman, 2013). As before, a greater distance from the embryo or fetus lowers the exposure and risk.

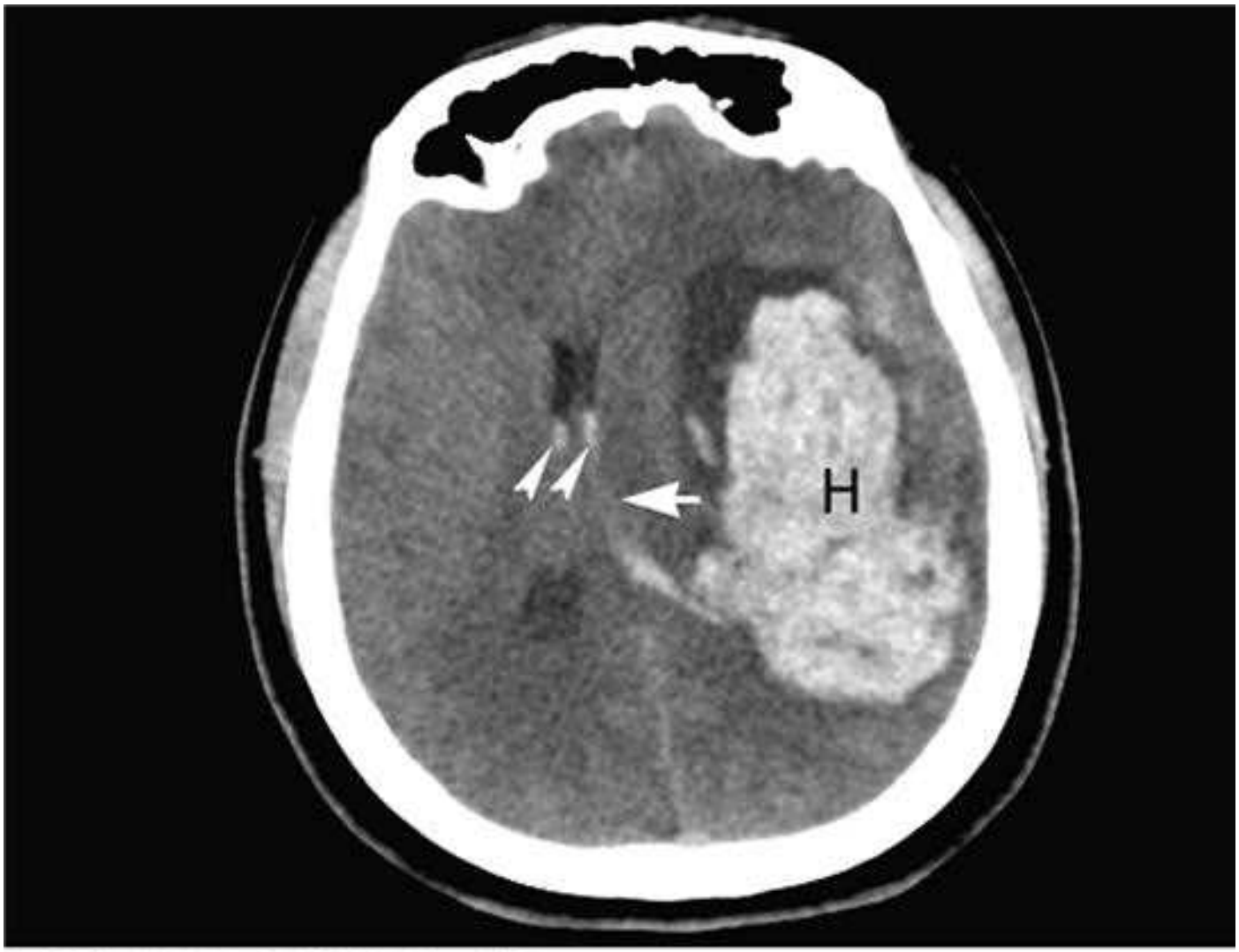
Computed Tomography

These x-ray images are usually performed by obtaining a spiral of 360-degree images that are postprocessed in multiple planes. Of these, the axial image remains the most commonly obtained. Multidetector CT (MDCT) images are now standard for common clinical indications. The most recent detectors have 16 or 64 channels, and multidetector protocols may result in increased dosimetry compared with traditional CT imaging. Several imaging parameters have an effect on exposure (Brenner, 2007). These include pitch, kilovoltage, tube current, collimation, number of slices, tube rotation, and total acquisition time. If a study is performed with and without contrast, the dose is doubled because twice as many images are obtained. Fetal exposure is also dependent on factors such as maternal size as well as fetal size and position. And as with plain radiography, the closer the target area is to the fetus, the greater the delivered dose.

Cranial CT scanning is the most commonly performed study in gravidas. It is used for neurological disorders as discussed in Chapter 60 (Central Nervous System Imaging) and with eclampsia as noted in Chapter 40 (Uteroplacental Perfusion). Nonenhanced CT scanning is commonly used to detect acute hemorrhage within the epidural, subdural, or subarachnoid spaces (Fig. 46-3). Because of the distance from the fetus, radiation dosage is negligible (Goldberg-Stein, 2012).

FIGURE 46-3

A 37-year-old with intrapartum eclampsia at term. An image from a noncontrast computed tomography head study demonstrates a large left-sided frontoparietal temporal intraparenchymal hematoma (*H*) with intraventricular extension (*arrowheads*). The midline (*arrow*) is shifted to the right due to mass effect from the hematoma. (From Kho KA: Diagnostic and operative laparoscopy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics 3rd ed, New York McGraw-Hill Education, 2017.)



Abdominal procedures are more problematic. Hurwitz and associates (2006) employed a 16-channel multidetector scanner to calculate fetal exposure at 0 and 3 months' gestation using a phantom model. Calculations were made for three commonly requested procedures in pregnant women (Table 46-7). The pulmonary embolism protocol has the same dosimetry exposure as the ventilation-perfusion (V/Q) lung scan discussed in Radiographic Contrast Agents. Because of the pitch used, the appendicitis protocol has the highest radiation exposure, however, it is very useful clinically when MR imaging is not available. Using a similar protocol in 67 women with suspected appendicitis, Lazarus and coworkers (2007) reported sensitivity of 92 percent, specificity of 99 percent, and a negative-predictive value of 99 percent. Here, dosimetry was markedly decreased compared with standard appendiceal imaging because of a different pitch. This is discussed further in Chapter 54 (Colonic Pseudo-obstruction). Last, for suspected urolithiasis, the multidetector-scan protocol is used if sonography is nondiagnostic. Using a similar protocol, White and colleagues (2007) identified urolithiasis in 13 of 20 women at an average of 26.5 weeks. Finally, as shown in Figure 46-4, abdominal tomography is performed if indicated in the pregnant woman with severe trauma (Matzon, 2015; Shakerian, 2015).

TABLE 46-7

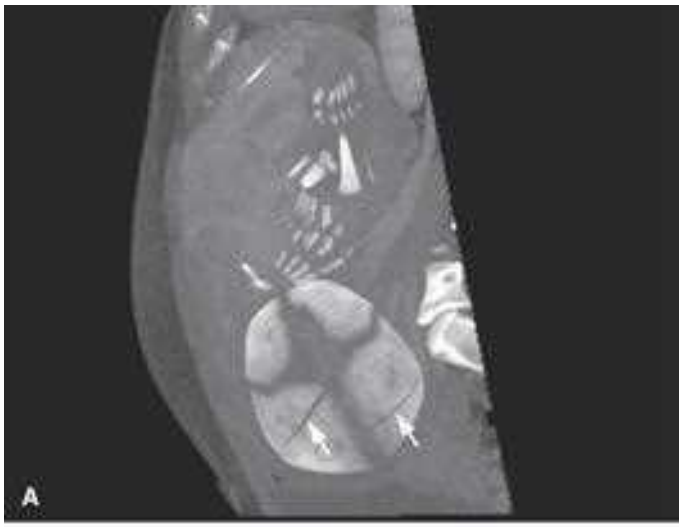
Estimated Radiation Dosimetry with 16-Channel Multidetector Computed-Tomographic (MDCT) Imaging Protocols

	Dosimetry (mGy)	
Protocol	**Preimplantation**	**3 Months' Gestation**
Pulmonary embolism	0.20–0.47	0.61–0.66
Renal stone	8–12	4–7
Appendix	15–17	20–40

Data from Hurwitz, 2006.

FIGURE 46-4

This woman in her third trimester was involved in a high-speed motor vehicle accident. **A.** Maximum intensity projection acquired for maternal indications readily identifies fetal skull fractures (*arrows*). **B.** 3-D reformatted CT image in a bone algorithm demonstrates the fetal skeleton from data acquired during the maternal examination. Again, the arrow marks one fracture site. (Reproduced with permission from Bailey AA, Twickler DM: Perioperative imaging. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics 3rd ed, New York, McGraw-Hill Education, 2017. Photo contributor: Dr. Travis Browning.)



Most experience with chest CT scanning is with suspected pulmonary embolism. The most recent recommendations for its use in pregnancy from the Prospective Investigation of Pulmonary Embolism Diagnosis—PIOPED—II investigators were summarized by Stein and associates (2007). They found that pulmonary scintigraphy—the V/Q scan—was recommended at that time for pregnant women by 70 percent of radiologists and chest CT angiography by 30 percent. Indeed, scintigraphy is still recommended by the American Thoracic Society for gravidas with a normal chest x-ray (Leung, 2012). That said, most agree that multidetector-CT angiography

has improved accuracy because of increasingly faster acquisition times (Brown, 2014). Others have reported a higher use rate for CT angiography and emphasize that dosimetry is similar to that with V/Q scintigraphy (Brenner, 2007; Greer, 2015; Hurwitz, 2006). Controversies on this topic continue, recognizing that fetal radiation doses are lower with CT angiography compared with the V/Q scan, but maternal chest radiation doses are substantially higher with CT scanning (van Mens, 2017). We prefer MDCT scanning initially for suspected pulmonary embolism (Chap. 52, Superficial Venous Thrombophlebitis).

CT pelvimetry is used by some before attempting breech vaginal delivery (Chap. 28, Delivery Complications). The fetal dose approaches 0.015 Gy or 1.5 rad, but use of a low-exposure technique may reduce this to 0.0025 Gy or 0.25 rad.

Radiographic Contrast Agents

These can be given intravenously or taken orally. Intravenous contrast agents are considered category B by the FDA. The types of intravenous contrast employed for imaging today are iodinated and low osmolality, thus, they cross the placenta to the fetus. With water-soluble iodinated contrast, no cases of neonatal hypothyroidism or other adverse effects have been documented (American College of Radiology, 2015). Oral contrast preparations, typically containing iodine or barium, have minimal systemic absorption and are unlikely to affect the fetus.

Nuclear Medicine Studies

These studies are performed by “tagging” a radioactive element to a carrier that can be injected, inhaled, or swallowed. For example, the radioisotope technetium-99m may be tagged to red blood cells, sulfur colloid, or pertechnetate. The method used to tag the agent determines fetal radiation exposure. The amount of placental transfer is obviously important, but so is renal clearance because of fetal proximity to the maternal bladder. Measurement of radioactive technetium is based on its decay, and the units used are the curie (Ci) or the becquerel (Bq). Dosimetry is usually expressed in millicuries (mCi). The effective tissue dose is expressed in sievert units (Sv) with conversion as discussed in Table 46-4: 1 Sv = 100 rem = 100 rad.

Depending on the physical and biochemical properties of a radioisotope, an average fetal exposure can be calculated (Wagner, 1997; Zanzonico, 2000). Commonly used radiopharmaceuticals and estimated absorbed fetal doses are given in Table 46-8. The radionuclide dose should be kept as low as possible (Adelstein, 1999; Zanotti-Fregonara, 2017). Exposures vary with gestational age and are greatest earlier in pregnancy for most radiopharmaceuticals. One exception is the later effect of iodine-131 on the fetal thyroid (Wagner, 1997).

TABLE 46-8

Radiopharmaceuticals Used in Nuclear Medicine Studies

Study	Estimated Activity Administered per Examination (mCi)[a]	Weeks' Gestation[b]	Dose to Uterus/Embryo (mSv)[c]
Brain	20 mCi ^{99m}Tc DTPA	<12	8.8
		12	7[c]
Hepatobiliary	5 mCi ^{99m}Tc sulfur colloid	12	0.45
	5 mCi ^{99m}Tc HIDA		1.5
Bone	20 mCi ^{99m}Tc phosphate	<12	4.6
Pulmonary			
Perfusion	3 mCi ^{99m}Tc-macroaggregated albumin	Any	0.45–0.57 (combined)
Ventilation	10 mCi ^{133}Xe gas		
Renal	20 mCi ^{99m}Tc DTPA	<12	8.8
Abscess or tumor	3 mCi ^{67}Ga citrate	<12	7.5
Cardiovascular	20 mCi ^{99m}Tc-labeled red blood cells	<12	5
	3 mCi ^{210}Tl chloride	<12	11
		12	6.4
		24	5.2
		36	3
Thyroid	5 mCi $^{99m}TcO_4$	<8	2.4
	0.3 mCi ^{123}I (whole body)[d]	1.5–6	0.10
	0.1 mCi ^{131}I		
	Whole body	2–6	0.15
	Whole body	7–9	0.88
	Whole body	12–13	1.6
	Whole body	20	3
	Thyroid-fetal	11	720
	Thyroid-fetal	12–13	1300
	Thyroid-fetal	20	5900
Sentinel lymphoscintigram	5 mCi ^{99m}Tc sulfur colloid (1–3 mCi)		5

[a]mCi = millicuries. To convert to mrad, multiply by 100.

[b]Exposures are generally greater prior to 12 weeks compared with increasing gestational ages.

[c]Some measurements account for placental transfer.

[d]The uptake and exposure of ^{131}I increases with gestational age.

DPTA = diethylenetriaminepentaacetic acid; Ga = gallium; HIDA = hepatobiliary iminodiacetic acid; I = iodine; mCi = millicurie; mSv = millisievert; Tc = technetium; TcO_4 = pertechnetate; Tl = thallium.

Data from Adelstein, 1999; Schwartz, 2003; Stather, 2002; Wagner, 1997; Zanzonico, 2000.

Discussed earlier, some still use the ventilation-perfusion lung scan for suspected pulmonary embolism. It is also used if CT angiography is nondiagnostic. Perfusion is measured with injected ^{99}Tc-macroaggregated albumin, and ventilation is measured with inhaled xenon-127 or xenon-133. Fetal exposure with either is negligible (Chan, 2002; Mountford, 1997).

Thyroid scanning with iodine-123 or iodine-131 seldom is indicated in pregnancy. With trace diagnostic doses used, however, fetal risk is minimal. Importantly, therapeutic radioiodine in doses to treat Graves disease or thyroid cancer may cause fetal thyroid ablation and cretinism.

The sentinel lymphoscintigram, which uses ^{99m}Tc-sulfur colloid to detect the axillary lymph node most likely to have metastases from breast cancer, is a commonly used preoperative study in nonpregnant women (Newman, 2007; Spanheimer, 2009; Wang, 2007). As shown in Table 46-8, the calculated dose is approximately 0.014 mSv or 1.4 mrad, which should not preclude its use during pregnancy.

SONOGRAPHY

Of all of the major advances in obstetrics, the development of sonography for study of the fetus and mother certainly is one of the greater achievements. The technique has become virtually indispensable in everyday practice. Its wide-ranging clinical uses are further discussed in Chapter 10 and in most other sections of this book.

MAGNETIC RESONANCE IMAGING

Magnetic resonance technology does not use ionizing radiation, and its application is cited throughout this book. Advantages include high soft-tissue contrast, ability to characterize tissue, and acquisition of images in any plane—particularly axial, sagittal, and coronal. An entire section in Chapter 10 (Magnetic Resonance Imaging) is devoted to mechanisms that generate MR images.

Safety

The most recent update of the expert panel on MR safety of the American College of Radiology was summarized by Kanal and colleagues (2013). The panel concluded that no harmful human effects are reported from MR imaging. Similar conclusions were reached by the Canadian Task Force on Preventive Health Care (Patenaude, 2014).

Early studies found differences in blastocyst formation of early murine embryos exposed to MR imaging with 1.5 T (T = tesla) (Chew, 2001). When operated within standardized limits, maternal and fetal imaging can be safely performed at clinical magnet strengths—3 T and below. MR imaging can be used, regardless of trimester: (1) if the information cannot be obtained with another nonionizing modality, namely sonography, (2) if the results of the study will guide maternal or fetal management during pregnancy, and (3) if the imaging cannot be delayed until the woman is no longer pregnant. The decision to use a magnetic field strength >1.5 T may be made for specific maternal indications. Early work also suggests imaging at 3 T can improve fetal assessment (Victoria, 2016). A magnetic field strength up to 4 T appears safe in animals (Magin, 2000). Vadeyar and associates (2000) reported no demonstrable fetal heart rate pattern changes during MR imaging of gravidas. Studies evaluating children exposed in utero have shown no deleterious effects (Clements, 2000; Kok, 2004; Reeves, 2010).

Contraindications to MR imaging include internal cardiac pacemakers, neurostimulators, implanted defibrillators and infusion pumps, cochlear implants, shrapnel or other metal in biologically sensitive areas, some intracranial aneurysm clips, and any metallic foreign body in the eye. Of more than 51,000 nonpregnant patients scheduled for MR imaging, Dewey and colleagues (2007) found that only 0.4 percent had an absolute contraindication to the procedure.

Contrast Agents

Elemental *gadolinium chelates* are used to create paramagnetic contrast. These cross the placenta and are found in the fetus, placenta, and amnionic fluid (Oh, 2015). In doses approximately 10 times the human dose, a gadolinium-based contrast agent caused slight developmental delay in rabbit fetuses. De Santis and associates described 26 women given a gadolinium derivative in the first trimester without adverse fetal effects (Kanal, 2013). According to Briggs and colleagues (2015), the American College of Obstetricians and Gynecologists (2017a), and the American College of Radiology (2015), routine use of gadolinium is not recommended unless there are potential benefits that outweigh fetal risks. This recommendation stems from a possible dissociation of the toxic gadolinium ion from its ligand in amnionic fluid and potential prolonged exposure of the fetus.

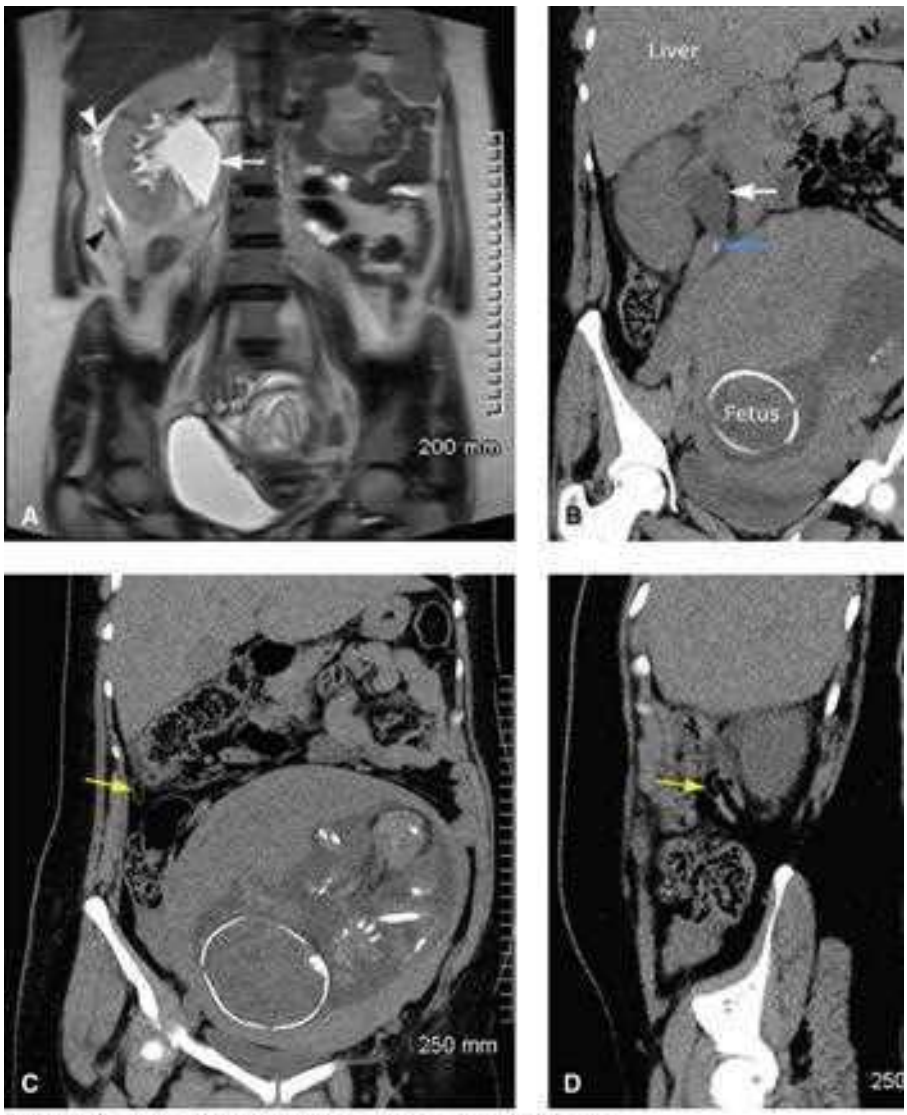
Maternal Indications

In some cases, MR imaging may be complementary to CT, and in others, MR imaging is preferable. Maternal central nervous system abnormalities, such as brain tumors or spinal trauma, are more clearly seen with MR imaging. As discussed in Chapter 40 (Cerebrovascular Pathophysiology), MR imaging has provided valuable insights into the pathophysiology of preeclampsia (Twickler, 2007; Zeeman, 2003, 2014). It is invaluable in the diagnosis of neurological emergencies (Edlow, 2013).

To evaluate the maternal abdomen and retroperitoneal space, MR imaging is a superb technique. It is chosen by many to determine the degree and extent of placenta accreta and its variants (Chap. 41, Clinical Presentation and Diagnosis). It has been employed for detection and localization of adrenal tumors, renal lesions, gastrointestinal lesions, and pelvic masses in pregnancy. For evaluating neoplasms of the chest, abdomen, and pelvis in pregnancy, it has particular value (Boyd, 2012; Tica, 2013). MR urography has been used successfully for renal urolithiasis (Mullins, 2012). As discussed in Chapter 37 (Parametrial Phlegmon), CT and MR imaging are useful for evaluation of puerperal infections, but MR imaging provides better visualization of the bladder flap area following cesarean delivery (Brown, 1999; Twickler, 1997). MR imaging now includes evaluation of right lower quadrant pain in pregnancy, specifically appendicitis (Fig. 46-5) (Baron, 2012; Dewhurst, 2013; Furey, 2014; Pedrosa, 2009; Tsai, 2017). Investigators have also found other disorders of the gastrointestinal tract to be easily diagnosed with MR imaging (Chap. 54, Upper Gastrointestinal Tract Disorders). Finally, cardiac MR imaging has shown promise in investigating normal physiology, complex defects, and cardiomyopathies (Kramer, 2015; Nelson, 2015; Stewart, 2016).

FIGURE 46-5

Multipara at 29 weeks' gestation with suspected appendicitis. **A.** Coronal T2-weighted magnetic resonance image demonstrates severe hydronephrosis (*arrow*) and perinephric fluid (*white arrowhead*) suggesting caliceal rupture. The normal appendix is seen laterally (*black arrowhead*). **B.** Coronal computed tomography (CT) better defines the source of obstruction as an 8-mm radiopaque stone at the ureteropelvic junction (*blue arrow*) and distal to the hydronephrosis (*white arrow*). **C** and **D.** In the same woman, more anterior coronal and sagittal CT images show the expected displacement of a noninflamed appendix (*yellow arrow*) into the upper abdomen with advancing gestation.



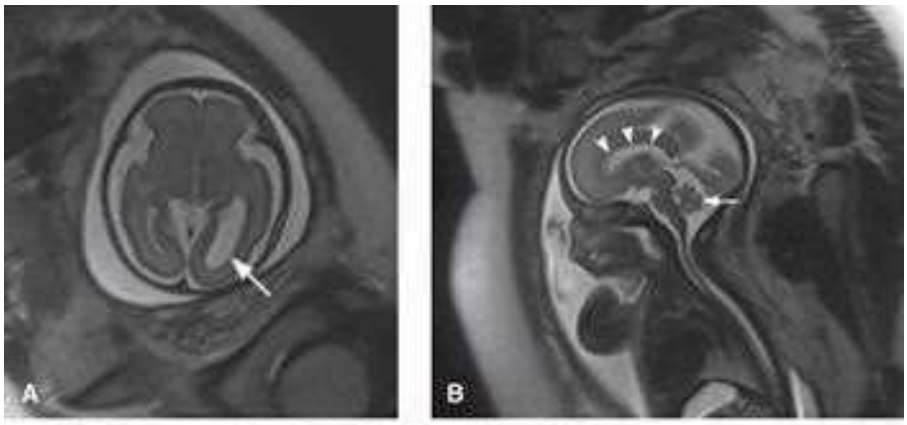
Fetal Indications

Fetal MR imaging provides a complement to sonography (Laifer-Narin, 2007; Sandrasegaran, 2006). According to Zaretsky and associates (2003a), MR imaging can be used to image almost all elements of the standard fetal anatomical survey. The most frequent fetal indications for MR imaging are evaluation of complex abnormalities of the brain, chest, and genitourinary system (Williams, 2017). Reichel (2003), Twickler (2002), and others have validated its use for fetal central nervous system anomalies and biometry (Fig. 46-6). Caire and coworkers (2003) reported its merits for fetal genitourinary anomalies. Hawkins and colleagues (2008) described MR imaging in 21 fetuses with renal anomalies and oligohydramnios. Zaretsky and associates (2003b) noted that fetal-weight estimation was more accurate using MR imaging than with sonography. Fetal movement is less problematic with faster acquisitions. Morphology is primarily assessed with fast T2-

weighted sequences such as *HASTE—Half-Fourier Acquisition Single Shot Turbo Spin Echo*, or *SSFSE—Single Shot Fast Spin Echo*. Fetal indications and findings of MR imaging are discussed more extensively in Chapter 10 (Fetal Anatomical Evaluation) and throughout this book.

FIGURE 46-6

Nullipara at 27 weeks' gestation. **A.** Axial T2-weighted MR image demonstrates mild fetal unilateral ventriculomegaly involving the left lateral ventricle (*arrow*). **B.** Sagittal T2-weighted MR image demonstrates normal development of the corpus callosum (*arrowheads*) and vermis (*arrow*).



IMAGING DURING PREGNANCY

The American College of Obstetricians and Gynecologists (2017a) has reviewed the effects of radiographic, sonographic, and magnetic-resonance exposure during pregnancy. Its suggested guidelines are shown in Table 46-9.

TABLE 46-9

Guidelines for Diagnostic Imaging During Pregnancy and Lactation

Sonography and magnetic resonance (MR) imaging are not associated with fetal risk and are preferred options for imaging in pregnancy
In general, radiation exposure during radiography, computed tomography (CT), or nuclear medicine imaging delivers a dose much lower than that associated with fetal harm. If needed to supplement sonography or MR imaging or if more readily available, these should not be withheld
With MR imaging, gadolinium contrast use should be restricted unless it significantly improves diagnostic accuracy to benefit fetal or maternal outcome
Breastfeeding should not be interrupted after gadolinium administration

Data from American College of Obstetricians and Gynecologists, 2017a.

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CHAPTER 47: Critical Care and Trauma

The pregnant women is exposed to the same possibility of injury as at other times, the prognosis not being naturally altered except that abortion frequently occurs.

—J. Whitridge Williams (1903)

INTRODUCTION

These observations made more than a century ago are less applicable today to critically ill pregnant women because of current intensive care capabilities. For example, severe medical, surgical, and obstetrical disorders complicating pregnancy are frequently managed by a multidisciplinary team for optimal care. It is axiomatic that obstetricians and other members of the health-care team must have a working knowledge of the unique considerations for pregnant women. Some of those discussed in Chapter 46 include pregnancy-induced physiological changes, alterations in normal laboratory values, and consideration for the second patient—the fetus. Because these critically ill women are usually young and in good health, their prognosis is generally better than that of many other patients admitted to intensive care units (ICUs) (Gaffney, 2014).

OBSTETRICAL INTENSIVE CARE

In the United States each year, 1 to 3 percent of pregnant women require critical care services, and the risk of death during such admissions ranges from 2 to 11 percent (American College of Obstetricians and Gynecologists, 2017b). Those with pregnancy-associated complications—especially hemorrhage and hypertension—have the greatest need for intensive care (Chantry, 2015; Gaffney, 2014; Guntupalli, 2015a,b). That said, many antepartum admissions are for nonobstetrical reasons, and these include diabetes, pneumonia or asthma, heart disease, chronic hypertension, pyelonephritis, and thyrotoxicosis (Guntupalli, 2015b; Zeeman, 2006). Additionally, intrapartum and postpartum critical care for hypertensive disorders, hemorrhage, sepsis, or cardiopulmonary complications is often required. In instances of life-threatening hemorrhage, surgical procedures may be necessary, and close proximity to a delivery-operating room is paramount. For women who are undelivered, fetal well-being is also better served by this close proximity, especially because many are delivered preterm (Kilpatrick, 2016).

Organization of Critical Care

The concept and development of critical care for all aspects of medicine and surgery began in the 1960s. The National Institutes of Health held a Consensus Conference (1983) and the Society of Critical Care Medicine (1988, 1999) subsequently established guidelines for ICUs. Especially pertinent to obstetrics, these costly units prompted the evolution of a step-down *intermediate care unit*. These latter units were designed for patients who did not require intensive care, but who needed a higher level of care than that provided on a general ward. The American College of Critical Care Medicine and the Society of Critical Care Medicine (1998) have published guidelines for these units (Table 47-1).

TABLE 47-1

Guidelines for Conditions That Could Qualify for Intermediate Care

Cardiac: evaluation for possible infarction, stable infarction, stable arrhythmias, mild-to-moderate congestive heart failure, hypertensive urgency without end-organ damage
Pulmonary: stable patients for weaning and chronic ventilation, patients with potential for respiratory failure who are otherwise stable
Neurological: stable central nervous system, neuromuscular, or neurosurgical conditions that require close monitoring
Drug overdose: hemodynamically stable
Gastrointestinal: stable bleeding, liver failure with stable vital signs
Endocrine: diabetic ketoacidosis, thyrotoxicosis that requires frequent monitoring
Surgical: postoperative from major procedures or complications that require close monitoring
Miscellaneous: early sepsis, patients who require closely titrated intravenous fluids, pregnant women with severe preeclampsia or other medical problems

Data from Nasraway, 1998.

Obstetrical Critical Care

Although the evolution of critical care for obstetrical patients has generally followed developments just described, there are no specific guidelines. Most hospitals employ a blend of these concepts, and in general, units can be divided into three types.

First, in most hospitals, severely ill women are transferred to medical or surgical ICUs that are operated by specialists often certified in critical care medicine. Admissions or transfers to these units are situation-specific and based on the acuity of care needed and on the ability of the facility to provide it. For example, pregnant women who require ventilatory support, invasive monitoring, or pharmacological support of circulation are typically transferred to an ICU (Chantry, 2015). Another example is the neurological ICU (Sheth, 2012). In an earlier review of more than 25 tertiary-care referral institutions, approximately 0.5 percent of obstetrical patients were transferred to these types of ICUs (Zeeman, 2006).

A second type is the obstetrical intermediate care unit, sometimes referred to as a high-dependency care unit (HDU). One example is found at Parkland Hospital. Located within the labor and delivery unit, it has designated rooms staffed by experienced personnel. The two-tiered system incorporates the guidelines for intermediate and intensive care. Care is provided by maternal-fetal medicine specialists and nurses with experience in critical care obstetrics. As needed, this team is expanded to include other obstetricians and anesthesiologists, hospitalists, gynecological oncologists, pulmonologists, cardiologists, surgeons, and other medical and surgical subspecialists (Stevens, 2015). Many tertiary-care centers have developed similar intermediate care units and use selected triage to ICUs. Guidelines for such transfers must follow the federal Emergency Medical Treatment and Labor Act (EMTALA) guidelines. According to the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), the minimal monitoring required for a critically ill patient during transport includes continuous pulse oximetry, electrocardiography, and regular assessment of vital signs. They must have secure venous access, and those who are mechanically ventilated must have endotracheal tube position confirmed and secured. Left uterine displacement and supplemental oxygen is applied routinely during transport of antepartum patients. Continuous fetal heart rate or tocodynamic monitoring is individualized.

Last, obstetrical ICUs are full-care ICUs but are operated by obstetrical and anesthesia personnel in the labor and delivery unit. Only a few obstetrical services have these capabilities (Zeeman, 2003, 2006).

For smaller hospitals, transfer to a medical or surgical ICU is usually preferable, and sometimes transfer to another hospital is necessary. As discussed, indications for admission to these types of critical care units vary, however, patient mix for these units is similar (Table 47-2). The American College of Obstetricians and Gynecologists (2017b) has summarized critical obstetrical care implementation depending on hospital size and technical facilities.

TABLE 47-2

Comparison of Acuity of Patient Mix for Obstetrical Critical Care Shown in Percent

Factor	Intermediate Care Unit (n = 483)[a]	Medical-Surgical ICU (n = 813)[b]
Stage		
Antepartum	20	23
Postpartum	80	77
Indication[c]		
Hypertension	45	40
Hemorrhage	18	21
Cardiopulmonary	12	16
Sepsis	5	8
Pregnancy-Related Mortality	0.2	2

[a]Data from Zeeman, 2003.

[b]Data from Baskett, 2009; Keizer, 2006; Paxton, 2014; Small, 2012; Stevens, 2006; Vasquez, 2007.

[c]Columns of indications do not total 100 percent because some diagnoses are not listed.

Pulmonary Artery Catheter

Data obtained during pregnancy with pulmonary artery catheterization (PAC) have contributed immensely to the understanding of normal pregnancy hemodynamics and pathophysiology of common obstetrical conditions. These include preeclampsia-eclampsia, acute respiratory distress syndrome, and amniotic-fluid embolism (Clark, 1988, 1995, 1997; Cunningham, 1986, 1987; Hankins, 1984, 1985). Also, because of these studies, most have concluded that such monitoring is seldom necessary (American College of Obstetricians and Gynecologists, 2013; Gidwani, 2013; Magder, 2015).

In nonobstetrical patients, randomized trials of nearly 5000 subjects have shown no benefits with PAC (Harvey, 2005; National Heart, Lung, and Blood Institute, 2006; Sandham, 2003). According to a Cochrane Database review, no randomized trials have used PAC for preeclampsia management (Li, 2012). The overall mechanisms, benefits, and risks were recently reviewed by Magder (2015).

Hemodynamic Changes in Pregnancy

Formulas for deriving some hemodynamic parameters are shown in Table 47-3. These measurements can be indexed for body size by dividing by body surface area (BSA). Normal values for nonpregnant adults are used, but with the caveat that these may not necessarily reflect changes induced by the more "passive" uteroplacental perfusion.

TABLE 47-3

Formulas for Deriving Various Cardiopulmonary Parameters

Mean arterial pressure (MAP) (mm Hg) = [SBP + 2 (DBP)] ÷ 3
Cardiac output (CO) (L/min) = heart rate × stroke volume
Stroke volume (SV) (mL/beat) = CO/HR
Stroke index (SI) (mL/beat/m^2) = stroke volume/BSA
Cardiac index (CI) (L/min/m^2) = CO/BSA
Systemic vascular resistance (SVR) (dynes × sec × cm^{-5}) = [(MAP − CVP)/CO] × 80
Pulmonary vascular resistance (PVR) (dynes × sec × cm^{-5}) = [(MPAP − PCWP)/CO] × 80

BSA = body surface area (m^2); CVP = central venous pressure (mm Hg); DBP = diastolic blood pressure; HR = heart rate (beats/min); MAP = mean systemic arterial pressure (mm Hg); MPAP = mean pulmonary artery pressure (mm Hg); PCWP = pulmonary capillary wedge pressure (mm Hg); SBP = systolic blood pressure.

In a landmark investigation, Clark and colleagues (1989) used PAC to obtain cardiovascular measurements in healthy pregnant women and again in these same women when nonpregnant (Chap. 4, Hemodynamic Function in Late Pregnancy). Because increased blood volume and cardiac output are compensated by decreased vascular resistance and increased pulse rate, ventricular performance remains within the normal range at term.

Cardiac complications are a common indication for ICU admission of pregnant women (Guntupalli, 2015b). Evaluation of cardiac function is frequently performed using echocardiography. This technology is indispensable in interrogating cardiac anatomy and especially right-ventricular function (Krishnan, 2015; Thiele, 2015). It is considered in more detail in Chapter 49 (Peripartum Management Considerations), and some normal values are listed in the Appendix (Maternal Echocardiographic Measurements). A working knowledge of cardiovascular physiology in pregnancy is paramount to understanding the pathophysiology of gestational complications discussed later in this chapter and throughout the book.

ACUTE PULMONARY EDEMA

The incidence of pulmonary edema complicating pregnancy averages 1 in 500 deliveries at tertiary referral centers. The two general causes are: (1) *cardiogenic,* namely, hydrostatic edema caused by high pulmonary capillary hydraulic pressures, and (2) *noncardiogenic,* that is, permeability edema caused by capillary endothelial and alveolar epithelial damage. In pregnancy, noncardiogenic pulmonary edema is more common. Taken in toto, studies in gravidas indicate that more than half who develop pulmonary edema have some degree of sepsis syndrome in conjunction with tocolysis, severe preeclampsia, or obstetrical hemorrhage combined with vigorous fluid therapy (O'Dwyer, 2014; Thornton, 2011).

Although cardiogenic pulmonary edema is less frequent, common precipitating causes include resuscitation for hemorrhage and vigorous treatment of preterm labor. In one study, the causes in 51 women with pulmonary edema were cardiac failure, tocolytic therapy, iatrogenic fluid overload, and preeclampsia (Sciscione, 2003). In another study, more than half of cases were associated with preeclampsia, and the other three causes had equal distribution (Hough, 2007). In still another study of 53 cases, 83 percent were caused by hypertensive disorders, 11 percent cardiac, and 6 percent sepsis (O'Dwyer, 2015). Although used less commonly today, tocolytic therapy with β-mimetic drugs at one time was the cause of up to 40 percent of pulmonary edema cases (DiFederico, 1998; Gandhi, 2014; Jenkins, 2003).

Noncardiogenic Permeability Edema

Endothelial activation is the common denominator that is associated with preeclampsia, sepsis syndrome, and acute hemorrhage—or frequently combinations thereof—and they are the most common predisposing factors to pulmonary edema (Table 47-4). As discussed, these clinical scenarios are often associated with corticosteroids given to induce fetal lung maturation along with vigorous fluid replacement and tocolytic therapy (Thornton, 2011). Parenteral β-agonists are indisputably linked to pulmonary edema. Studies have also associated magnesium sulfate given for preeclampsia (Gandhi, 2014; Wilson, 2014; Xiao, 2014). Combined therapy is also causative. In one study of nearly 800 women given magnesium sulfate for preterm labor, 8 percent developed pulmonary edema, and half of this affected group had also received terbutaline (Samol, 2005).

TABLE 47-4

Some Causes and Associated Factors for Pulmonary Edema in Pregnancy

Noncardiogenic permeability edema: endothelial activation with capillary-alveolar leakage
Preeclampsia syndrome
Acute hemorrhage
Sepsis syndrome: pyelonephritis, metritis
Tocolytic therapy: β-mimetics, $MgSO_4$
Aspiration pneumonitis
Vigorous intravenous fluid therapy
Pancreatitis
Cardiogenic pulmonary edema: myocardial failure with hydrostatic edema from excessive pulmonary capillary pressure
Hypertensive cardiomyopathy
Obesity—adipositas cordis
Left-sided valvular disease
Vigorous intravenous fluid therapy
Pulmonary hypertension

Cardiogenic Hydrostatic Edema

Ventricular failure causing pulmonary edema in pregnancy is usually associated with some form of gestational hypertension. Although it can be due to congenital or acquired anatomical defects, diastolic dysfunction is frequently from chronic hypertension, obesity, or both (Jessup, 2003; Kenchaiah, 2002). In these women, acute systolic hypertension exacerbates diastolic dysfunction and causes pulmonary edema (Dennis, 2012; Gandhi, 2001). Of note, concentric and eccentric hypertrophy is two- to threefold more common in black women compared with white women (Drazner, 2005). In a case-control study of 28 gravidas with preeclampsia and pulmonary edema, half of them were undelivered (Gandhi, 2014).

In women with an underlying cardiomyopathy, heart failure is commonly precipitated by preeclampsia, hypertension, hemorrhage and anemia, and puerperal sepsis (Cunningham, 1986; Sibai, 1987). In many of these, when echocardiography is done later, systolic function is normal as measured by ejection fraction, but evidence for diastolic dysfunction can often be found (Aurigemma, 2004). The use of *brain natriuretic peptide (BNP)* has not been evaluated extensively in pregnancy (Seror, 2014). This neurohormone is secreted from ventricle myocytes and fibroblasts with distention seen in heart failure. In nonpregnant patients, values <100 pg/mL have an excellent negative-predictive value, and levels >500 pg/mL have an excellent positive-predictive value. It is problematic that levels frequently are 100 to 500 pg/mL, and thus nondiagnostic (Ware, 2005). Values for N-terminal BNP and atrial natriuretic peptide (ANP) are both elevated with preeclampsia (Szabo, 2014; Tihtonen, 2007). This is discussed in greater detail in Chapter 4 (Renin, Angiotensin II, and Plasma Volume), and normal values for pregnancy are given in the Appendix (Serum and Blood Constituents).

Management

Acute pulmonary edema requires emergency care. Furosemide is given in 20- to 40-mg intravenous doses along with therapy to control severe hypertension. Further treatment depends on whether a woman is ante- or postpartum. A live fetus prohibits the use of cardioactive drugs that might rapidly lower peripheral resistance and in turn severely diminish uteroplacental circulation. The cause of cardiogenic failure is determined by echocardiography, which will help direct further therapy. Acute pulmonary edema is not, per se, an indication for emergency cesarean delivery.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute lung injury that causes a form of severe permeability pulmonary edema and respiratory failure is termed acute respiratory distress syndrome (ARDS). This is a pathophysiological continuum from mild pulmonary insufficiency to dependence on high inspired oxygen concentrations and mechanical ventilation. Uniform criteria for its diagnosis are lacking, and thus the incidence is variably reported for pregnancy. In one survey of the Nationwide Inpatient Sample, 2808 pregnant women with ARDS were identified (Rush, 2017). The incidence ranged from 36 to 60 cases per 100,000 births, and the maternal mortality rate was 9 percent. In its

most extreme form, requiring ventilatory support, the associated mortality rate is 45 percent. This rate can be as high as 90 percent if caused or complicated by sepsis (Phua, 2009). Although gravidas are younger and usually healthier than the overall population, they still have mortality rates of 25 to 40 percent (Catanzarite, 2001; Cole, 2005). Finally, if ARDS develops antepartum, the perinatal mortality rate is correspondingly high.

Definitions

Most investigators define ARDS as radiographically documented pulmonary infiltrates, a ratio of arterial oxygen tension to the fraction of inspired oxygen (Pao_2:Fio_2) <200, and no evidence of heart failure (Mallampalli, 2010; Thompson, 2017). Revised by international consensus, the *Berlin Definition* was described by the ARDS Definition Task Force (2012) and includes categories of mild, moderate and severe. To date, for most interventional studies, a working diagnosis of *acute lung injury* is made when the Pao_2:Fio_2 ratio is <300 and is coupled with dyspnea, tachypnea, oxygen desaturation, and radiographic pulmonary infiltrates (Wheeler, 2007).

Etiopathogenesis

ARDS is a pathophysiological description that begins with an acute lung injury from various causes (Table 47-5). In pregnant women, sepsis and diffuse infectious pneumonia are the two most common single-agent ARDS causes. Pyelonephritis, puerperal pelvic infection, and chorioamnionitis are the most frequent causes of sepsis. As discussed in Acute Pulmonary Edema, severe preeclampsia and obstetrical hemorrhage are also commonly associated with permeability edema. Importantly, more than half of pregnant women with ARDS have some combination of sepsis, hemorrhage, shock, and fluid overload. The contribution of *transfusion-related acute lung injury (TRALI)* is unclear (Chap. 41, Topical Hemostatic Agents).

TABLE 47-5

Some Causes of Acute Lung Injury and Respiratory Failure in Pregnant Women

Pneumonia: bacterial, viral, aspiration
Sepsis syndrome: chorioamnionitis, pyelonephritis, puerperal infection, septic abortion
Hemorrhage: shock, massive transfusion, transfusion-related acute lung injury (TRALI)
Preeclampsia syndrome
Tocolytic therapy
Embolism: amnionic fluid, trophoblastic disease, air, fat
Connective-tissue disease
Substance abuse
Irritant inhalation and burns
Pancreatitis
Drug overdose
Fetal surgery
Trauma
Sickle-cell disease
Miliary tuberculosis
Cerebral hemorrhage

Data from Cole, 2005; Duarte, 2014; Golombeck, 2006; Lapinsky, 2015; Martin, 2006; Sheffield, 2005; Sibai, 2014; Snyder, 2013; Zeeman, 2003, 2006.

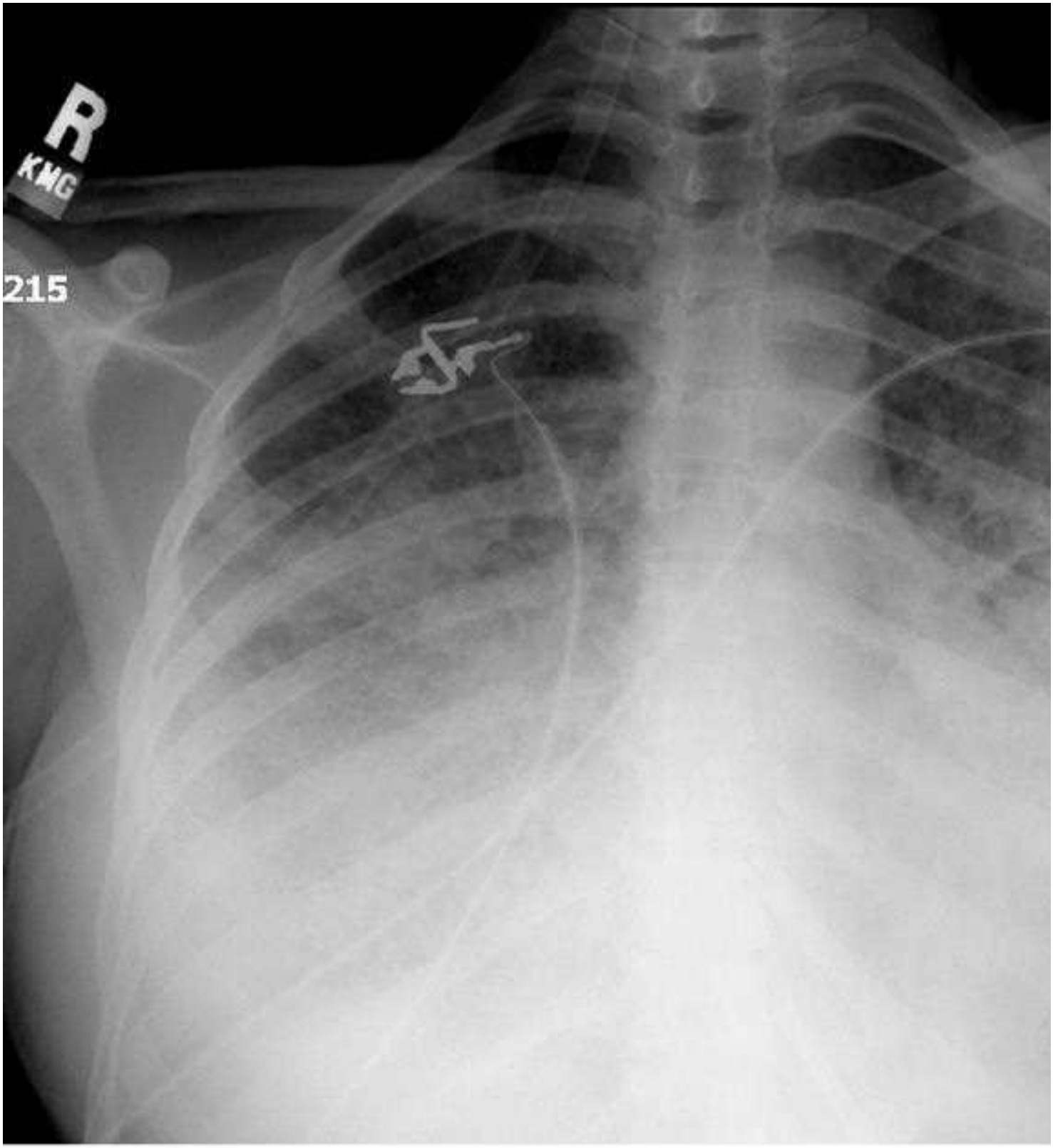
Endothelial injury in the lung capillaries releases cytokines that recruit neutrophils to the inflammation site. Here, they elaborate more cytokines to worsen tissue injury. There are three stages of ARDS development. First, the *exudative phase* follows widespread injury to microvascular endothelium, including the pulmonary vasculature, and there is also alveolar epithelial injury. These result in increased pulmonary capillary permeability, surfactant loss or inactivation, diminished lung volume, and vascular shunting with resultant arterial hypoxemia. Next, the *fibroproliferative phase* usually begins 3 to 4 days later and lasts up to day 21. Last, the *fibrotic phase* results from healing, and despite this, the long-term prognosis for pulmonary function is surprisingly good (Herridge, 2003; Levy, 2015).

Clinical Course

With pulmonary injury, the clinical condition depends largely on the insult magnitude, the ability to compensate for it, and the disease stage. For example, soon after the initial injury, physical findings are absent except perhaps hyperventilation. And at first, arterial oxygenation usually is adequate. Pregnancy-induced mild metabolic alkalosis may be accentuated by hyperventilation. With worsening, clinical and radiological evidence for pulmonary edema, decreased lung compliance, and increased intrapulmonary blood shunting become apparent. Progressive alveolar and interstitial edema develop with extravasation of inflammatory cells and erythrocytes.

Ideally, pulmonary injury is identified at this early stage, and specific therapy is directed at the underlying insult. Further progression to acute respiratory failure is characterized by marked dyspnea, tachypnea, and hypoxemia. Additional lung volume loss results in worsening of pulmonary compliance and increased shunting. Diffuse abnormalities are heard by auscultation, and a chest radiograph characteristically demonstrates bilateral lung involvement (Fig. 47-1). At this phase, the injury ordinarily would be lethal in the absence of ventilatory support. When shunting exceeds 30 percent, severe refractory hypoxemia develops along with metabolic and respiratory acidosis that can result in myocardial irritability, dysfunction, and cardiac arrest.

FIGURE 47-1
Anteroposterior chest radiograph of a second-trimester pregnant woman with marked bilateral parenchymal and pleural opacification secondary to acute respiratory distress syndrome (ARDS) due to pyelonephritis.



Management

Reduced ARDS mortality rates have resulted from advances in care of the critically ill (Levy, 2015). This requires close attention to: (1) recognizing and treating underlying medical and surgical disorders, (2) minimizing procedures and their complications, (3) administering prophylaxis against venous thromboembolism, gastrointestinal bleeding, aspiration, and central venous catheter infection, (4) promptly diagnosing nosocomial infections, and (5) providing adequate nutrition.

In cases of severe acute lung injury, providing adequate oxygenation of peripheral tissues is balanced against maneuvers that further aggravate lung injury. At least intuitively, increasing oxygen delivery should produce a corresponding increase in tissue uptake, but this is difficult to measure. Support of systemic perfusion with

intravenous crystalloid and blood is imperative. As discussed earlier, the trial conducted by the National Heart, Lung, and Blood Institute (2006) showed that pulmonary artery catheter use did not improve outcomes. Because sepsis is commonplace in lung injury, vigorous antimicrobial therapy is given for infection, and any necrotic tissues are debrided. Oxygen delivery can be greatly improved by correction of anemia. Specifically, each gram of hemoglobin carries 1.25 mL of oxygen when 90-percent saturated. By comparison, increasing the arterial Po_2 from 100 to 200 mm Hg results in the transport of only 0.1 mL of additional oxygen for each 100 mL of blood.

Reasonable goals in caring for the woman with severe lung injury are to attain a Pao_2 of 60 mm Hg or 90-percent oxygen saturation using an inspired oxygen content <50 percent and positive end-expiratory pressures <15 mm Hg. With regard to the pregnancy, it remains controversial whether delivery of the fetus improves maternal oxygenation (Mallampalli, 2010). In a study of 29 women undergoing mechanical ventilation, 10 were delivered while intubated (Lapinsky, 2015). This was associated with a modest improvement in respiratory function in perhaps half, but no factors were identified that predicted a better outcome.

Mechanical Ventilation

Noninvasive ventilation, that is, positive pressure ventilation by face mask, may be effective in some women in early stages of pulmonary insufficiency (Duarte, 2014). Early intubation is preferred in the gravida if respiratory failure is more likely than not, and especially if it appears imminent. Many successful formulas for mechanical ventilation are employed, and initially a tidal volume ≤6 mL/kg is optimal (Levy, 2015; Schwaiberger, 2016). High-frequency oscillation ventilation (HFOV) is controversial in ARDS (Ferguson, 2013; Slutsky, 2013). Adjustments are made to obtain a Pao_2>60 mm Hg or a hemoglobin oxygen saturation ≥90 percent and a $Paco_2$ of 35 to 45 mm Hg. Lower levels for Pao_2 are avoided, because placental perfusion may be impaired (Levinson, 1974).

For women who require ventilation for any length of time, the maternal mortality rate is 10 to 20 percent. In a study of 51 such women, almost half had severe preeclampsia, and most required intubation postpartum. Eleven were delivered while being ventilated, and another six were discharged undelivered (Jenkins, 2003). There were two maternal deaths, including a woman who died as a complication of tocolytic treatment. In three other reports, maternal mortality rates ranged from 10 to 25 percent (Chen, 2003; Lapinsky, 2015; Schneider, 2003). In most cases, delivery did not improve maternal outcome.

Positive End-Expiratory Pressure

With severe lung injury and high intrapulmonary shunt fractions, it may not be possible to provide adequate oxygenation with usual ventilatory pressures, even with 100-percent oxygen. Positive end-expiratory pressure is usually successful in decreasing the shunt by recruiting collapsed alveoli. At low levels of 5 to 15 mm Hg, positive pressure can typically be used safely. At higher levels, impaired right-sided venous return can result in decreased cardiac output, lowered uteroplacental perfusion, alveolar overdistention, falling compliance, and barotrauma (Schwaiberger, 2016; Slutsky, 2013).

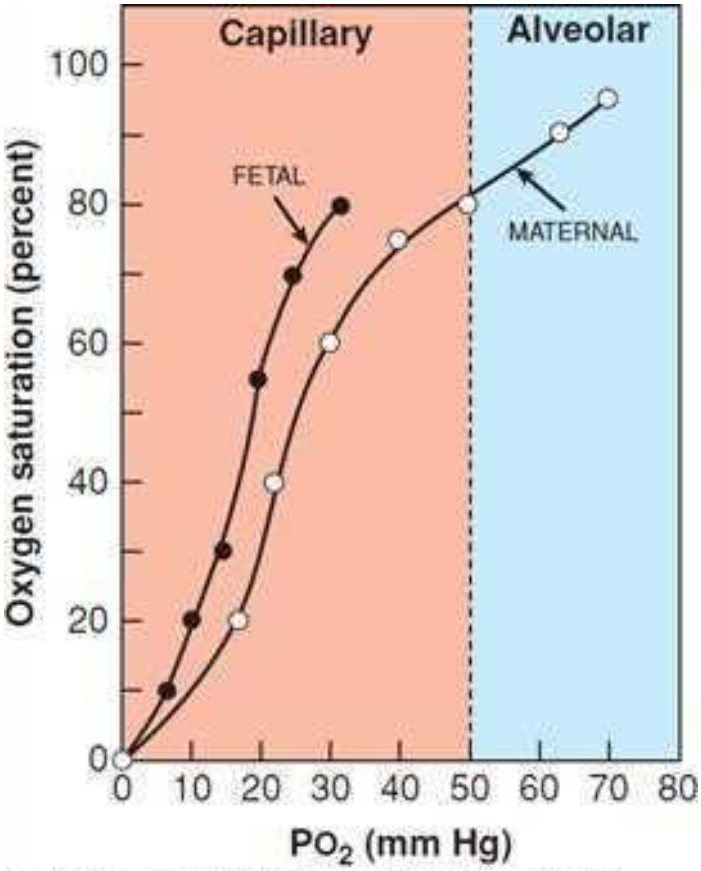
Extracorporeal Membrane Oxygenation

As discussed in Chapter 33 (Neonatal Encephalopathy and Cerebral Palsy), extracorporeal membrane oxygenation (ECMO) has been successfully used for neonatal meconium aspiration syndrome. Preliminary observation suggests that it may be useful in adults with ARDS (Brodie, 2011; Levy, 2015; Peek, 2009). ECMO use has been reported in pregnant women. In one study, 12 patients with influenza-induced lung failure were treated with ECMO, and of four maternal deaths, three were due to anticoagulation-related hemorrhage (Nair, 2011). In another study, the duration of support in four survivors was 2 to 28 days (Cunningham, 2006). In a review of 29 treated gravidas, 80 percent of cases were due to ARDS, and the maternal and perinatal mortality rate was 28 percent (Anselmi, 2015). Technical aspects of ECMO were reviewed by Brodie and Bacchetta (2011).

Fetal Oxygenation

The propensity of the hemoglobin molecule to release oxygen is described by the *oxyhemoglobin dissociation curve* (Fig. 47-2). For clinical purposes, the curve can be divided into an upper oxygen association curve representing the alveolar-capillary environment and a lower oxygen dissociation portion representing the tissue-capillary environment. Shifts of the curve have their greatest effect at the steep portion because they affect oxygen delivery. A rightward shift is associated with decreased hemoglobin affinity for oxygen and hence increased tissue-capillary oxygen interchange. Rightward shifts are produced by hypercapnia, metabolic acidosis, fever, and increased 2,3-diphosphoglycerate levels. During pregnancy, the erythrocyte concentration of 2,3-diphosphoglycerate is increased by approximately 30 percent. This favors oxygen delivery to both the fetus and maternal peripheral tissues.

FIGURE 47-2
Oxyhemoglobin dissociation curve. With higher oxygen tension (Pao_2) in the pulmonary alveoli, adult hemoglobin is maximally saturated compared with that at the lower oxygen tension in the tissue capillaries. Note that at any given oxygen tension, fetal hemoglobin carries more oxygen than adult hemoglobin, as indicated by percent saturation.



Fetal hemoglobin has a higher oxygen affinity than adult hemoglobin. As seen in Figure 47-2, its curve is positioned to the left of the adult curve. To achieve 50-percent hemoglobin saturation, the Pa_{O_2} must be 27 mm Hg in the mother compared with only 19 mm Hg in the fetus. Under normal physiological conditions, the fetus is constantly on the dissociation, or tissue, portion of the curve. Even with severe maternal lung disease and very low Pa_{O_2} levels, oxygen displacement to fetal tissues is favored. Another example of this comes from pregnant women who live at high altitudes. Here, despite a maternal Pa_{O_2} of only 60 mm Hg, the fetal Pa_{O_2} is equivalent to that of fetuses at sea level (Subrevilla, 1971).

Intravenous Fluids

Although mortality outcomes are similar, conservative rather than liberal fluid management is associated with fewer days of mechanical ventilation (Wiedemann, 2006). Some pregnancy-induced physiological changes predispose to a greater risk of permeability edema from vigorous fluid therapy. Colloid oncotic pressure (COP) is determined by serum albumin concentration, and 1 g/dL exerts approximately 6 mm Hg pressure. As discussed in Chapter 4 (Gastrointestinal Tract), serum albumin concentrations normally drop in pregnancy. This results in a decline in oncotic pressure from 28 mm Hg in the nonpregnant woman to 23 mm Hg at term and to 17 mm Hg in the puerperium (Benedetti, 1979; Dennis, 2012). With preeclampsia, endothelial activation with leakage causes extravascular albumin loss and lowered serum albumin levels. As a result in these cases, oncotic pressure averages only 16 mm Hg antepartum and 14 mm Hg postpartum (Zinaman, 1985). These changes have a significant clinical effect on the *colloid oncotic pressure/wedge pressure gradient.* Normally, this gradient exceeds 8 mm Hg. However, when it is 4 mm Hg or less, the risk for pulmonary edema rises. No benefits are gained by albumin rather than crystalloid infusions in these women (Uhlig, 2014). These associations were reviewed by Dennis and Solnordal (2012).

Long-Term Outcomes

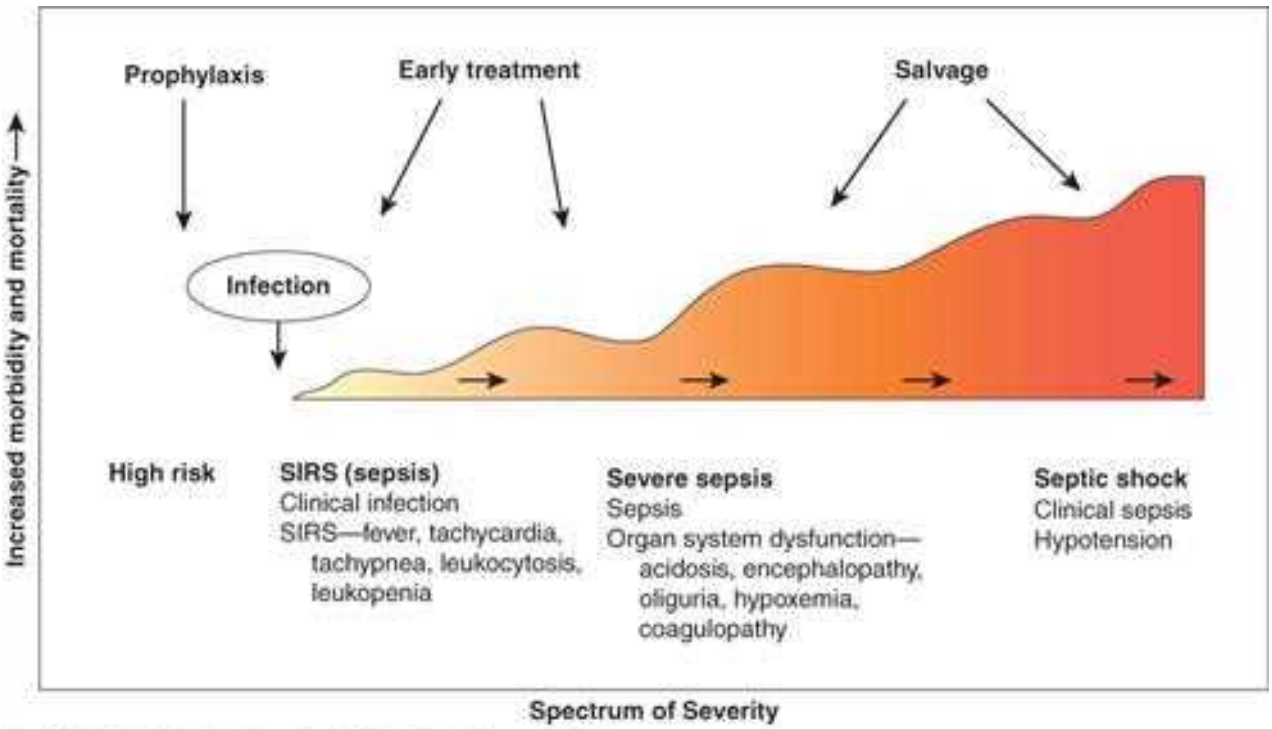
No long-term follow-up studies address gravidas who recover from ARDS. In nonpregnant subjects, risks for impaired global cognitive function at 3 and 12 months are significant (Pandharipande, 2013). Data from nonpregnant patients indicate a 1- to 2-year hiatus before basic normal activity is restored in all. In a 5-year follow-up study, Herridge and associates (2011) reported normal lung function but significant exercise limitation, physical and psychological sequelae, decreased physical quality of life, and increased use of health-care services.

SEPSIS SYNDROME

This syndrome is induced by a systemic inflammatory response to bacteria or viruses or their by-products such as endotoxins or exotoxins. The severity of the syndrome is a continuum or spectrum (Fig. 47-3). According to the Centers for Disease Control and Prevention (CDC), sepsis caused 6.2 percent of pregnancy-related deaths in the United States from 2011 to 2013 (Creanga, 2017). It was also a significant cause of maternal mortality in Michigan and the United Kingdom (Bauer, 2015; Mohamed-Ahmed, 2015; Nair, 2015).

FIGURE 47-3

The sepsis syndrome begins with a systemic inflammatory response syndrome (SIRS) in response to infection that may progress to septic shock.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Infections that most commonly cause sepsis syndrome in obstetrics are pyelonephritis (Chap. 53, Cystitis and Urethritis), chorioamnionitis and puerperal sepsis (Chap. 37, Uterine Infection), septic abortion (Chap. 18, Inevitable Abortion), and necrotizing fasciitis (Chap. 37, Necrotizing Fasciitis). With severe sepsis, the mortality rate in nonpregnant patients is 20 to 35 percent and is 40 to 60 percent with septic shock (Angus, 2013; Munford, 2015). With shock, the mortality rate in pregnancy has been reported to be 30 percent (Mabie, 1997; Snyder, 2013). That said, the maternal mortality risk from sepsis is significantly underestimated (Bauer, 2015; Chebbo, 2016; Mohamed-Ahmed, 2015).

Etiopathogenesis

Most of what is known concerning sepsis pathogenesis comes from study of lipopolysaccharide—LPS or endotoxin (Munford, 2015). The lipid A moiety is bound by mononuclear blood cells, becomes internalized, and stimulates release of mediators and a series of complex downstream perturbations. Clinical aspects of the sepsis syndrome are manifest when cytokines are released that have endocrine, paracrine, and autocrine actions (Angus, 2013; Singer, 2016).

Although the sepsis syndrome in obstetrics may be caused by several pathogens, most cases represent a small group. For example, pyelonephritis complicating pregnancy caused by *Escherichia coli* and *Klebsiella* species commonly is associated with bacteremia and sepsis syndrome (Cunningham, 1987; Snyder, 2013). And although pelvic infections are usually polymicrobial, bacteria that cause severe sepsis syndrome are frequently endotoxin-producing Enterobacteriaceae, most commonly *E coli* (Eschenbach, 2015). Other pelvic pathogens are aerobic and anaerobic streptococci, *Bacteroides* species, and *Clostridium* species. Some strains of group A β-hemolytic streptococci and *Staphylococcus aureus*—including community-acquired methicillin-resistant strains (CA-MRSA)—produce a superantigen that activates T cells to rapidly cause all features of the sepsis syndrome—*toxic shock syndrome* (Moellering, 2011; Soper, 2011). This is discussed further in Chapter 37 (Breast Infections).

Potent bacterial *exotoxins* can also cause severe sepsis syndrome. Examples include exotoxins from *Clostridium perfringens* or *sordellii,* toxic-shock-syndrome toxin-1 (TSST-1) from *S aureus,* and toxic shock-like exotoxin from group A β-hemolytic streptococci (Daif, 2009; Soper, 2011). These last exotoxins cause rapid and extensive tissue necrosis and gangrene, especially of the postpartum uterus, and may cause profound cardiovascular collapse and maternal death (Nathan, 1993; Sugiyama, 2010). In a review discussed subsequently, the maternal mortality rate from these infections was 58 percent (Yamada, 2010).

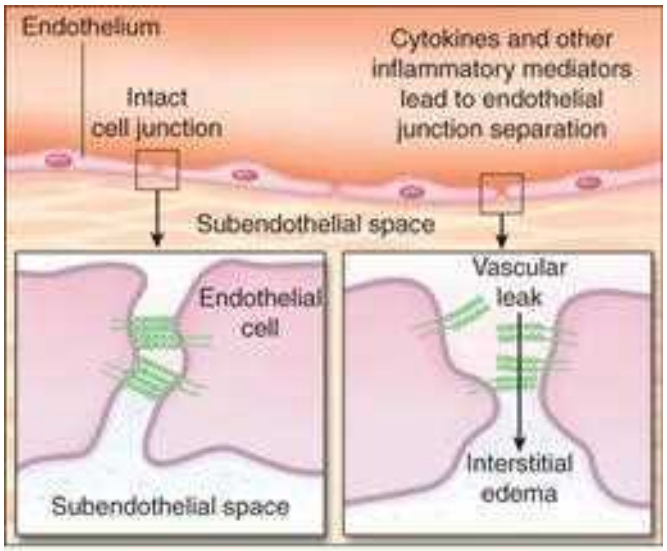
Thus, the sepsis syndrome begins with an inflammatory response that is directed against microbial endotoxins and exotoxins (Angus, 2013). CD4 T cells and leukocytes are stimulated to produce proinflammatory compounds that include tumor necrosis factor-α (TNF-α), several interleukins, other cytokines, proteases, oxidants, and bradykinin that result in a "cytokine storm" (Russell, 2006). Many other cellular reactions then follow that include stimulation of pro- and antiinflammatory compounds, procoagulant activity, gene activation, receptor regulation, and immune suppression (Filbin, 2009; Moellering, 2011). It is also likely that interleukin-6 (IL-6) mediates myocardial suppression (Pathan, 2004).

The pathophysiological response to this cascade is selective vasodilation with maldistribution of blood flow. Leukocyte and platelet aggregation cause capillary plugging. Worsening endothelial injury causes profound permeability, capillary leakage, and interstitial fluid accumulation (Fig. 47-4). Depending on the degree of injury and inflammatory response, a pathophysiological and clinical continuum evolves as depicted in Figure 47-3. The clinical syndrome begins with subtle signs of sepsis from infection and terminates with *septic shock,* which is defined by hypotension unresponsive to intravenous hydration. In its early stages, clinical shock

results primarily from decreased systemic vascular resistance that is not compensated fully by increased cardiac output. Hypoperfusion results in lactic acidosis, decreased tissue oxygen extraction, and end-organ dysfunction that includes acute lung and kidney injury.

FIGURE 47-4

Endothelial permeability. The normal interendothelial interface is shown in the left inset. Cytokines and other inflammatory mediators disassemble the cellular junctions, resulting in microvascular leaks (*right*).



Clinical Manifestations

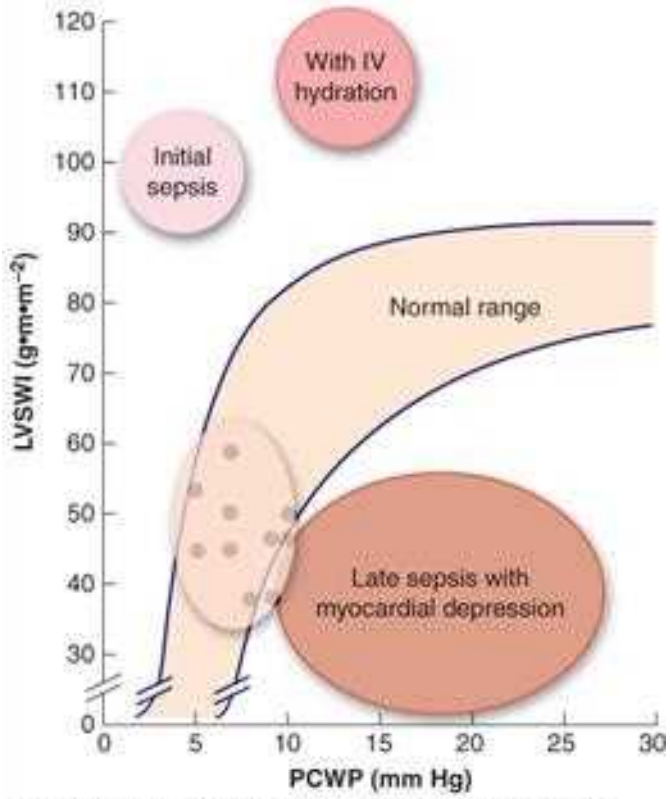
The sepsis syndrome has myriad clinical manifestations that, at least in part, are dependent on the specific invading microorganism and its particular endo- or exotoxins. Some of the general effects of LPS are as follows:

1. Central nervous system: confusion, delirium, somnolence, coma, combativeness, fever
2. Cardiovascular: tachycardia, hypotension
3. Pulmonary: tachypnea, arteriovenous shunting with dysoxia and hypoxemia, exudative infiltrates from endothelial-alveolar damage, pulmonary hypertension
4. Gastrointestinal: gastroenteritis—nausea, vomiting, and diarrhea; ileus; hepatocellular necrosis—jaundice, transaminitis
5. Renal: prerenal oliguria, azotemia, acute kidney injury, proteinuria
6. Hematological: leukocytosis or leukopenia, thrombocytopenia, activation of coagulation with disseminated intravascular coagulopathy
7. Endocrine: hyperglycemia, adrenal insufficiency
8. Cutaneous: acrocyanosis, erythroderma, bullae, digital gangrene.

Thus, although capillary leakage initially causes hypovolemia, if intravenous crystalloid is given at this point, then sepsis hemodynamically can be described as a high cardiac output, low systemic vascular resistance condition (Fig. 47-5). Concomitantly, pulmonary hypertension develops, and despite the high cardiac output, severe sepsis also causes myocardial depression (Munford, 2015; Ognibene, 1988). This is often referred to as the *warm phase* of septic shock. These findings are the most common cardiovascular manifestations of early sepsis, but they can be accompanied by some of the other clinical or laboratory aberrations listed above.

FIGURE 47-5

Hemodynamic effects of sepsis syndrome. Values for normal women at term are shown by dots. With early sepsis, there is high cardiac output and low vascular resistance. With fluid resuscitation, cardiac output increases even more, but so does capillary hydraulic pressure. With continued sepsis, there may be myocardial depression to further increase capillary hydraulic pressure. Decreased plasma oncotic pressure (serum albumin [g] × 6 mm Hg) contributes to interstitial lung fluid and endo/epithelial leak causes alveolar flooding. LVSWI = left ventricular stroke work index; PCWP = pulmonary capillary wedge pressure.



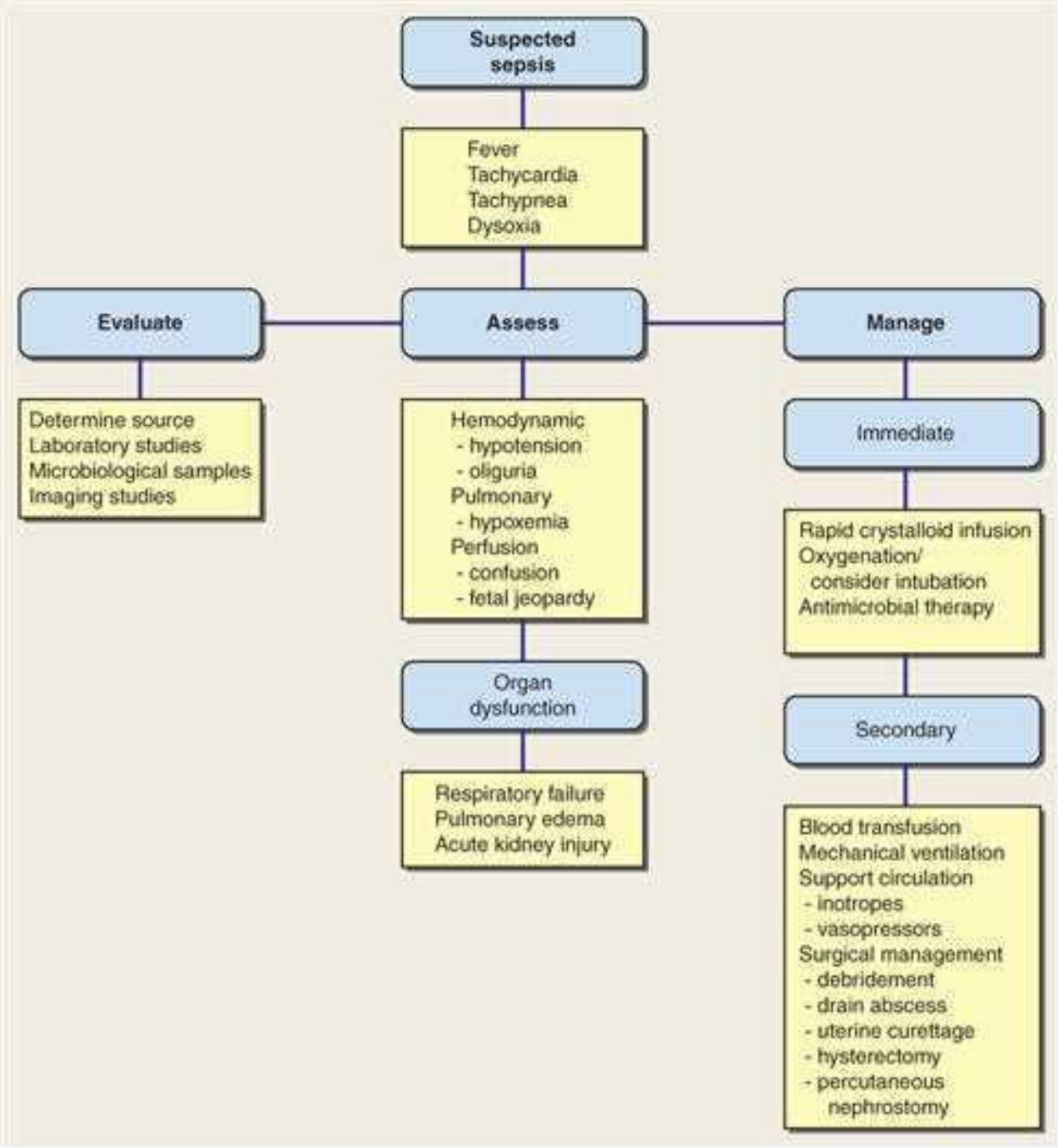
The response to initial intravenous hydration may be prognostic. Most pregnant women who have early sepsis show a salutary response with crystalloid and antimicrobial therapy, and if indicated, debridement of infected tissue. Conversely, if hypotension is not corrected following vigorous fluid infusion, then the prognosis is more guarded. At this juncture, if there also is no response to β-adrenergic inotropic agents, this indicates severe and unresponsive extracellular fluid extravasation with vascular insufficiency, overwhelming myocardial depression, or both. Oliguria and continued peripheral vasoconstriction characterize a secondary, *cold phase* of septic shock that is rarely survived. Another poor prognostic sign is continued renal, pulmonary, and cerebral dysfunction once hypotension has been corrected (Angus, 2013; Chebbo, 2016). The average risk of death increases by 15 to 20 percent with failure of each organ system. With three systems, mortality rates are 70 percent (Martin, 2003; Wheeler, 1999).

Management

In 2004, an international consensus effort was launched as the *Surviving Sepsis Campaign* (Dellinger, 2013). The cornerstone of management is *early goal-directed management,* and it stresses prompt recognition of serious bacterial infection and close monitoring of vital signs and urine flow. It remains controversial if institution of this protocol has improved survival rates (ARISE Investigators, 2014; Mouncey, 2015; ProCESS Investigators, 2014). Similar conclusions were reached with sets of early warning systems in obstetrics (Edwards, 2015; Mhyre, 2014). Albright and associates (2017) have validated the Sepsis in Obstetrics Score to identify the risk of ICU admission for sepsis.

An algorithm for management of sepsis syndrome is shown in Figure 47-6. The three basic steps are performed as simultaneously as possible and include evaluation of the sepsis source and its sequelae, cardiopulmonary function assessment, and immediate management. The most important step in sepsis management is rapid infusion of 2 L and sometimes as many as 4 to 6 L of crystalloid fluids to restore renal perfusion in severely affected women (Vincent, 2013). Simultaneously, appropriately chosen broad-spectrum antimicrobials are begun. Because hemoconcentration is caused by the capillary leak, if anemia coexists, then blood is given. Maintaining the hemoglobin concentration at ≥9 g/dL did not have superior outcomes compared with that of ≥7 g/dL (Holst, 2014). That said, fetal oxygenation is improved by the higher concentration.

FIGURE 47-6
Algorithm for evaluation and management of sepsis syndrome. Rapid and aggressive implementation is paramount for success. The three steps—Evaluate, Assess, and Manage—are carried out as simultaneously as possible.



The use of colloid solution such as hetastarch is controversial (Angus, 2013; Ware, 2000). One randomized trial comparing hydroxyethyl starch and Ringer acetate reported a higher mortality rate with the starch solution (Perner, 2012). Another study found equivalent results with 6-percent hydroxyethyl starch compared with normal saline (Myburgh, 2012). Albumin was not found to be superior to crystalloids (Caironi, 2014).

Aggressive volume replacement ideally is promptly followed by urinary output of at least 30 and preferably 50 mL/hr, as well as other indicators of improved perfusion. If not, then consideration is given for vasoactive drug therapy (Pacheco, 2014). Mortality rates are high when sepsis is further complicated by respiratory or renal failure. With severe sepsis, damage to pulmonary capillary endothelium and alveolar epithelium causes alveolar flooding and pulmonary edema. This may occur even with low or normal pulmonary capillary wedge pressures, as with the ARDS discussed in Acute Respiratory Distress Syndrome and depicted in Figure 47-1.

Broad-spectrum antimicrobials are chosen empirically based on the probable source of infection. They are given promptly in maximal doses after appropriate cultures are taken of blood, urine, or exudates not contaminated by normal flora. In severe sepsis, appropriate empirical coverage results in better survival rates (Barochia, 2010; MacArthur, 2004). In obstetrics acute pyelonephritis is usually caused by Enterobacteriaceae, as discussed in Chapter 53 (Cystitis and Urethritis). For pelvic infections, empirical coverage with regimens such as ampicillin plus gentamicin plus clindamycin generally suffices (Chap. 37, Pathogenesis and Clinical Course). Associated incisional and other soft-tissue infections are increasingly likely to be caused by methicillin-resistant *S aureus*, thus vancomycin therapy may be added (Klevens, 2007; Rotas, 2007). With a septic abortion, a Gram-stained smear may be helpful in identifying *Clostridium* species or group A streptococcal organisms. This is also true for deep fascial infections.

Surgical Treatment

Continuing sepsis may prove fatal, and debridement of necrotic tissue or drainage of purulent material is crucial (Nelson, 2015; Pacheco, 2014). In obstetrics, the major causes of sepsis are infected abortion, pyelonephritis, and puerperal pelvic infections, which include metritis and infections of perineal lacerations or of hysterotomy or laparotomy incisions. With a septic abortion, uterine contents must be removed promptly by curettage as described in Chapter 18 (Inevitable Abortion). Hysterectomy is seldom indicated unless gangrene has resulted.

For women with pyelonephritis, continuing sepsis should prompt a search for obstruction caused by calculi or by a perinephric or intrarenal phlegmon or abscess. Renal sonography or "one-shot" pyelography can help diagnose obstruction and calculi. With obstruction, ureteral catheterization, percutaneous nephrostomy, or flank exploration may be lifesaving (Chap. 53, Reflux Nephropathy). Computed tomography (CT) or magnetic-resonance imaging aids in identifying a phlegmon or abscess.

Puerperal Infections

Most cases of puerperal pelvic sepsis are clinically manifested in the first several days postpartum, and intravenous antimicrobial therapy without tissue debridement is generally curative. There are at least three exceptions.

First, massive uterine myonecrosis can be caused by group A β-hemolytic streptococcal or clostridial infections (Soper, 2011; Sugiyama, 2010; Yamada, 2010). Those with early-onset disease present with findings listed in Table 47-6. The mortality rate in these women with gangrene as shown in Figure 47-7 is high, and prompt hysterectomy may be lifesaving (Mabie, 1997; Nathan, 1993). Group A β-hemolytic streptococci and clostridial colonization or infection also cause toxic-shock syndrome without obvious gangrene (Mason, 2012). These are due to either streptococcal toxic-shock-syndrome-like toxin or clostridial exotoxin that evolved from *S aureus* (Chap. 37, Breast Infections). In many of these cases, there is bacteremia and widespread tissue invasion, but with an intact uterus and abdominal incision. If uterine necrosis can be excluded—usually by CT scanning—then in our experiences, as well as in others, hysterectomy may not be necessary (Soper, 2011). Still, these infections are highly lethal (Yamada, 2010).

TABLE 47-6

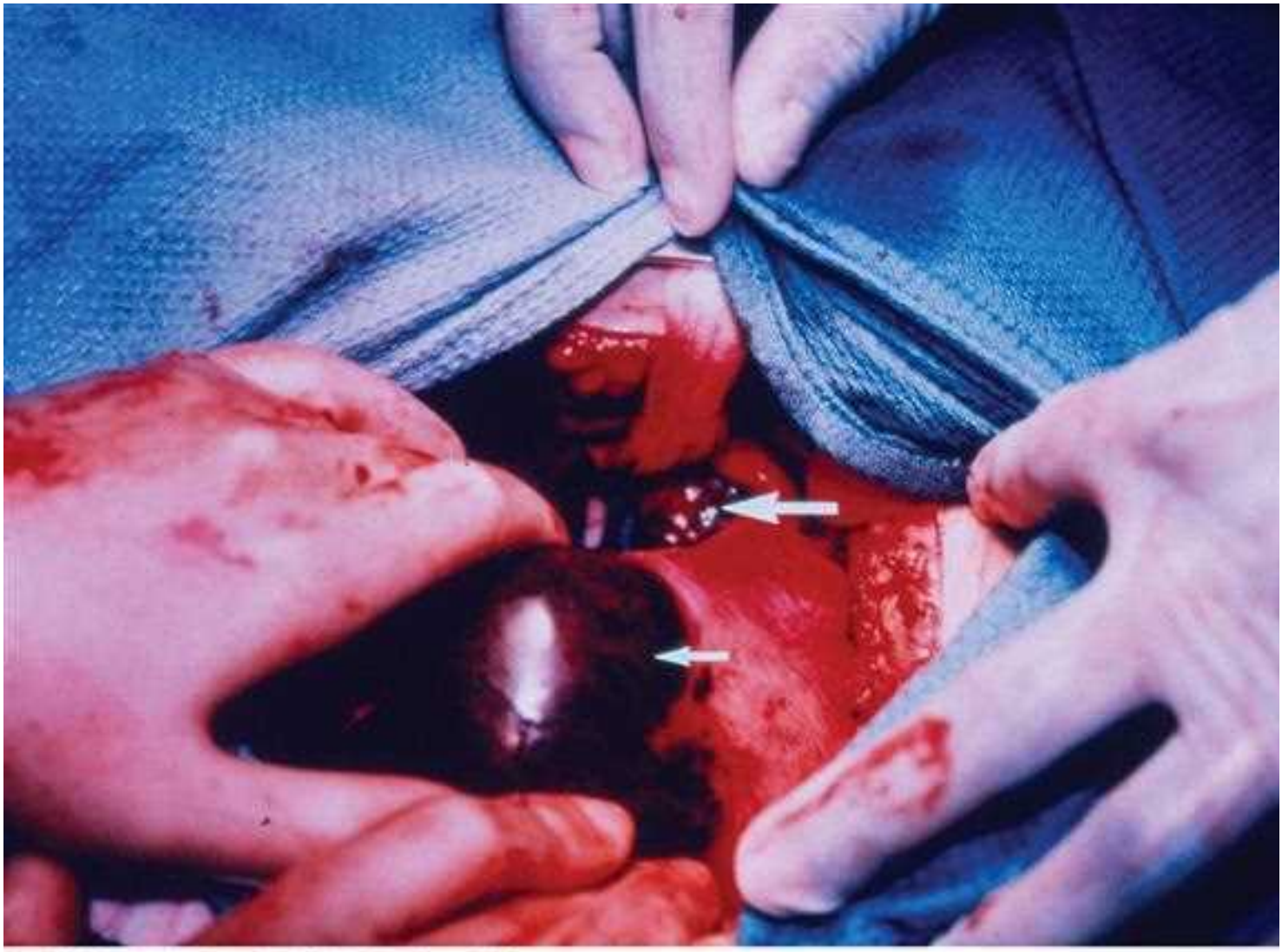
Clinical Findings in 55 Women with Group A β-Hemolytic Infection Manifest within 12 Hours of Delivery

Finding	Frequency (%)
Multiparous	83
Third-trimester	90
Flulike symptoms	
High fever	94
Upper respiratory	40
Gastrointestinal	49
Uterine hypertonus	73
Early-onset shock	91
Mortality	
Maternal	58
Perinatal	66

Data from Yamada, 2010.

FIGURE 47-7

A fatal case of group A β-hemolytic *Streptococcus pyogenes* puerperal infection following an uncomplicated vaginal delivery at term. The infection caused uterine gangrene and overwhelming sepsis syndrome. Arrows point to overtly "ballooned-out" black gangrenous areas of the postpartum uterus at the time of laparotomy for hysterectomy.



As a second exception, necrotizing fasciitis of the episiotomy site or of the abdominal surgical incision is a surgical emergency. As described by Gallup and coworkers (2002), these infections are aggressively managed as discussed in Chapter 37 (Necrotizing Fasciitis). Sinha and colleagues (2015) described a woman with *Fournier gangrene* who required radical debridement and colostomy.

As a final exception, persistent or aggressive postpartum uterine infection with necrosis, uterine incision dehiscence, and severe peritonitis may lead to sepsis (Chap. 37, Parametrial Phlegmon). In this regard, women following cesarean delivery who are suspected of having peritonitis should be carefully evaluated for uterine incisional necrosis or bowel perforation. These infections tend to be less aggressive than necrotizing group A streptococcal infections and develop later postpartum. CT imaging of the abdomen and pelvis can frequently disclose these. If either is suspected, then prompt surgical exploration is indicated. With incisional necrosis, hysterectomy is usually necessary (Fig. 37-5). Finally, peritonitis and sepsis much less commonly may result from a ruptured parametrial, intraabdominal, or ovarian abscess (Chap. 37, Necrotizing Fasciitis).

Adjunctive Therapy

As shown in Figure 47-6, a woman with severe sepsis syndrome is supported with continuing crystalloid infusion, blood transfusions, and ventilation. In some cases, other measures may be necessary. Vasoactive drugs are not given unless aggressive fluid treatment fails to correct hypotension and perfusion abnormalities. First-line vasopressors are norepinephrine, epinephrine, dopamine, dobutamine, or phenylephrine (Vincent, 2013).

The use of corticosteroids remains controversial. Some studies, but not all, show a salutary effect of corticosteroid administration. It is thought that *critical illness-related corticosteroid insufficiency—CIRCI*—may play a role in recalcitrant hypotension. Thus, corticosteroids may be considered for use in vasopressor-dependent patients (Angus, 2013; Munford, 2015).

Endotoxin stimulates endothelial cells to upregulate tissue factor and thus procoagulant production (Cunningham, 2015). Consumptive coagulopathy associated with sepsis is discussed in Chapter 41 (Obstetrical Coagulopathies). At the same time, it decreases the anticoagulant action of activated protein C. Several agents developed to block coagulation, however, did not improve outcomes. Some include *recombinant activated protein C, antithrombin III, platelet-activating factor antagonist,* and *tissue factor pathway inhibitor* (Munford, 2015; Wenzel, 2012).

TRAUMA

Depending on definitions used, 10 to 20 percent of gravidas suffer physical trauma (Jain, 2015; Lucia, 2016). Moreover, injury-related deaths are the most commonly identified nonobstetrical cause of maternal mortality (Brown, 2013a; Horon, 2001). In a California study of 4.8 million pregnancies, almost 1 in 350 women were hospitalized for injuries from assaults (El Kady, 2005). From Parkland Hospital, motor vehicle accidents and falls accounted for 85 percent of injuries sustained by 1682 pregnant women (Hawkins, 2007). From the National Violent Death Reporting System, Palladino and colleagues (2011) found 2.0 pregnancy-associated suicides per 100,000 live births. The rate was 2.9 per 100,000 for pregnancy-associated homicides. Notably, intimate-partner violence may be linked to these suicides (Martin, 2007). Finally, injury prevention and education of high-risk patients may help to decrease morbidity (Chisolm, 2017; Lucia, 2016).

Physical Abuse

According to the CDC, intimate-partner violence describes physical, sexual, or psychological harm by a current or former partner or spouse (Breiding, 2015). Such violence affects 1 in 5 women each year. One goal in violence prevention for *Healthy People 2010* was the reduction of physical abuse directed at women by male partners. The Pregnancy Risk Assessment Monitoring Systems (PRAMS) report showed some improvement in these areas (Suellentrop, 2006).

Even more appalling is that physical violence directed at women continues during pregnancy. Abuse is linked to poverty, poor education, and use of tobacco, alcohol, and illicit drugs (Centers for Disease Control and Prevention, 2008). Unfortunately, abused women tend to remain with their abusers, and the major risk factor for intimate-partner homicide is prior domestic violence (Campbell, 2007). Finally, women seeking pregnancy termination have a higher incidence of intimate-partner violence (Bourassa, 2007).

The woman who is physically abused tends to present late, if at all, for prenatal care. In one study, pregnant women hospitalized in California as a result of assault had significantly increased perinatal morbidity rates (El Kady, 2005). Immediate sequelae included uterine rupture, preterm delivery, and maternal and perinatal death. Subsequent outcomes included increased rates of placental abruption, preterm and low-birthweight newborns, and other adverse outcomes. Silverman and associates (2006) reported similar results from PRAMS, which included more than 118,000 pregnancies in 26 states.

Preventatively, the American College of Obstetricians and Gynecologists (2012) recommend universal screening for intimate-partner violence at the initial prenatal visit, during each trimester, and again at the postpartum visit (Chap. 9, Alcohol). Others recommend a case-finding approach based on clinical suspicion (Robertson-Blackmore, 2013).

Sexual Assault

According to the National Intimate Partner and Sexual Violence Survey (Black, 2014), an estimated 1.2 million women will be sexually assaulted each year. Satin and coworkers (1992) reviewed more than 5700 female sexual assault victims in Dallas County and reported that 2 percent were pregnant. Associated physical trauma is common (Sugar, 2004). From a forensic standpoint, the evidence collection protocol is not altered (Linden, 2011).

In addition to attention to physical injuries, exposure to sexually transmitted diseases must be considered. The CDC (2015) recommends antimicrobial prophylaxis against gonorrhea, chlamydial infection, bacterial vaginosis, and trichomoniasis (Table 47-7). If the woman is not pregnant, another very important aspect is emergency contraception, as recommended by the American College of Obstetricians and Gynecologists (2016; 2017a) and discussed in Chapter 38 (Emergency Contraception).

TABLE 47-7

Guidelines for Prophylaxis against Sexually Transmitted Disease in Pregnant Victims of Sexual Assault

Prophylaxis Against	Regimen	Alternative
Neisseria gonorrhoeae	Ceftriaxone 250 mg IM single dose ***plus*** Azithromycin 1 g orally single dose	Cefixime 400 mg orally single dose ***plus*** Azithromycin 1 g orally single dose
Chlamydia trachomatis	Azithromycin 1 g orally single dose[a] ***or*** Amoxicillin 500 mg orally three times daily for 7 days	Erythromycin-base 500 mg orally four times daily for 7 days ***or*** Levofloxacin 500 mg orally once daily for 7 days[b] ***or*** Ofloxacin 300 mg orally twice daily for 7 days[b]
Bacterial vaginosis	Metronidazole 500 mg orally twice daily for 7 days ***or*** Metronidazole gel 0.75%, one full applicator (5 g) intravaginally once daily for 5 days ***or*** Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days	Tinidazole 2 g orally once daily for 2 days[b] ***or*** Tinidazole 1 g orally daily for 5 days ***or*** Clindamycin 300 mg orally twice daily for 7 days ***or*** Clindamycin ovules 100 mg intravaginally at bedtime for 3 days
Trichomonas vaginalis	Metronidazole 2 g orally single dose ***or*** Tinidazole 2 g orally single dose[b]	Metronidazole 500 mg orally twice daily for 7 days
Hepatitis B (HBV)	If not previously vaccinated, give first dose HBV vaccine, repeat at 1–2 and 4–6 months	
HIV	Consider retroviral prophylaxis if risk for HIV exposure is high	

[a]For nonpregnant women, doxycycline, 100 mg orally twice daily for 7 days, can be given instead.

[b]Pregnancy category C.

HIV = human immunodeficiency virus; IM = intramuscularly.

Data from Centers for Disease Control and Prevention, 2015.

Finally, the importance of psychological counseling for the rape victim and her family cannot be overemphasized. A 30- to 35-percent lifetime risk each for posttraumatic stress disorder, major depression, and suicide contemplation follows sexual assault (Linden, 2011).

Automobile Accidents

At least 3 percent of pregnant women are involved in motor vehicle accidents each year in the United States. Using data from PRAMS, Sirin and colleagues (2007) estimated that 92,500 gravidas are injured annually. Motor-vehicle crashes are the most common causes of serious, life-threatening, or fatal blunt trauma during pregnancy (Brown, 2013a; Mendez-Figueroa, 2013, 2016; Vladutiu, 2013). Mattox and Goetzl (2005) report these accidents to be the leading cause of traumatic fetal deaths as well. This was also true from our experiences from Parkland Hospital (Hawkins, 2007). Traffic crashes are most frequent in the second trimester (Redelmeier, 2014). As with all motor vehicle crashes, alcohol use is often associated. But sadly, as many as half of accidents occur without seat-belt use, and many of these deaths would likely be preventable by the three-point restraints shown in Figure 47-8 (Luley, 2013; Schuster, 2016). Seat belts prevent contact with the steering wheel, and they reduce abdominal impact pressure (Motozawa, 2010).

FIGURE 47-8

Illustration showing correct use of three-point automobile restraint. The upper belt is *above* the uterus, and the lower belt fits snugly across the upper thighs and well *below* the uterus.

Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Original concerns regarding injuries caused by airbag deployment have been somewhat allayed (Luley, 2013; Matsushita, 2014). One study included 30 such women from 20 to 37 weeks' gestation whose airbag deployed in accidents with a median speed of 35 mph (Metz, 2006). A third did not use seat belts, and there was one

fetal death from the single case of placental abruption. In a retrospective cohort study that included 2207 pregnant women in crashes with airbag deployment, perinatal outcomes were not clinically different from 1141 controls without airbags (Schiff, 2010). Importantly, 96 percent of both groups used seat belts. Thus, it appears that injuries with airbag deployment are related to the severity of the crash (Mendez-Figueroa, 2016).

Other Blunt Trauma

Some other common causes of blunt trauma are falls and aggravated assaults. In the California review reported by El Kady and associates (2005), intentionally inflicted injuries were present in approximately a third of pregnant women who were hospitalized for trauma. Less common are blast or crush injury (Sela, 2008). With blunt trauma, intraabdominal injuries can be serious. Even so, bowel injuries are less frequent because of the protective effect of a large uterus. Still, diaphragmatic, splenic, liver, and kidney damage may also be sustained. Particularly worrisome is the specter of amnionic-fluid embolism, which has been reported with even mild trauma (Ellingsen, 2007; Pluymakers, 2007). Retroperitoneal hemorrhage is possibly more common than in nonpregnant women (Takehana, 2011).

Orthopedic injuries are also encountered with some regularity (Desai, 2007). From the Parkland Hospital trauma unit, 6 percent of 1682 pregnant women evaluated had orthopedic injuries. This subset was also at increased risk for placental abruption, preterm delivery, and perinatal mortality. In a review of 101 pelvic fractures during pregnancy, there was a 9-percent maternal and 35-percent fetal mortality rate (Leggon, 2002). In another study of pelvic and acetabular fractures during 15 pregnancies, there was one maternal death, and four of 16 fetuses died (Almog, 2007). Finally, head trauma and neurosurgical care raise unique issues (Qaiser, 2007).

Fetal Injury and Death

Perinatal death rates increase with the severity of maternal injuries. Fetal death is more likely with direct fetoplacental injury, maternal shock, pelvic fracture, maternal head injury, or hypoxia (Ikossi, 2005; Pearlman, 2008). Motor vehicle accidents caused 82 percent of fetal deaths from trauma. Death was caused by placental injury in half and by uterine rupture in 4 percent (Weiss, 2001).

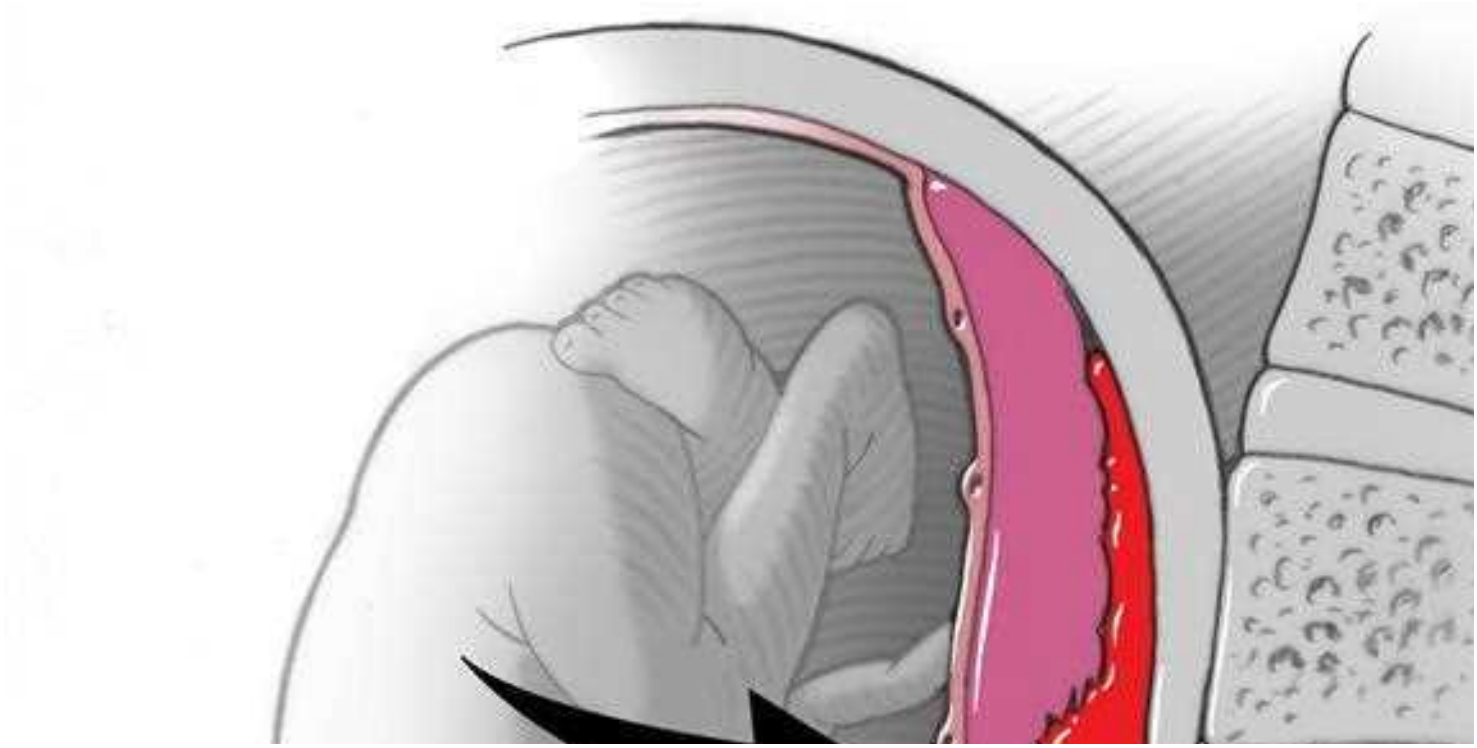
Although uncommon, fetal skull and brain injuries are more likely if the head is engaged and the maternal pelvis is fractured (Palmer, 1994). Conversely, fetal head injuries, presumably from a contrecoup effect, may be sustained in unengaged vertex or nonvertex presentations. Fetal skull fractures are rare and best seen using CT imaging (Sadro, 2012). One example is Figure 46-4. Other sequelae include intracranial hemorrhage (Gherman, 2014; Green-Thompson, 2005). A newborn with paraplegia and contractures associated with a motor vehicle accident sustained several months before birth was described by Weyerts and colleagues (1992). Other injuries have included fetal decapitation or incomplete midabdominal fetal transection at midpregnancy (Rowe, 1996; Weir, 2008).

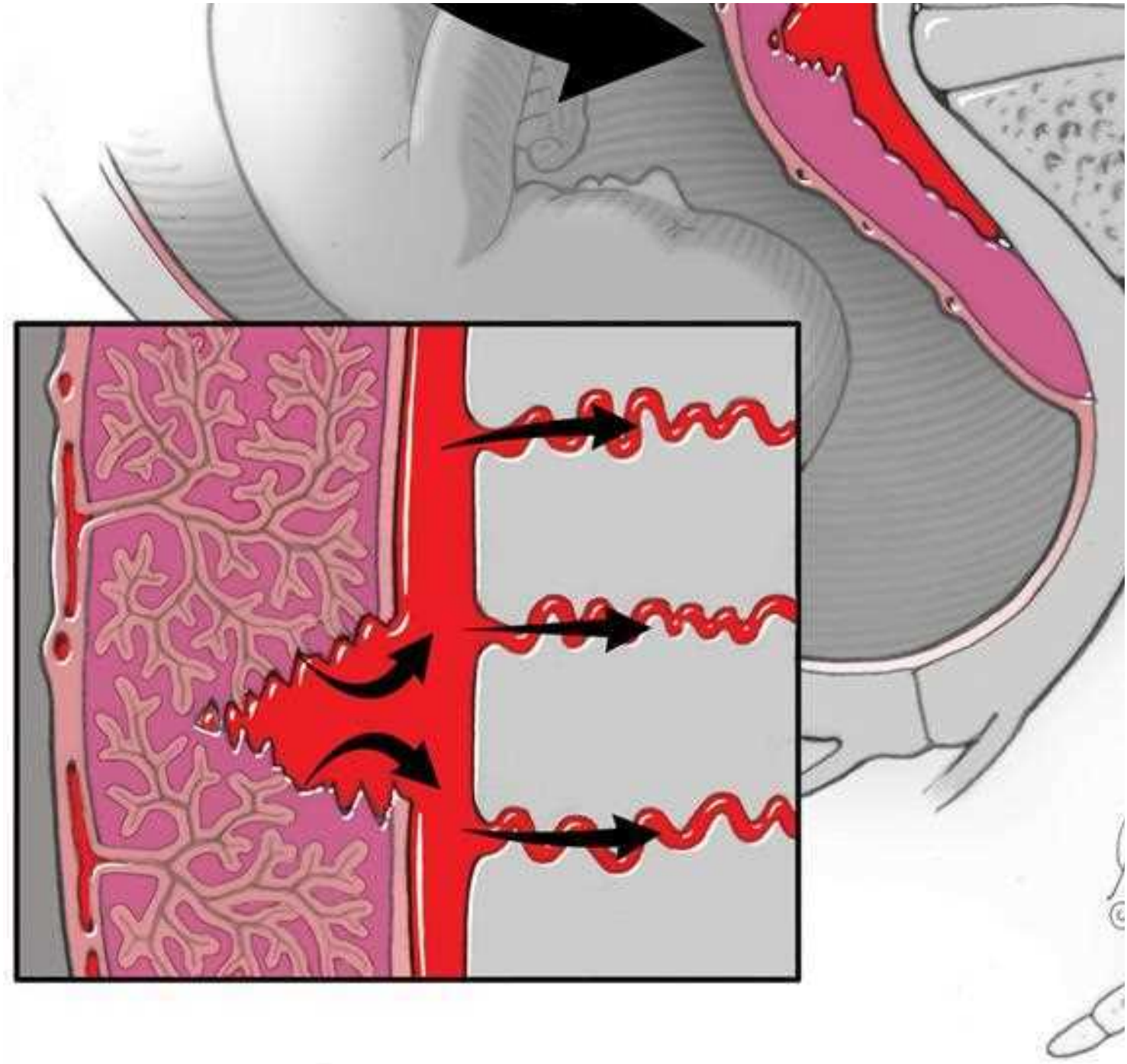
Placental Injuries

Catastrophic events that occur with blunt trauma include placental injuries—abruption or placental tears (Fig. 47-9). Placental separation from trauma is likely caused by deformation of the elastic myometrium around the relatively inelastic placenta (Crosby, 1968). This may result from a deceleration injury as the large uterus meets the immovable steering wheel or seat belt. Some degree of abruption complicates 1 to 6 percent of minor injuries and up to 50 percent of major injuries (Pearlman, 1990; Schiff, 2002). Abruption was found to be more likely if vehicle speed exceeded 30 mph (Reis, 2000).

FIGURE 47-9

Mechanism of placental tear or “fracture” caused by a deformation-reformation injury. Placental abruption is seen as blood collecting in the retroplacental space. **Inset**. From here, blood can be forced into placental bed venules and enter maternal circulation. Such fetomaternal hemorrhage may be identified with Kleihauer-Betke testing.



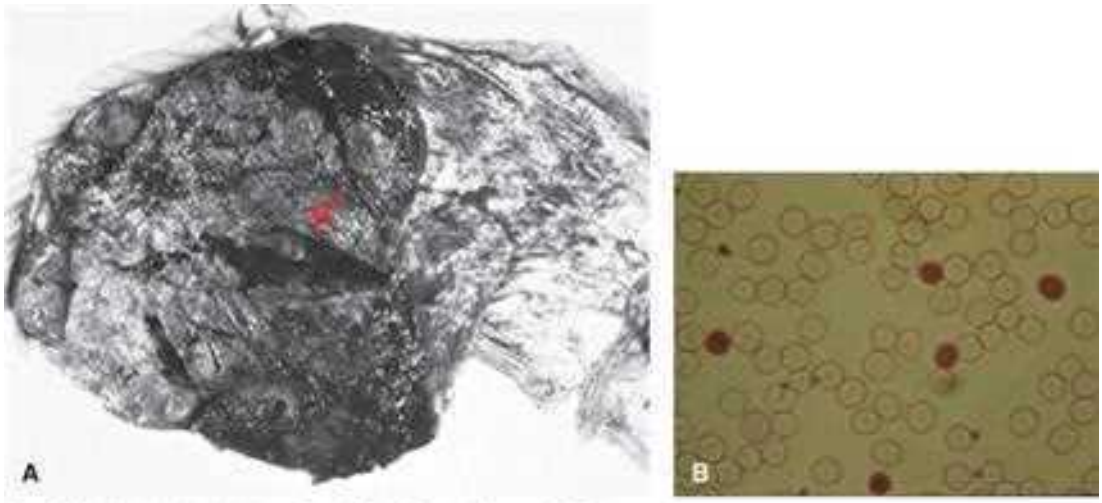


Clinical findings with traumatic abruption may be similar to those for spontaneous placental abruption (Chap. 41, Frequency). Kettel and coworkers (1988) emphasized that traumatic abruption may be occult and unaccompanied by uterine pain, tenderness, or bleeding. In our experiences with 13 such women at Parkland Hospital, 11 had uterine tenderness, but only five had vaginal bleeding. Because traumatic abruption is more likely to be concealed and generate higher intrauterine pressures, associated coagulopathy is more likely than with nontraumatic abruption (Cunningham, 2015). Partial separation may also generate uterine activity, which is described more fully in Thermal Injury. Other features are evidence of fetal compromise such as fetal tachycardia, sinusoidal pattern, late decelerations, acidosis, and fetal death.

If the abdominal force associated with trauma is considerable, then the placenta can be torn or “fractured” (see Fig. 47-9). If so, then life-threatening fetal hemorrhage may be encountered either into the amnionic sac or by fetomaternal hemorrhage (Pritchard, 1991). The tear is linear or stellate and is caused by rapid deformation and reformation (Fig. 47-10). Especially if there is ABO compatibility, fetomaternal hemorrhage is quantified using a Kleihauer-Betke stain of maternal blood. A small amount of fetal-maternal bleeding has been described in up to a third of trauma cases, and in 90 percent of these, the volume is <15 mL (Goodwin, 1990; Pearlman, 1990). Parenthetically, nontraumatic placental abruption is much less often associated with significant fetomaternal hemorrhage because only minimal fetal blood enters into the intervillous space. With traumatic abruption, however, massive fetomaternal hemorrhage may follow. In one study, the risk of associated uterine contractions and preterm labor was a 20-fold if there was evidence for a fetomaternal bleed (Muench, 2004). With severe fetal bleeding, long-term adverse neurological outcomes are frequent (Kadooka, 2014).

FIGURE 47-10

A. Partial placental abruption in which the adherent blood clot has been removed. Note the laceration of the placenta (*arrow*), which caused fetal death from massive fetomaternal hemorrhage. **B.** Kleihauer–Betke stain of a peripheral smear of maternal blood. The dark cells that constituted 4.5 percent of red blood cells are fetal in origin, whereas the empty cells are maternal.



Uterine Rupture

Blunt trauma leads to uterine rupture in <1 percent of severe cases (American College of Obstetricians and Gynecologists, 2017b). Rupture is more likely in a previously scarred uterus and is usually associated with a direct impact of substantial force. Decelerative forces following a 25-mph collision can generate up to 500 mm Hg of intrauterine pressure in a properly restrained woman (Crosby, 1968). Clinical findings may be identical to those for placental abruption with an intact uterus, and maternal and fetal deterioration are soon inevitable. Pearlman and Cunningham (1996) described uterine fundal "blowout" with fetal decapitation in a 20-week pregnancy following a high-speed collision. Similarly, Weir and colleagues (2008) described supracervical uterine avulsion and fetal transection at 22 weeks. CT scanning may be useful to diagnose uterine rupture with a dead fetus or placental separation (Kopelman, 2013; Manriquez, 2010; Sadro, 2012).

Penetrating Trauma

In a study of 321 pregnant women with abdominal trauma, Petrone (2011) reported a 9-percent incidence of penetrating injuries. Of these, 77 percent were gunshot wounds and 23 percent were stab wounds. The incidence of maternal visceral injury with penetrating trauma is only 15 to 40 percent compared with 80 to 90 percent in nonpregnant individuals (Stone, 1999). When the uterus sustains penetrating wounds, the fetus is more likely than the mother to be seriously injured. Indeed, although the fetus sustains injury in two thirds of cases with penetrating uterine injuries, maternal visceral injuries are seen in only 20 percent. Still, their seriousness is underscored in that maternal-fetal mortality rates are significantly higher than those seen with blunt abdominal injuries in pregnancy. Specifically, maternal mortality rates were 7 versus 2 percent, and fetal mortality rates were 73 versus 10 percent, respectively.

Management of Trauma

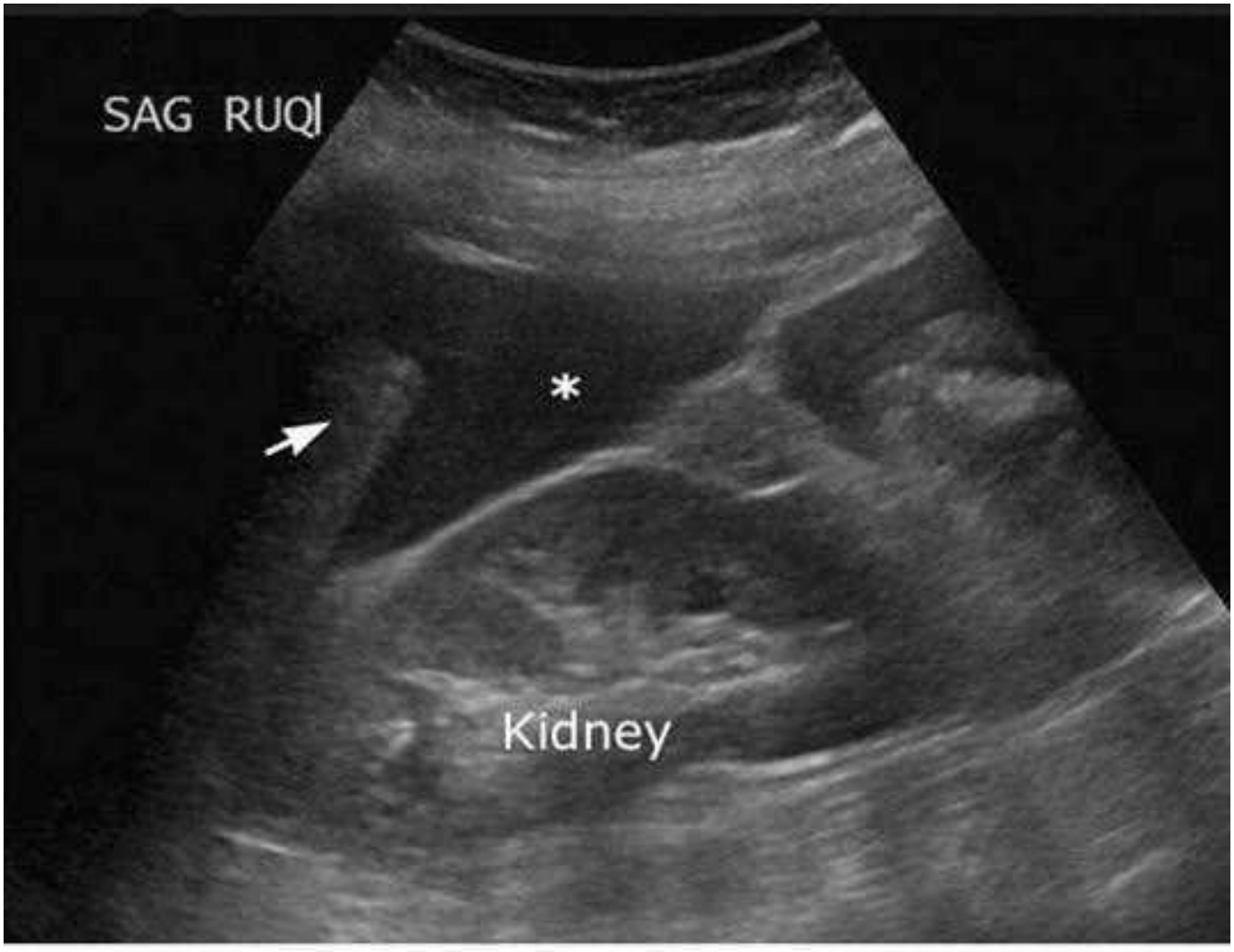
Maternal and fetal outcomes are directly related to the severity of injury. That said, commonly used methods of severity scoring do not take into account significant morbidity and mortality rates related to placental abruption and thus to pregnancy outcomes. In a study of 582 pregnant women hospitalized for injuries, the injury severity score did not accurately predict adverse pregnancy outcomes (Schiff, 2005). Importantly, relatively minor injuries were associated with preterm labor and placental abruption. Others have reached similar conclusions (Biester, 1997; Ikossi, 2005). In a study of 317 women at 24 weeks' gestation or more who had "minor trauma," 14 percent had clinically significant uterine contractions requiring extended fetal evaluation past 4 hours (Cahill, 2008).

With few exceptions, treatment priorities in injured pregnant women are multidisciplinary (Barraco, 2010; Mendez-Figueroa, 2016). Primary goals are evaluation and stabilization of maternal injuries. Attention to fetal assessment during the acute evaluation may divert attention from life-threatening maternal injuries (American College of Obstetricians and Gynecologists, 2017b; Brown, 2009). Basic rules of resuscitation include ventilation, arrest of hemorrhage, and treatment of hypovolemia with crystalloid and blood products. After midpregnancy, the large uterus is positioned off the great vessels to diminish its effect on vessel compression and cardiac output (Nelson, 2015).

Following emergency resuscitation, evaluation is continued for fractures, internal injuries, bleeding sites, and placental, uterine, and fetal trauma. Radiography is not proscribed, but special attention is given each indication. Not surprisingly, one report observed that pregnant trauma victims had less radiation exposure than nonpregnant controls (Ylagan, 2008). Some advocate screening abdominal sonography followed by CT scanning for positive sonographic findings (Brown, 2005; Saphier, 2014). Procedures used include the *FAST scan—focused assessment with sonography for trauma.* This examination is a 5-minute, four- to six-view imaging study that evaluates perihepatic, perisplenic, pelvic, and pericardial views (Mendez-Figueroa, 2016). In general, if fluid is seen in any of these views, then the volume is >500 mL (Fig. 47-11). Importantly, this amount has not been corroborated for pregnancy. In some cases, open peritoneal lavage may be informative (Tsuei, 2006).

FIGURE 47-11

Fast scan. Upper quadrant scan shows anechoic free fluid (asterisk) between the liver edge (arrow) and kidney (Morison pouch). The patient had 2500 mL of blood in the peritoneal cavity. (From Mendez-Figueroa H, Rouse DJ: Trauma in pregnancy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al (eds): Cunningham and Gilstrap's Operative Obstetrics 3rd ed, New York McGraw-Hill Education, 2016, In press.)



Penetrating injuries in most cases must be evaluated using radiography. Because clinical response to peritoneal irritation is blunted during pregnancy, an aggressive approach to exploratory laparotomy is pursued. Whereas exploration is mandatory for abdominal gunshot wounds, some clinicians advocate close observation for selected stab wounds. Diagnostic laparoscopy has also been used (Chap. 46, Medications and Surgeries).

Cesarean Delivery

The necessity for cesarean delivery depends on several factors. Laparotomy itself is not an indication for hysterotomy. Some considerations include gestational age, fetal condition, extent of uterine injury, and whether the large uterus hinders adequate management of other intraabdominal injuries (Tsuei, 2006).

Electronic Monitoring

Because fetal well-being may reflect the status of the mother, fetal monitoring is another "vital sign" that helps evaluate the extent of maternal injuries. Even if the mother is stable, electronic monitoring may suggest placental abruption. In a study by Pearlman and coworkers (1990), no woman had an abruption if uterine contractions were less often than every 10 minutes within the 4 hours after trauma was sustained. Almost 20 percent of women who had contractions more frequently than every 10 minutes in the first 4 hours had an associated placental abruption. In these cases, abnormal tracings were common and included fetal tachycardia and late decelerations. Conversely, no adverse outcomes were reported in women who had normal monitor tracings (Connolly, 1997). Importantly, if tocolytics are used for these contractions, they may obfuscate findings, and we do not recommend them.

Because placental abruption usually develops early following trauma, fetal monitoring is begun as soon as the mother is stable. The ideal duration of posttrauma monitoring is not precisely known. From data cited above, observation for 4 hours is reasonable with a normal tracing and no other sentinel findings such as contractions, uterine tenderness, or bleeding. Certainly, monitoring should be continued as long as there are uterine contractions, nonreassuring fetal heart patterns, vaginal bleeding, uterine tenderness or irritability, serious maternal injury, or ruptured membranes (American College of Obstetricians and Gynecologists, 2017b). In rare cases, placental abruption has developed days after trauma (Higgins, 1984).

Fetal-Maternal Hemorrhage

It is unclear whether routine use of the Kleihauer-Betke or an equivalent test in pregnant trauma victims might modify adverse outcomes associated with fetal anemia, cardiac arrhythmias, and death (Pak, 1998). In a retrospective review of 125 pregnant women with blunt injuries, the Kleihauer-Betke test was judged to be of little value during acute trauma management (Towery, 1993). Others have reached similar conclusions, although a positive test with fetal cells of 0.1 percent was predictive of uterine contractions or preterm labor (Connolly, 1997; Muench, 2003, 2004).

For the woman who is D-negative, administration of anti-D immunoglobulin should be considered. This may be omitted if a test for fetal bleeding is negative. Even with anti-D immunoglobulin, alloimmunization may still develop if the fetal-maternal hemorrhage exceeds 15 mL of fetal cells (Chap. 15, Fetomaternal Hemorrhage).

For the pregnant trauma patient, confirmation of current tetanus immunization status is pertinent. When indicated, a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) is preferred for its neonatal pertussis immunity benefits (Chap. 9, Automobile and Air Travel).

THERMAL INJURY

Treatment of the burned gravida is similar to that for nonpregnant patients (Mendez-Figueroa, 2016). With treatment, it is generally agreed that pregnancy does not alter maternal outcome from thermal injury compared with that of nonpregnant women of similar age. As perhaps expected, maternal and fetal survival parallels the percentage of burned surface area (Parikh, 2015). Karimi and colleagues (2009) reported higher mortality rates for both with suicidal attempts and with inhalational injuries. The composite mortality rate for nearly 400 women from seven studies increased in a linear fashion as the percent of burned body surface area increased (Fig. 47-12). For 20-, 40-, and 60-percent burns, the maternal mortality rates were approximately 4, 30, and 93 percent, respectively. The corresponding fetal mortality rates were 20, 48, and 96 percent, respectively. With severe burns, the woman usually enters labor spontaneously within a few days to a week and often delivers a stillborn. Contributory factors are hypovolemia, pulmonary injury, septicemia, and the intensely catabolic state (Radosevich, 2013).

FIGURE 47-12
Maternal and fetal mortality rates by burn severity in nearly 400 women. (Data from Akhtar, 1994; Amy, 1985; Mabrouk, 1977; Maghsoudi, 2006; Parikh, 2015; Rayburn, 1984; Rode, 1990.)

Following serious abdominal burns, skin contractures that develop may be painful during a subsequent pregnancy and may even require surgical decompression and split-skin autografts (Mitsukawa, 2015; Radosevich, 2013). Loss or distortion of nipples may cause problems in breastfeeding. Mitsukawa and associates (2015) reported that contracture release was indicated with scars spanning more than >75 percent of the total abdominal area. Alternatively, normal abdominal tissue expansion due to pregnancy appears to be an excellent source for obtaining skin grafts postpartum to correct scar deformities at other body sites (Del Frari, 2004).

Electrical and Lightning Injuries

Earlier case reports suggested a high fetal mortality rate with electric shock (Fatovich, 1993). In a prospective cohort study, however, Einarson and coworkers (1997) showed similar perinatal outcomes in 31 injured women compared with those of noninjured controls. They concluded that traditional 110-volt North American electrical current likely is less dangerous than the 220-volt currents available in Europe. A woman with iliofemoral thrombosis at 29 weeks' gestation that *may* have been related to a mild electrical shock at 22 weeks was described (Sozen, 2004). Another woman with brain death from cardiac arrest was reported (Sparic, 2014). Thermal burns with electrocution may be extensive.

The pathophysiological effects of lightning injuries can be devastating. García Gutiérrez and coworkers (2005) reviewed 13 case reports of lightning injuries during pregnancy and cited a 50-percent stillbirth rate.

CARDIOPULMONARY RESUSCITATION

According to estimates from the Nationwide Inpatient Sample, cardiac arrest complicates approximately 1 in 12,000 delivery admissions (Mhyre, 2014). The most common underlying causes were hemorrhage, heart failure, amnionic-fluid embolism, and sepsis. General topics regarding planning and equipment have been reviewed by the American College of Obstetricians and Gynecologists (2017b) and the Society for Obstetric Anesthesia and Perinatology (Lipman, 2014). Special considerations for cardiopulmonary resuscitation (CPR) conducted in the second half of pregnancy are outlined in the American Heart Association 2010 guidelines (Jeejeebhoy, 2015). The committee acknowledges the following as standards for critically ill gravidas: (1) relieve possible vena caval compression by left lateral uterine displacement, (2) administer 100-percent oxygen, (3) establish intravenous access above the diaphragm, (4) assess for hypotension that warrants therapy, which is defined as systolic blood pressure <100 mm Hg or <80 percent of baseline, and (5) review possible causes of critical illness and treat conditions as early as possible.

The position of the heart for external compressions is not different from that in nonpregnant women (Holmes, 2015). In nonpregnant women, external chest compression results in a cardiac output approximately 30 percent of normal. In late pregnancy, this may be even less with compressions because of uterine aortocaval compression (Clark, 1997; Nelson, 2015). Thus, it is paramount to accompany other resuscitative efforts with uterine displacement. This can be accomplished by tilting the operating table laterally, by placing a wedge under the patient's right hip, or by pushing the uterus to the left manually (Rees, 1988; Rose, 2015). If no equipment is available, an individual may kneel on the floor with the maternal back on his or her thighs to form a "human wedge" (Whitty, 2002).

Cesarean Delivery

During maternal resuscitation, because of pregnancy-induced hindrances on CPR efforts, emergent *perimortem cesarean delivery* for fetal salvage and improved maternal resuscitation may be considered. Some have stated that cesarean delivery is indicated within 4 to 5 minutes of beginning CPR if the fetus is viable (Drukker, 2014). In women delivered by perimortem cesarean, neurologically intact neonatal survival and the cardiac arrest-to-delivery interval are inversely related (Katz, 2012). Specifically, of newborns delivered within 5 minutes of arrest, 98 percent are neurologically intact; within 6 to 15 minutes, 83 percent are intact; within 16 to 25 minutes, 33 percent are intact; and within 26 to 35 minutes, only 25 percent are intact (Clark, 1997). This, coupled with some evidence that delivery *may* also enhance maternal resuscitation, has led the American College of Obstetricians and Gynecologists (2017b) to recommend *consideration* for cesarean delivery to begin within 4 minutes of cardiac arrest in these cases.

This serious and sometimes contentious issue is far from evidence based. To wit, Katz and associates (2005) reviewed 38 perimortem cesarean deliveries with a "large selection bias." They concluded that these reports supported—but "fell far from proving"—that perimortem cesarean delivery within 4 minutes of maternal cardiac arrest improves maternal and fetal outcomes. Even so, as emphasized by Clark (1997) and Rose (2015) and their coworkers, and in our experiences, these goals rarely can be met in actual practice. For example, most cases of cardiac arrest occur in uncontrolled circumstances, and thus, the time to CPR initiation alone would require the first 5 minutes. Thus "crash" cesarean delivery would supersede resuscitative efforts, would necessarily be done without appropriate anesthesia or surgical equipment, and more likely than not, would lead to maternal death. Moreover, the distinction between a perimortem versus postmortem cesarean operation is imperative (Katz, 2012; Rose, 2015). Last, in the balance, any choice *may* favor survival of the mother over the fetus, or vice versa, and thus there are immediate unresolvable ethical concerns. Katz (2012) has provided a scholarly review of perimortem cesarean delivery.

Maternal Brain Death

Occasionally, a pregnant woman with a supposedly healthy intact fetus will be kept on somatic support to await fetal viability or maturity. This is discussed in Chapter 60 (Idiopathic Intracranial Hypertension).

ENVENOMATION

According to their review, Brown and coworkers (2013b) reported that clinically significant envenomations in pregnant women are from snakes, spiders, scorpions, jellyfish, and hymenoptera such as bees, wasps, hornets, and ants. Adverse outcomes are related to maternal effects. These investigators conclude that limited evidence supports the use of a venom-specific approach that includes symptomatic care, antivenom administration when appropriate, anaphylaxis treatment, and fetal assessment. One management scheme for North American snakebites was provided by Lei and associates (2015).

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CHAPTER 48: Obesity

I recently saw a patient who imagined herself in the last month of pregnancy, and who, while talking to me, exclaimed at the violence of the movements, but on examination I found that her uterus was normal in size, and that her enlarged abdomen was due to a rapidly increasing deposit of fat.

—J. Whitridge Williams (1903)

INTRODUCTION

At the beginning of the last century, obesity was not terribly problematic, and with few exceptions, Williams did not refer to its adverse obstetrical effects. Fast forward to today when excessive weight is a major health problem in many affluent societies (GBD 2015 Obesity Collaborators, 2017). Indeed, by 2014, more than a third of all adults in the United States were obese (Ogden, 2015).

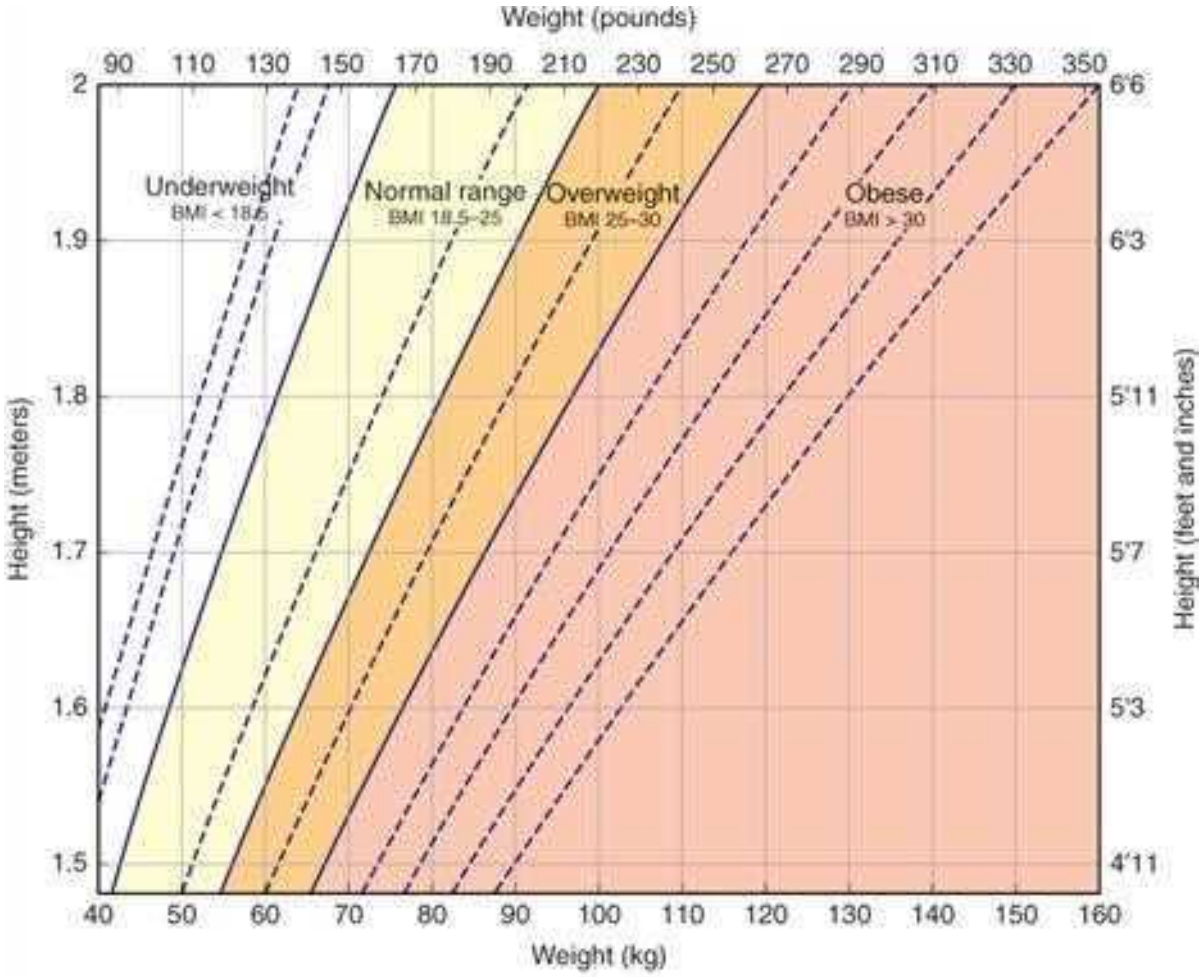
The adverse health aspects of obesity are staggering and include risks for diabetes mellitus, heart disease, hypertension, stroke, and osteoarthritis. Obese gravidas and their fetuses are predisposed to various serious pregnancy-related complications and to higher long-term morbidity and mortality rates.

GENERAL CONSIDERATIONS

Definitions and Prevalence

Of systems to classify obesity, the *body mass index* (*BMI*), also known as the *Quetelet index,* is most often used. The BMI is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Calculated BMI values are available in various chart and graphic forms (Fig. 48-1). The National Institutes of Health (2000) classifies adults according to BMI as follows: *normal* is 18.5 to 24.9 kg/m^2, *overweight* is 25 to 29.9 kg/m^2, and *obese* is ≥30 kg/m^2. Obesity is further divided into: *class 1* is 30 to 34.9 kg/m^2, *class 2* is 35 to 39.9 kg/m^2, and *class 3* is ≥40 kg/m^2. Class 3 obesity is often referred to as morbid obesity, with *super-morbid obesity* describing a BMI ≥50 kg/m^2.

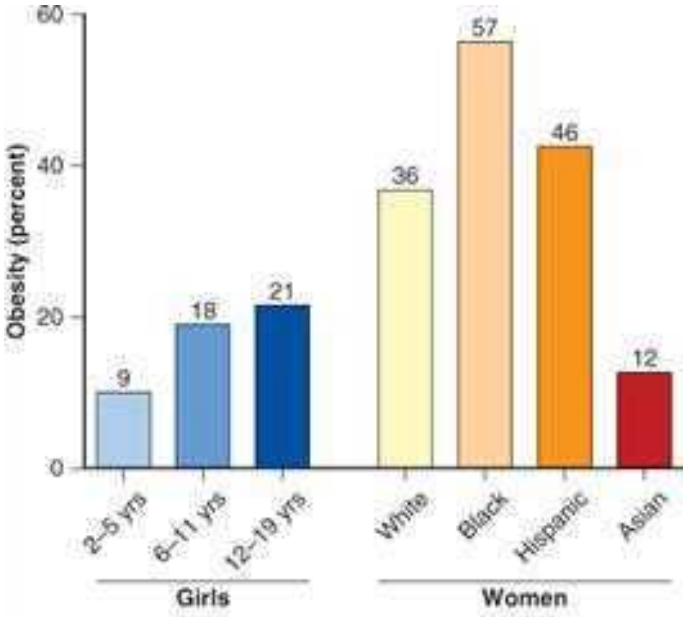
FIGURE 48-1
Chart for estimating body mass index (BMI). To find the BMI category for a particular subject, locate the point at which the height and weight intersect.



Using these definitions, from 2011 to 2014, slightly more women than men were designated obese—36 versus 34 percent (Ogden, 2015). Among girls and women, the prevalence of obesity rises with age and varies among ethnicities (Fig. 48-2). Although obesity is now common among all socioeconomic levels, the overall severity advances with increasing poverty (Bilger, 2017). Also, a genetic predisposition has been identified from several gene loci (Locke, 2015; Shungin, 2015).

FIGURE 48-2

Prevalence of obesity in girls and women in the United States for 2009–2014. (Data from Ogden, 2015.)



Adipose Pathophysiology

Fat tissue is much more complex than merely its energy storage function. Many fat tissue cells communicate with all other tissues via endocrine and paracrine factors, which are cytokines specifically termed *adipocytokines*. Also simply called *adipokines*, some of these with metabolic functions include adiponectin, leptin, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), resistin, visfatin, apelin, vascular endothelium growth factor (VEGF), lipoprotein lipase, and insulin-like growth factor. A principal adipokine is adiponectin, which is a 30-kDa protein. It enhances insulin sensitivity, blocks hepatic glucose release, and has cardioprotective effects on circulating plasma lipids. An adiponectin deficit is linked with diabetes, hypertension, endothelial cell activation, and cardiovascular disease.

Cytokines that result in insulin resistance are leptin, resistin, TNF-α, and IL-6, and higher levels of these are found during pregnancy. Indeed, adipokines, especially the inflammatory cytokines, may be the primary stimulant of insulin resistance (Al-Badri, 2015; Yang, 2016). Conversely, adiponectin has antiinflammatory and insulin-sensitizing roles and is negatively regulated by fat mass. As one example of the discordant effects of these adipokines, gestational diabetes is associated with lower adiponectin but higher leptin levels. Placental production of these adipokines is also important and related to fetal growth and adiposity by mechanisms yet to be defined (Sartori, 2016).

Metabolic Syndrome

Given its multifaceted endocrine and paracrine functions, the detrimental effects of excessive adipose tissue are not surprising (Cornier, 2011; Gilmore, 2015). Obesity interacts with inherited factors to cause *insulin resistance*. This resistance is characterized by impaired glucose metabolism and a predisposition to type 2 diabetes. Insulin resistance also causes several subclinical abnormalities that predispose to cardiovascular disease and accelerate its onset. The most important among these are type 2 diabetes, dyslipidemia, and hypertension, which are constituents of the *metabolic syndrome*.

Criteria to define this syndrome are found in Table 48-1 (Alberti, 2009). Waist circumference is the preferred measurement for screening, but any three of five factors listed are sufficient to diagnosis the metabolic syndrome. Notably, most patients with type 2 diabetes have metabolic syndrome according to these criteria. Also, obese women with hypertension typically demonstrate elevated plasma insulin levels. These are even higher in women with central obesity (Fu, 2015).

TABLE 48-1

Criteria for Diagnosis of the Metabolic Syndrome

Patients with three or more of the following:	
Elevated waist circumference[a]	
Elevated triglycerides[b]:	≥150 mg/dL
Reduced high-density lipoprotein cholesterol[b]:	
	<40 mg/dL in males
	<50 mg/dL in females
Elevated blood pressure[b]: systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg	
Elevated fasting glucose[b]: ≥100 mg/dL	

[a]According to country- and population-specific thresholds.

[b]Those with normal values while taking medications are considered to meet these criteria.

Data from Alberti, 2009.

The National Health Nutrition Examination Survey (NHANES) of the Centers for Disease Control and Prevention documented an overall 34-percent prevalence of the metabolic syndrome in the United States by 2012 (Moore, 2017). As expected, the prevalence rose with age. It was 20 percent for those aged 18 to 29 years and was 36 percent for those aged 30 to 49 years.

Nonalcoholic Fatty Liver Disease

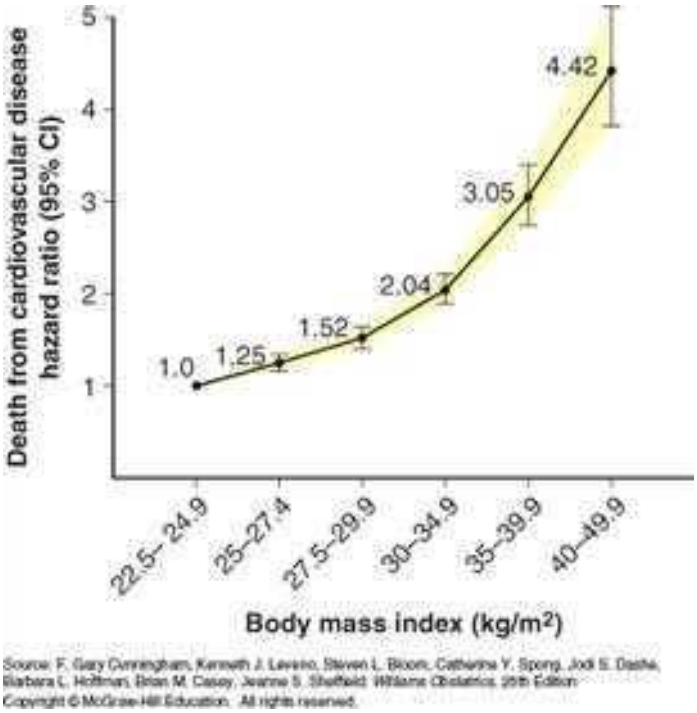
Generally speaking, visceral adiposity correlates with hepatic fat content (Cornier, 2011). With obesity, excessive fat accumulates in the liver—*hepatic steatosis*, which is also called nonalcoholic fatty liver disease (NAFLD). In persons with the metabolic syndrome, steatosis can progress to *nonalcoholic steatohepatitis (NASH)* and cirrhosis, as well as hepatocellular carcinoma. Indeed, one fourth of chronic liver disease cases worldwide are caused by NAFLD (Younossi, 2016). Moreover, NAFLD is strongly associated with both fatal and nonfatal cardiovascular disease (Targher, 2016).

Obesity-Associated Morbidity

Obese individuals suffer well-known consequences such as glucose intolerance, hypertension, dyslipidemia, and metabolic syndrome. Furthermore, metabolic syndrome and obesity are linked with cardiovascular disease, including myocardial infarction, atrial fibrillation, heart failure, and stroke (Long, 2016). Insulin resistance and metabolic syndrome cause structural cerebral changes and lower executive functioning and memory in adults. Similar consequences are also found in adolescents, suggesting that metabolic syndrome's effects on neurocognitive function are independent of significant occlusive vascular disease (Rusinek, 2014).

Obesity is associated with higher rates of all-cause early mortality (Fontaine, 2003; Peeters, 2003). Cardiovascular mortality data from 19 prospective studies are shown in Figure 48-3. In these and other studies, mortality risk from cardiovascular disease and cancer grew proportionally with increasing BMI. Importantly, however, an *obesity* paradox—whereby certain groups actually derive a survival advantage from being obese—has been hypothesized (Hainer, 2013). Despite this, the health benefits of weight normalization are well documented (Cheung, 2017).

FIGURE 48-3
Estimated hazard ratios (95% CI) for death due to cardiovascular disease according to body mass index among 1.46 million white adult men and women. (Data from de Gonzalez, 2010.)



Obesity Treatment

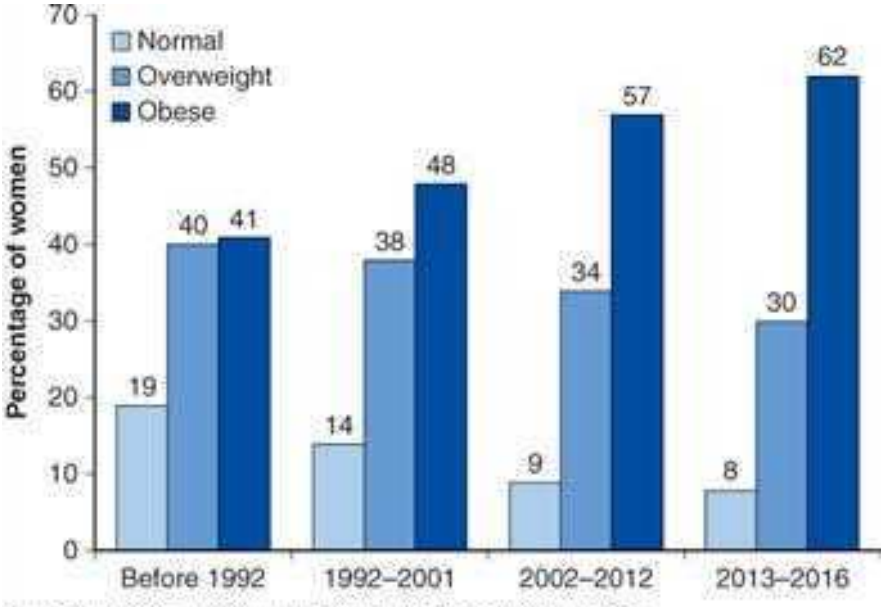
Weight loss is tremendously difficult for obese individuals. If achieved, long-term maintenance poses equally daunting challenges. Obstetrician-gynecologists are encouraged to aid weight loss in obese adult women. Successful approaches include behavioral, pharmacological, and surgical techniques or a combination of these methods (Dixon, 2016). Dietary changes and exercise reduce weight and rates of the associated metabolic syndrome (Garvey, 2016; Martin, 2016). When used in conjunction with bariatric surgery, glucose control in those with type 2 diabetes is improved (Schauer, 2014). However, both surgical and medical interventions are associated with appreciable long-term failure rates—up to 50 percent in patients with type 2 diabetes undergoing bariatric surgery (Mingrone, 2015).

PREGNANCY AND OBESITY

Obese women unequivocally have reproductive disadvantages (American Society for Reproductive Medicine, 2015). This translates into difficulty in achieving pregnancy, early and recurrent pregnancy loss, preterm delivery, and several obstetrical, medical, and surgical complications with pregnancy, labor, delivery, and the puerperium (American College of Obstetricians and Gynecologists, 2015). Also, oral contraceptive failure may be more likely in overweight women (Chap. 38, Method-Specific Effects). Last, infants—and later, adult children—of obese mothers have correspondingly higher morbidity rates (Godfrey, 2017; Reynolds, 2013).

Obesity complicating pregnancy has grown substantially in this country. Our experience at Parkland Hospital over three epochs is shown in Figure 48-4.

FIGURE 48-4
Increasing prevalence of obesity during four epochs in pregnant women classified at the time of their first prenatal visit at Parkland Hospital.



Maternal Morbidity

For *overweight women*, higher rates of adverse outcomes complicate pregnancy (Schummers, 2015). Shown in Table 48-2 are results from five studies including more than 1 million singleton pregnancies. Although not as magnified as in the obese cohort, rates of almost all complications are significantly greater in overweight women than in those whose BMI is normal.

TABLE 48-2

Adverse Pregnancy Effects in Overweight and Obese Women

Complication	Prevalence (%) Normal BMI 18.5–24.9 n = 621,048	Prevalence (%) with Odds Ratio and 95% Confidence Interval[a]	
		Overweight BMI 25–29.9 n = 228,945	Obese BMI > 30 n = 78,043
Gestational diabetes	2.3	4.3 (OR 1.91, 1.86–1.96)	8.6 (OR 4.04, 3.94–4.15)
Preeclampsia	2.7	4.3 (OR 1.60, 1.56–1.64)	8.1 (OR 3.17, 3.08–3.25)
Preterm birth	3.8	4.1 (OR 1.09, 1.05–1.13)	4.8 (OR 1.28, 1.23–1.34)
Labor induction	20.9	23.8 (OR 1.19, 1.17–1.21)	29.7 (OR 1.60, 1.57–1.64)
Prelabor or elective cesarean delivery	6.6	8.3 (OR 1.28, 1.26–1.31)	11.5 (OR 1.85, 1.81–1.89)
Cesarean delivery	25.2	31.5 (OR 1.37, 1.34–1.39)	39.3 (OR 1.92, 1.88–1.96)
Shoulder dystocia	2.0	2.4 (OR 1.22, 1.17–1.28)	2.3 (OR 1.14, 1.08–1.21)
Postpartum hemorrhage	6.7	8.4 (OR 1.29, 1.26–1.31)	8.7 (OR 1.34, 1.31–1.37)
Pelvic infection	0.6	0.7 (OR 1.16, 1.06–1.26)	0.8 (OR 1.28, 1.15–1.43)
Wound infection or complication	0.4	0.5 (OR 1.42, 1.28–1.58)	1.0 (OR 2.70, 2.42–3.01)
Large for gestational age	8.7	13.1 (OR 1.57, 1.54–1.61)	16.3 (OR 2.04, 1.99–2.10)
Macrosomia	2.0	3.6 (OR 1.81, 1.74–1.88)	5.1 (OR 2.60, 2.50–2.71)
Stillbirth	0.3	1.8 (OR 5.89, 5.57–6.22)	0.5 (OR 1.71, 1.56–1.87)

[a]Odds ratios with 95% CI are significant when compared to normal BMI group.

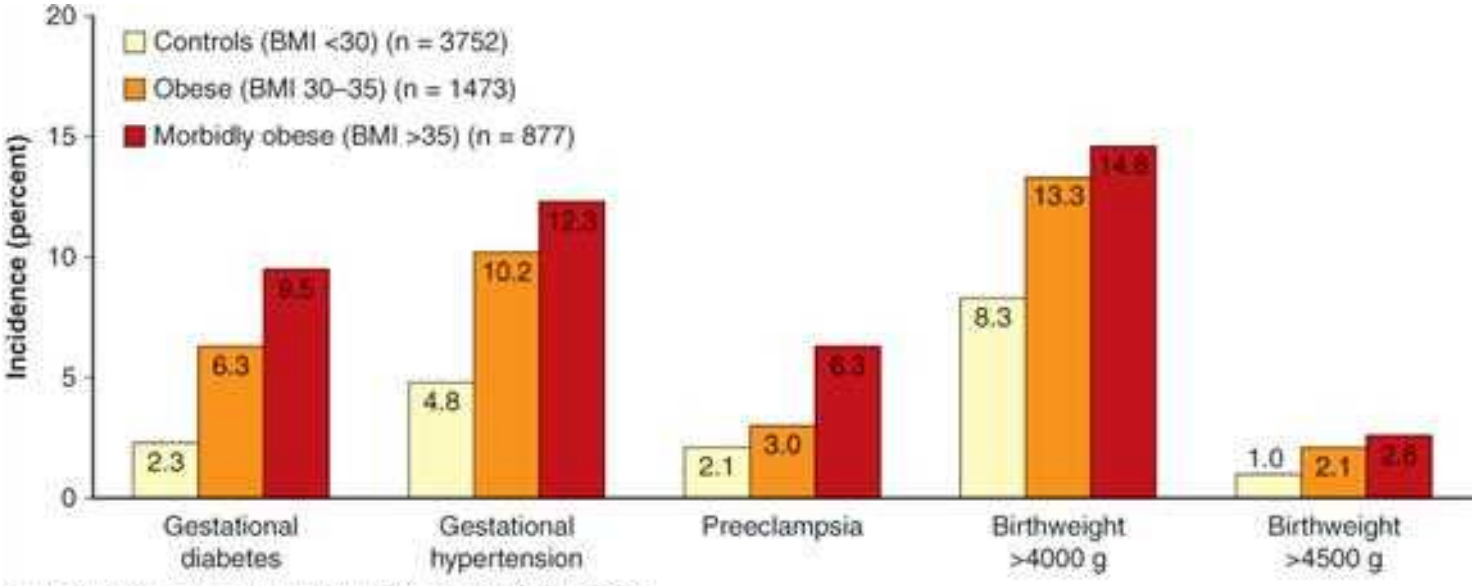
BMI = body mass index.

Data from Kim, 2016; Lisonkova, 2017; Ovesen, 2011; Schummers, 2015; Sebire, 2001.

For *obese women*, definitions used in studies of adverse outcomes vary widely, and BMIs from >30 kg/m^2 to >50 kg/m^2 have served as thresholds (Crane, 2013; Denison, 2008; Stamilio, 2014). Of outcomes, Mariona (2017) reviewed maternal deaths in Michigan and found that the risk of a maternal death was nearly fourfold higher in obese women. Women with super-morbid obesity experience very high rates of maternal and neonatal complications including preeclampsia, fetal overgrowth, and cesarean delivery, with even higher rates of meconium aspiration, ventilator support, and neonatal death (Marshall, 2014; Smid, 2016). Data from one large study is shown in Figure 48-5.

FIGURE 48-5

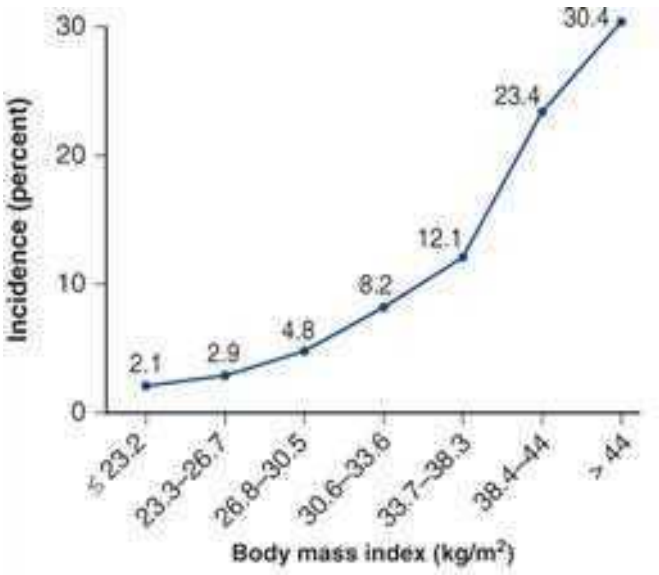
Incidence of selected pregnancy outcomes in 16,102 women enrolled in the FASTER (First- and Second-Trimester Evaluation of Risk) trial according to BMI. (Data from Weiss, 2004.)



Especially striking are the markedly elevated rates of hypertension and gestational diabetes. As discussed previously, obesity and the metabolic syndrome are characterized by insulin resistance, which causes low-grade inflammation and endothelial activation (Ma, 2016). These latter effects play a central role in preeclampsia (Chap. 40, Pathogenesis). The overwhelming evidence between rising maternal BMI and the incidence of preeclampsia is depicted in Figure 48-6. Similar observations were reported from a large Canadian study and by the Safe Labor Consortium (Kim, 2016; Schummers, 2015).

FIGURE 48-6

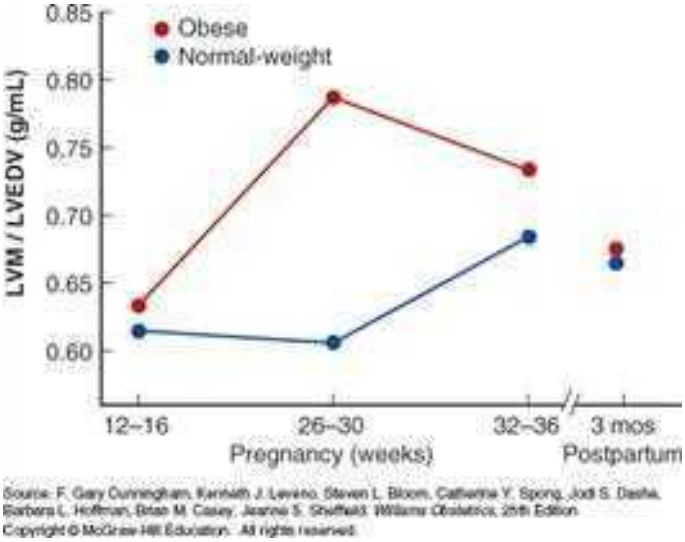
Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: frequency of preeclampsia according to BMI. (Data from the HAPO Study Cooperative Research Group, 2008.)



Obesity and hypertension are common cofactors in peripartum heart failure (Cunningham, 1986, 2012). Stewart and colleagues (2016) prospectively studied the effect of obesity on cardiac remodeling in pregnancy among 14 normal and 9 overweight or obese women (Fig. 4-8). Concentric remodeling was greater in overweight or obese women (Fig. 48-7). This, however, regressed to normal by 3 months postpartum.

FIGURE 48-7

Geometric changes of ventricular remodeling across pregnancy in obese and normal-weight women. LVM = left ventricular mass, LVEDV = left ventricular end-diastolic volume. (Data from Stewart, 2016.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Obesity and gestational diabetes are inextricably linked as shown in Table 48-2. Their coexistence with and adverse effects on pregnancy outcomes are discussed in Chapter 57 (Types of Diabetes and Management).

Nonalcoholic fatty liver disease is associated with several adverse pregnancy outcomes. In a cohort of 110 women with NAFLD, risks for preeclampsia, preterm birth, low-birthweight neonates, cesarean delivery, and gestational diabetes were elevated (Hagström, 2016). In one prospective study of 476 pregnancies, first-trimester sonographic evidence of maternal NAFLD was strongly associated with gestational diabetes (De Souza, 2016a,b). Meyer and associates (2013) found that overweight and obese gravidas had a higher proportion of low-density lipoprotein III (LDL-III) compared with that of normal-weight women. LDL-III predominance is a hallmark of ectopic liver fat accumulation that is typical of NAFLD. At Parkland Hospital, we are now frequently encountering obese gravidas who have NAFLD and evidence of steatohepatitis manifest by elevated serum hepatic transaminase levels. In rare cases, liver biopsy is necessary to exclude other causes.

In addition to these metabolic complications, quality-of-life measures are also negatively affected by obesity during pregnancy (Amador, 2008; Ruhstaller, 2017). One systematic review found significantly higher risks of depression in overweight and obese women during and after pregnancy (Molyneaux, 2014). Obese women were also significantly more likely to experience anxiety during pregnancy.

Perinatal Mortality

Stillbirths are more prevalent as the degree of obesity accrues (Ovesen, 2011; Schummers, 2015). In a review of almost 100 studies, obesity was the highest ranking modifiable risk factor for stillbirth (Flenady, 2011). In super-morbidly obese compared with normal-weight gravidas, Yao and associates (2014) found 5.7 and 13.6-fold higher stillbirth rates at 39 and 41 weeks' gestation, respectively. Remarkably, 25 percent of term stillbirths in this study involved obese women. Chronic hypertension with superimposed preeclampsia associated with obesity is one cause of excessive stillbirths.

Evaluating *perinatal death* rates, Lindam and coworkers (2016) reported that high maternal BMI in early pregnancy was a risk factor. The risk of neonatal death is also greater for obese women (Johansson, 2014; Meehan, 2014). Finally, Cnattingius and Villamor (2016) noted that accruing weight between pregnancies is a risk factor for perinatal mortality, whereas weight loss between pregnancies for overweight women lowers this risk.

Perinatal Morbidity

Both fetal and neonatal complications are increased in obese women. Two important and interrelated cofactors that contribute to excessive rates of perinatal morbidity are chronic hypertension and diabetes, both of which are associated with maternal obesity. These comorbidities each may play a role in the higher rates of fetal-growth restriction and indicated preterm birth that are seen in obese women (Schummers, 2015). Pregestational diabetes also raises the birth defect rate, and gestational diabetes is complicated by excessive numbers of large-for-gestational-age and macrosomic fetuses (Chap. 44, Definition).

Even when diabetes is not considered, the prevalence of macrosomic newborns is greater in obese women (Kim, 2016; Ovesen, 2011; Schummers, 2015). The group from MetroHealth Medical Center in Cleveland has extensively studied prepregnancy obesity, gestational weight gain, and diabetes and their relationship to adverse pregnancy outcomes and to greater newborn weight and fat mass (Catalano, 2009, 2015; Lassance, 2015; Ma, 2016; Yang, 2016). Although each of these variables is associated with larger and more corpulent newborns, prepregnancy BMI and its effect on inflammation and placental gene expression has the strongest influence on the prevalence of macrosomic neonates.

Rates of birth defects are also higher with comorbid obesity (Stothard, 2009). For neural-tube defects, elevated risks of 1.2-, 1.7-, and 3.1-fold are found in overweight, obese, and severely obese women, respectively (Rasmussen, 2008). The National Birth Defect Prevention Study reported a correlation between BMI and congenital heart defects (Gilboa, 2010). However, this may be related to diabetes as a cofactor (Biggio, 2010). Importantly, obesity is

detrimental to the accuracy of obstetrical sonographic examination and to antepartum identification of birth defects (Adekola, 2015; Dashe, 2009; Weichart, 2011).

Long-Term Offspring Morbidity

Obese women beget obese children, who themselves become obese adults. Catalano and coworkers (2009) studied offspring at a mean age of 9 years and found a direct association with maternal prepregnancy obesity and childhood obesity. They also reported associations with central obesity, elevated systolic blood pressure, increased insulin resistance, and lipid abnormalities—all elements of the metabolic syndrome. Reynolds and associates (2013) reported higher rates of cardiovascular disease and all-cause mortality in 37,709 adult offspring of overweight and obese mothers. Similar cardiometabolic health effects in offspring were echoed by Gaillard and colleagues (2016). Other data support that excessive maternal weight gain in pregnancy may predict obesity in adult offspring (Lawrence, 2014; Reynolds, 2010). Last, rates of glucose intolerance and metabolic syndrome are higher among offspring of obese women (Gaillard, 2016; Tan, 2015).

The potential biological mechanisms of these associations are unclear. But such studies raise the possibility of *fetal programming*, that is, the fetal environment may lead to adverse adult health outcomes. Elucidation is limited by insufficient data on potential maternal and genetic predisposing factors and on the environment of the infant and child in relation to diet and activity. The science of *epigenetics* has provided some support for the possibility that perturbations of the maternal-fetal environment can adversely alter postdelivery events (Kitsiou-Tzeli, 2017). Also possible are contributions of the maternal-child environment subsequent to birth (Gluck, 2009). These and other factors regarding fetal programming are discussed in Chapter 44 (Accelerated Lung Maturation).

ANTEPARTUM MANAGEMENT

Maternal Weight Gain

The Institute of Medicine (2009) has updated its previous maternal weight gain determinants (Table 9-4). For overweight women, weight gain of 15 to 25 pounds is suggested. For obese women, the Institute advocates a gain of 11 to 20 pounds. Intuitively, maternal weight must increase sufficiently to provide for fetal and placental tissue accrual and for amnionic fluid and maternal blood volume expansion. Thus, maternal weight loss is during pregnancy is discouraged. The American College of Obstetricians and Gynecologists (2015) endorses these Institute guidelines.

However, these recommendations were issued without firm scientific evidence to support them, and their value remains unproven (Rasmussen, 2010). For example, recent studies differ with respect to the effect of insufficient weight gain for obese women. Bodnar and colleagues (2016) reported no greater risk for low-birthweight or small-for-gestational-age newborns among 47,494 obese women who had inadequate weight gain during pregnancy. Bogaerts and associates (2015) found that even weight loss among obese women did not yield poor fetal growth. In contrast, however, Hannaford and coworkers (2017) reported that obese women who gained less than the Institute recommendations were almost three times more likely to deliver a small-for-gestational-age neonate. Another study similarly found an almost twofold greater risk among obese women who lost weight during pregnancy (Cox Bauer, 2016).

Apart from inadequate weight gain, excessive gestational weight gain may portend greater risks for the obese mother. Berggren and coworkers (2016) noted that overweight and obese women accrued maternal fat rather than lean mass with excessive gestational weight gain. From another analysis, overall higher rates of hypertensive disorders, cesarean delivery, and fetal overgrowth as well as lower rates of spontaneous preterm birth and fetal undergrowth were found among women gaining more than recommended (Johnson, 2013). However, when analyzed according to BMI category, significantly higher rates of preeclampsia, cesarean delivery, and fetal overgrowth were identified among the 1937 overweight women, but not for the 1445 obese women, who gained excess weight.

During pregnancy, overweight and obese women gain more weight than recommended compared with normal-weight gravidas (Endres, 2015). Moreover, overweight and obese women have excessive postpartum weight retention at 1 year, and one third retain at least 20 pounds more than their prepregnancy weight.

Dietary Intervention

Several dietary interventions can help limit and achieve the weight-gain targets listed in the previous section. Options include lifestyle interventions and physical activity. In one randomized trial of exercise in 300 overweight women, risks for gestational diabetes were lowered (Wang, 2017). That said, in another trial, 75 overweight women were randomly assigned to routine care or to a 16-week moderate-intensity stationary cycling program starting after midpregnancy. Maternal and neonatal outcomes did not differ between groups (Seneviratne, 2016). Also, a Cochrane database analysis of 11,444 women suggests that lifestyle interventions confer only a modest reduction in maternal weight gain, and their benefits for fetal overgrowth, cesarean delivery rate, and adverse neonatal outcome are not significant (Muktabhant, 2015). Regarding neonatal outcomes, the poor success of lifestyle interventions during pregnancy has been attributed to their late introduction, that is, after early gene expression within the placenta has already been programmed (Catalano, 2015).

Prenatal Care

Close prenatal monitoring detects most early signs of diabetes or hypertension. Standard screening tests for fetal anomalies are sufficient, while remembering the sonographic limitations for fetal anomaly detection in this group. Accurate fetal growth surveillance in obese women usually requires serial sonographic assessment. Antepartum external fetal heart rate monitoring is likewise more difficult.

INTRAPARTUM MANAGEMENT

Obese women are at increased risk for multiple labor or intrapartum complications. These include postterm pregnancy or labor abnormalities (Carpenter, 2016). In one study of 143,519 women, the odds of spontaneous labor at term in obese women was approximately half that of normal-weight women (Denison, 2008). In an analysis of more than 5000 parturients, women with a BMI >30 kg/m^2 had a longer duration of and slower early progression in first-stage labor (Norman, 2012).

Labor Induction

Compared with normal-weight women, obese women are twice as likely to undergo labor induction (Denison, 2008). Unfortunately, obese women are also twice as likely to experience a failed induction, and this risk rises with greater degrees of obesity (Wolfe, 2011). In a retrospective analysis of 470 nulliparous women with a BMI >30 kg/m^2 and an unfavorable cervix, those who underwent labor induction at 39 weeks' gestation were compared with those expectantly managed beyond 39 weeks (Wolfe, 2014). Two thirds of pregnancies expectantly managed either labored or had spontaneously ruptured membranes. Compared with this cohort, those who underwent planned labor induction had an elevated cesarean delivery rate—26 versus 40 percent. Moreover, their newborns were more frequently admitted to the neonatal intensive care unit—6 versus 18 percent. Conversely, Lee and associates (2016) reviewed statistics from 74,725 deliveries in obese women and reported that elective induction at 37 to 39 weeks in nulliparas and especially multiparas was actually associated with a lower cesarean delivery rate. These conflicting results highlight the difficulties faced by obstetrical providers as they contemplate the seemingly competing interests of the fetus and the obese mother. To address this, the Maternal-Fetal Medicine Units Network is conducting a randomized trial of planned labor induction at 39 weeks' gestation in nulliparous women.

Anesthesia Risks

Obese women present anesthesia challenges that include difficult epidural and spinal analgesia placement and complications from failed or difficult intubations. Evaluation of super-morbidly obese gravidas by the anesthesiologist is recommended during prenatal care or upon arrival to the labor unit (American College of Obstetricians and Gynecologists, 2017). Although the rationale for antepartum anesthesia consultation and early epidural analgesia access seems logical, little published data truly demonstrates benefits from these practices (Eley, 2016).

Regional analgesia for morbidly obese women is associated with longer neuraxial procedure times and more failed placement attempts (Tonidandel, 2014). Importantly, however, spinal analgesia in obese women for cesarean delivery does not appear to have benefits over combined spinal-epidural. For example, Ross and colleagues (2014) compared single-shot spinal analgesia with combined spinal-epidural analgesia and found that both methods could be placed with equal expediency and function similarly in morbidly obese patients.

Obese women who undergo regional analgesia that is complicated by relative hypotension more frequently have neonates with umbilical artery cord blood acidemia, probably due to delayed delivery. Edwards and colleagues (2013) studied 5742 obese women and found that pH significantly dropped, and base deficit rose, with increasing BMI. The rate of pH <7.1 doubled from 3.5 percent for a BMI <25 kg/m^2 to 7.1 percent for a BMI ≥40 kg/m^2. Anesthetic risks and complications are discussed in more detail in Chapter 25.

Cesarean Delivery

These rates are significantly greater in obese women. In one study, the primary rate was 33.8 percent for obese and 47.4 percent for morbidly obese women. These values compare strikingly with the rate of only 20.7 percent for normal-weight gravidas (Weiss, 2004). In an analysis of 226,958 women, cesarean delivery rates rose significantly for overweight (34 percent), class I (38 percent), class II (43 percent), and class III (50 percent) obesity (Schummers, 2015). In the same study, rates of gestational diabetes, itself a risk factor for cesarean delivery, increased from 6 percent for women with a BMI <25 kg/m^2 to 21 percent for those with a BMI of ≥40 kg/m^2. More worrisome is that obese women also have higher rates of *emergency* cesarean delivery, and obesity lengthens times for decision-to-incision and for delivery (O'Dwyer, 2013; Pulman, 2015). Girsen and associates (2014) found significantly increased incision-to-delivery times for both emergent and nonemergent cases.

Discussed in Chapter 31 (Prior Uterine Rupture), the incidence of failed trial of labor after cesarean is higher in obese women (Grasch, 2017; Hibbard, 2006). Women who gain weight between pregnancies also have significantly lower rates of vaginal birth after cesarean.

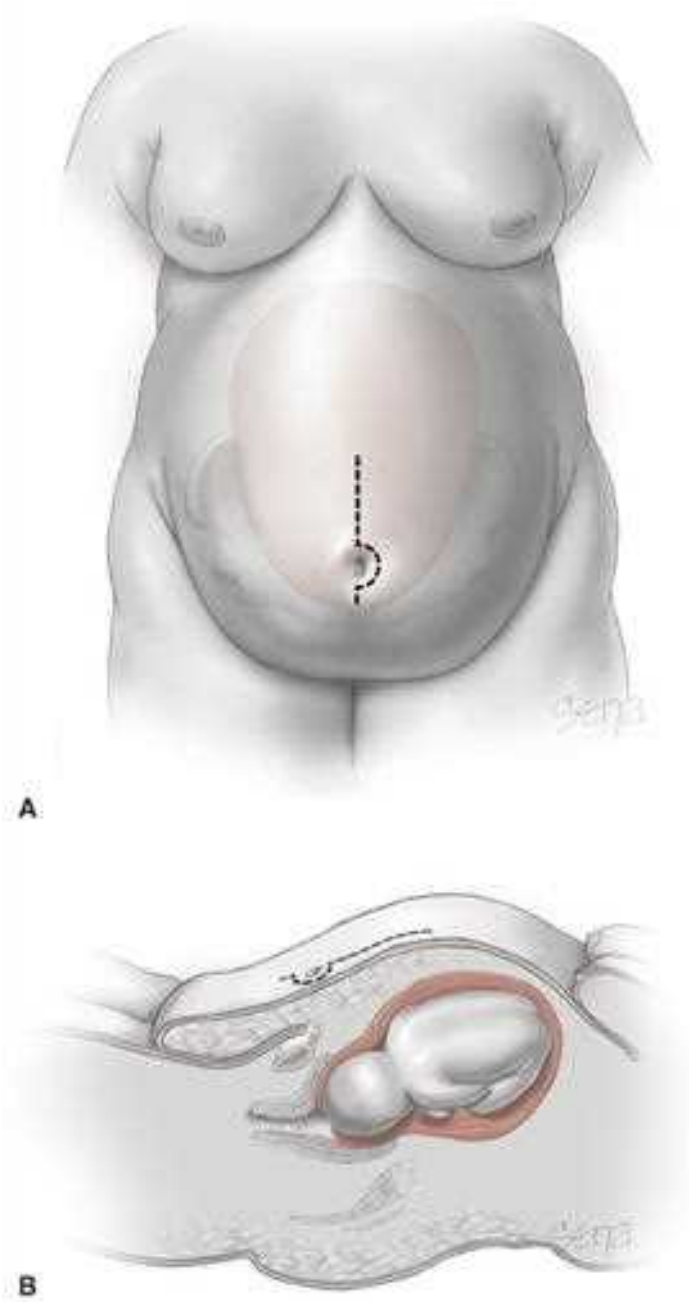
Surgical Concerns

For cesarean delivery, forethought is given to optimal placement and type of abdominal incision to allow access to the fetus and to effect the best wound closure. We prefer a vertical incision in obese women to provide the most direct access (Fig. 48-8). Others prefer a low transverse abdominal incision, with or without rostral taping of the pendulous abdomen. Individual differences in maternal body habitus preclude naming any one approach as superior

(McLean, 2012; Turan, 2016). Some observational studies have compared wound outcomes associated with vertical and transverse skin incisions, but results are conflicting as to a superiority of either (Brocato, 2013; Marrs, 2014; McClean, 2012; Sutton, 2016; Thornburg, 2012).

FIGURE 48-8

Abdominal incision for the obese woman. **A.** Frontal view. The dotted line indicates an appropriate skin incision for abdominal entry relative to the panniculus. As shown by the uterus in the background, selection of this periumbilical site permits access to the lower uterine segment. **B.** Sagittal view.



The frequency of abdominal wound infections is directly related to BMI. Conner and associates (2014) found the risk of wound infection is threefold higher for super-morbidly obese women compared with nonobese women—23 versus 7 percent. Among women with a BMI >45 kg/m^2, wound complication rates range from 14 to 19 percent (Smid, 2015; Stamilio, 2014). Comorbid diabetes apparently raises this risk (Leth, 2011). Other studies describe wound complication rates ranging from 2 to >40 percent in obese women (Conner, 2014; Marrs, 2014; Smid, 2015; Thornburg, 2012).

Several interventions may be preventive. Closure of subcutaneous tissue when at least 2 cm deep reduces wound complication rates (Tipton, 2011). Studies have also examined the use of higher doses of perioperative prophylactic antibiotics. Pharmacokinetic studies indicate that tissue concentrations of prophylactic antibiotics are lower with increasing BMI (Pevzner, 2011; Young, 2015). One prospective study showed that a 3-g dose of cefazolin resulted in higher tissue concentrations compared with a 2-g dose (Swank, 2015). That said, a retrospective analysis of 335 women with a median weight of 310 pounds found that the higher dose of cefazolin did not result in few surgical site infections (Ahmadzia, 2015). In one recent study, obese women

administered perioperative cephalosporin prophylaxis had a surgical infection rate of 13.4 percent compared with a rate of 6.4 percent for those given a 2-day course of oral cephalexin and metronidazole in addition to perioperative prophylaxis (Valent, 2017).

Negative-pressure wound therapy (NPWT) has also been used prophylactically (Mark, 2014). To address this, Hussamy and colleagues (2018) designed a randomized trial of NPWT versus routine dressing in more than 400 obese women undergoing cesarean delivery. Such therapy did not significantly lower the postoperative wound complication rate compared with routine care—19 versus 17 percent, respectively.

To lower thromboembolic complications, graduated compression stockings, hydration, and early mobilization after cesarean delivery in obese women are recommended by the American College of Obstetricians and Gynecologists (2015). Some also recommend "mini-dose" heparin prophylaxis, but we do not routinely use this (Chap. 52, Thromboprophylaxis).

BARIATRIC SURGERY

Several surgical procedures are designed to treat morbid obesity either by diminishing gastric volume—*restrictive*, or by bypassing gastrointestinal absorption—*restrictive malabsorptive*. In nonpregnant patients, these procedures improve or resolve diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea and reduce risks of myocardial infarction and death (Beamish, 2016).

Restrictive Procedures

Of options, the two approved laparoscopic adjustable silicone gastric banding (LASGB) procedures—*LAPBAND* and *REALIZE*—place a band 2 cm below the gastroesophageal junction to create a small stomach pouch above the ring. The ring diameter is controlled by a saline reservoir in the band.

These procedures can have positive effects on pregnancy outcomes. For example, Dixon and colleagues (2005) compared pregnancy outcomes in bariatric surgery patients against their preprocedural outcomes and those of a matched cohort of obese women. Following banding, the incidences of gestational hypertension—10 versus 45 percent—and gestational diabetes—6 versus 15 percent—were significantly lower in the bariatric surgery patients compared with their preprocedural pregnancies. The results from these and other studies are shown in Table 48-3.

TABLE 48-3

Pregnancy Outcomes Following Bariatric Surgery

Outcome[a]	Gastric Banding[b] (n = 651)	Roux-en-Y Gastric Bypass[c] (n = 361)
Hypertension	11%	4%
Gestational diabetes	7%	4%
Cesarean delivery	35%	33%
Mean birthweight	3206 g	3084 g
Low birthweight	7%	11%
Stillbirth	3/1000	3/1000

[a]Data not reported identically—frequencies are approximations.

[b]Data from Adams, 2015; Bar-Zohar, 2006; Carelli, 2011; Dixon, 2005; Ducarme, 2013; Facchiano, 2012; Lapolla, 2010; Pilone, 2014; Sheiner, 2009; Skull, 2004.

[c]Data from Adams, 2015; Ducarme, 2013; Facchiano, 2012; González, 2015; Sheiner, 2009.

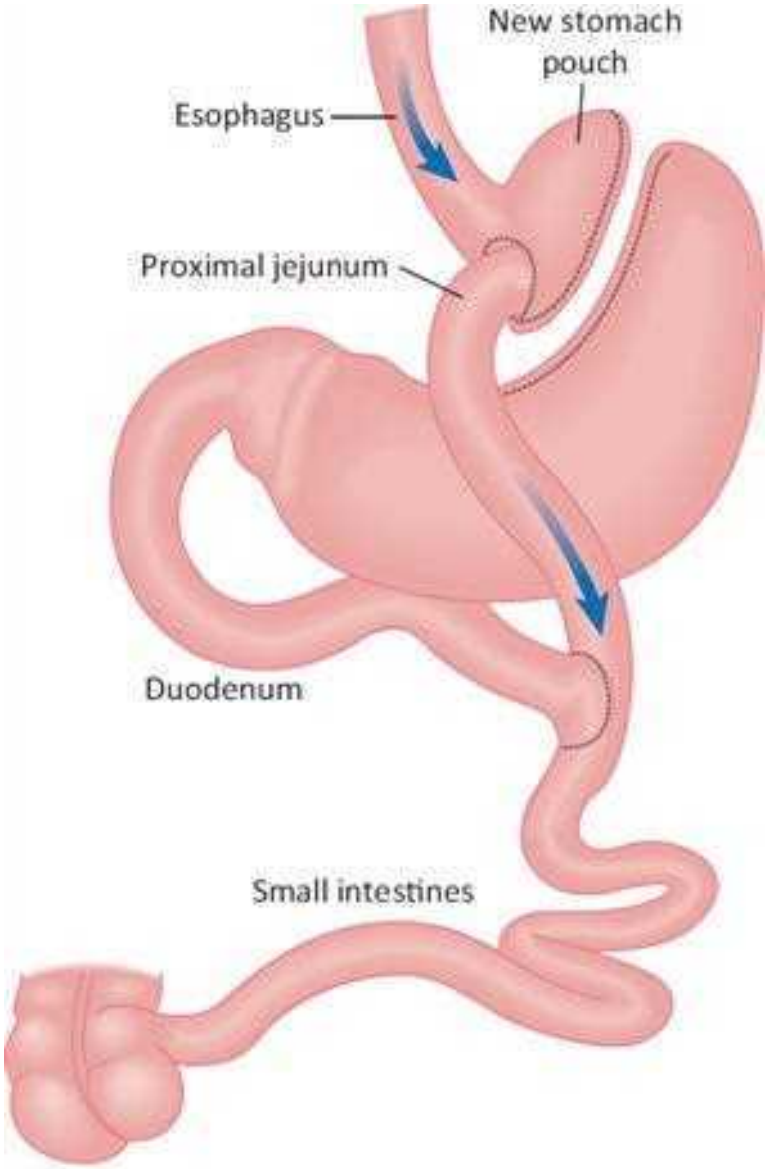
Deflation of the band during pregnancy affects maternal and fetal weight gain. Pilone and coworkers (2014) studied 22 pregnancies after band placement and reported that all women underwent full deflation of the band in the first trimester and gained an average of 14.7 kg during pregnancy. In another study, 42 women underwent deflation of the band, whereas 54 women maintained band inflation. A deflated band was associated with higher mean weight gain—15.4 kg versus 7.6 kg, increased birthweight—3712 versus 3380 g, and a twofold greater risk of macrosomia compared with an inflated one (Cornthwaite, 2015). Rarely, the band may slip from nausea and vomiting, especially with advancing gestation or postpartum (Pilone, 2014; Schmitt, 2016; Suffee, 2012). One fatal fetal cerebral hemorrhage developed from maternal vitamin K deficiency secondary to prolonged vomiting due to band slippage that created a gastric outlet obstruction (Van Mieghem, 2008).

Restrictive Malabsorptive Procedures

The laparoscopically performed *Roux-en-Y gastric bypass* is the most commonly used procedure for gastric restriction and selective malabsorption. Its surgical steps are described in Figure 48-9.

FIGURE 48-9

Roux-en-Y bypass. With this, the proximal stomach is completely transected to leave a 30-mL pouch. The proximal end of the distal jejunum is then connected to the small pouch. This bypasses a large part of the stomach and duodenum. At a site 60 cm distal to this gastrojejunostomy, a Roux-en-Y enteroenterostomy is also completed to allow drainage of secretions from the unused stomach and duodenum.



As with other bariatric procedures, pregnancy outcomes are changed remarkably following Roux-en-Y bypass (Adams, 2015). As shown in Table 48-3, rates of hypertension, gestational diabetes, and fetal macrosomia are reduced. Serious complications are uncommon, however, upper abdominal pain is frequent in pregnancy and often associated with internal herniation, which is protrusion of the bowel through a mesentery defect. Petersen and associates (2017) described outcomes in a birth cohort including 139 pregnancies. Upper abdominal pain complicated 46 percent, and a third of these had internal herniation. The preterm birth rate was 14 of 64 among those with upper abdominal pain versus 1 of 75 in those without pain. Intussusception and small bowel obstruction can develop from internal herniation, and maternal deaths from herniation and obstruction have been reported (Moore, 2004; Renault, 2012). Bowel obstruction is notoriously difficult to diagnose (Vannevel, 2016; Wax, 2013).

Pregnancy

Because of its associated health successes, bariatric surgery is popular, and many women subsequently become pregnant (Narayanan, 2016). From observational studies, fertility rates improve and obstetrical complication rates decline in women after bariatric surgery compared with morbidly obese controls (Kominiarek, 2017; Yi, 2015). In one these studies, despite surgical treatment, almost half of 670 women were still obese at the time of their first pregnancy after bypass (Johansson, 2015). Nevertheless, the frequency of large-for-gestational-age newborns dropped from 22 to 8.6 percent and of

small-for-gestational-age neonates *rose* from 7.6 to 15.6 percent. In a systematic review, Yi and colleagues (2015) confirmed these fetal weight trends after bariatric surgery. Also, risks for diabetes and preeclampsia were reduced.

Currently, the American College of Obstetricians and Gynecologists (2015) recommends that women who have undergone bariatric surgery be assessed for vitamin and nutritional sufficiency. When indicated, vitamins B_{12} and D, folic acid, and calcium supplementation are given. Vitamin A deficiency is also possible (Chagas, 2013). Women with a gastric band should be monitored by their bariatric team during pregnancy because adjustments of the band may be necessary. Finally, special vigilance is appropriate for signs of internal herniation with intestinal obstruction (Stuart, 2017; Wax, 2013).

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CHAPTER 49: Cardiovascular Disorders

Some authorities recommend that women suffering from heart lesions be dissuaded from marriage. This, however, appears to be an extreme view, though, of course, when the lesion is serious and the compensation faulty, the dangers of childbearing should be carefully explained.

—J. Whitridge Williams (1903)

INTRODUCTION

As Williams recognized more than a century ago, pregnancy in those with significant heart disease can be extremely hazardous and may lead to decompensation and death. In an analysis of maternal mortality in the United States between 2011 and 2013, the causes previously responsible for most maternal deaths—hemorrhage, hypertensive disorders, and embolism—continued to show declining rates. In contrast, deaths attributable to cardiovascular diseases were responsible for approximately 26 percent of all pregnancy-related deaths (Creanga, 2017). Cardiovascular diseases also account for significant maternal morbidity and are a prominent reason for obstetrical intensive care unit admissions (Small, 2012).

The rising prevalence of cardiovascular diseases complicating pregnancy is likely multifactorial and includes the higher rates of obesity, hypertension, and diabetes (Klingberg, 2017). Indeed, according to the National Center for Health Statistics, almost half of adults aged 20 and older have at least one risk factor for cardiovascular disease (Fryar, 2012). Another related reason is delayed childbearing. Last, as discussed subsequently (Congenital Heart Disease), an increasing number of women with congenital heart disease are now becoming pregnant.

PHYSIOLOGICAL CONSIDERATIONS IN PREGNANCY

Cardiovascular Physiology

The marked pregnancy-induced anatomical and functional changes in cardiac physiology can have a profound effect on underlying heart disease (Chap. 4, Cardiovascular System). Some of these changes are listed in Table 49-1. Importantly, cardiac output increases approximately 40 percent during pregnancy. Almost half of this total takes place by 8 weeks' gestation and is maximal by midpregnancy (Capeless, 1989). This early rise stems from augmented stroke volume, which results from lowered vascular resistance. Later in pregnancy, resting pulse and stroke volume are even higher because of greater end-diastolic ventricular volume that results from pregnancy hypervolemia. These changes translate to a cardiac output that enlarges across pregnancy to average 40 percent higher at term. These adaptations are even more profound in multifetal pregnancies (Kametas, 2003; Kuleva, 2011). Importantly, intrinsic left ventricular contractility does not change. Thus, normal left ventricular function is maintained during pregnancy. Namely, pregnancy is not characterized by hyperdynamic function or a high cardiac-output state.

TABLE 49-1

Hemodynamic Changes in 10 Normal Pregnant Women at Term Compared with Repeat Values Obtained 12 Weeks Postpartum

Parameter	Change (%)
Cardiac output	+43
Heart rate	+17
Left ventricular stroke work index	+17
Vascular resistance	
Systemic	−21
Pulmonary	−34
Mean arterial pressure	+4
Colloid osmotic pressure	−14

Data from Clark, 1989.

Women with underlying cardiac disease may not always accommodate these changes, and ventricular dysfunction leads to cardiogenic heart failure. A few women with severe cardiac dysfunction can experience evidence of heart failure before midpregnancy. In others, heart failure may develop after 28 weeks' gestation, when pregnancy-induced hypervolemia and cardiac output reach their maximum. In most, however, heart failure develops peripartum, when labor, delivery, and several common obstetrical conditions add undue cardiac burdens. Some of these include preeclampsia, hemorrhage and anemia, and sepsis.

Ventricular Function in Pregnancy

Ventricular volumes and mass accrue to accommodate pregnancy-induced hypervolemia. This is reflected by greater end-systolic and end-diastolic dimensions. At the same time, however, septal thickness and ejection fraction are unchanged. This is because these alterations are accompanied by substantive ventricular remodeling—*plasticity*—which is characterized by eccentric expansion of left-ventricular mass that averages 30 to 35 percent near term. All of these adaptations return to prepregnancy values within a few months postpartum.

Certainly for clinical purposes, ventricular function during pregnancy is normal as estimated by the *Braunwald ventricular function* graph depicted in Figure 4-9. For given filling pressures, there is appropriate cardiac output so that cardiac function during pregnancy is eudynamic. In nonpregnant subjects with a normal heart who sustain a high-output state, the left ventricle undergoes *longitudinal remodeling,* and echocardiographic functional indices of its deformation provide normal values. In pregnancy, there instead appears to be *spherical remodeling,* and these calculated indices that measure longitudinal deformation are depressed. Thus, normal nonpregnant indices are likely inaccurate when used to assess function in pregnant women because they do not take into account the spherical remodeling characteristic of normal pregnancy (Savu, 2012; Stewart, 2016).

Adjusting for these geometrical changes, Melchiorre and coworkers (2016) studied normal cardiac echocardiographic findings in 559 nulliparas at four points during pregnancy and again at 1 year postpartum. At term, significant chamber diastolic dysfunction and impaired myocardial relaxation were evident in approximately 18 and 28 percent of the women studied, respectively. Moreover, a significant proportion of women studied demonstrated a drop in stroke volume index and a tendency toward eccentric remodeling. These findings suggest cardiovascular maladaptation to the increased volume demands in a substantial proportion of apparently normal pregnancies. Of note, significant dyspnea at rest was reported by 7.4 percent of the women at term, most of whom had chamber diastolic dysfunction. Cardiac function and all signs of dyspnea fully recovered at 1 year postpartum.

Cardiac magnetic resonance (MR) imaging increasingly is used to evaluate cardiac structure and function. Stewart and associates (2016) performed cardiac MR imaging studies in 23 women longitudinally across pregnancy and at 12 weeks postpartum. Compared with studies performed at 12 to 16 weeks' gestation, left ventricular mass grew significantly for both normal-weight and overweight women. The calculated geometrical ratio of left ventricular mass to left ventricular end-diastolic volume demonstrated concentric remodeling throughout gestation, which resolved by 12 weeks' postpartum. The right ventricle also remodels (Martin, 2017). Taken together, these observations likely mean that pregnancy causes a mixture of eccentric and concentric ventricular remodeling.

DIAGNOSIS OF HEART DISEASE

The physiological adaptations of normal pregnancy can induce symptoms and alter clinical findings that may confound the diagnosis of heart disease. For example, in normal pregnancy, functional systolic heart murmurs are common, respiratory effort is accentuated, edema frequently accrues in lower extremities after midpregnancy, and fatigue and exercise intolerance often develop. Some systolic flow murmurs can be loud, and normal changes in the various heart sounds depicted in Figure 49-1 may erroneously suggest cardiac disease. In contrast, clinical findings that are more likely to suggest heart disease are listed in Table 49-2.

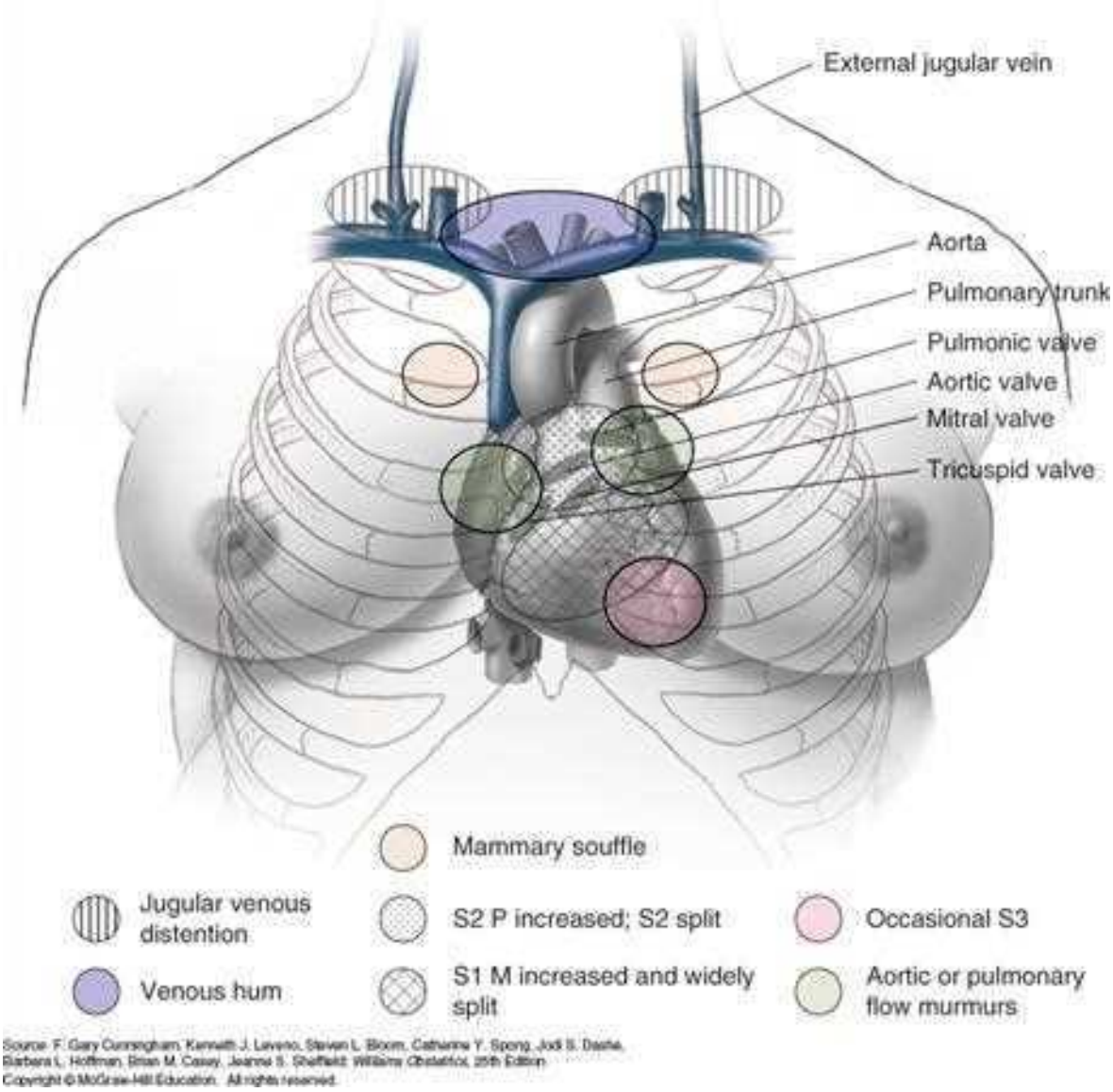
TABLE 49-2

Clinical Indicators of Heart Disease During Pregnancy

Symptoms
Progressive dyspnea or orthopnea
Nocturnal cough
Hemoptysis
Syncope
Chest pain
Clinical Findings
Cyanosis
Clubbing of fingers
Persistent neck vein distention
Systolic murmur grade 3/6 or greater
Diastolic murmur
Cardiomegaly
Persistent tachycardia and/or arrhythmia
Persistent split second sound
Fourth heart sound
Criteria for pulmonary hypertension

FIGURE 49-1

Normal cardiac examination findings in the pregnant woman. S_1 = first sound; M_1 = mitral first sound; S_2 = second sound; P_2 = pulmonary second sound. (Data from Gei, 2001; Hytten, 1991.)

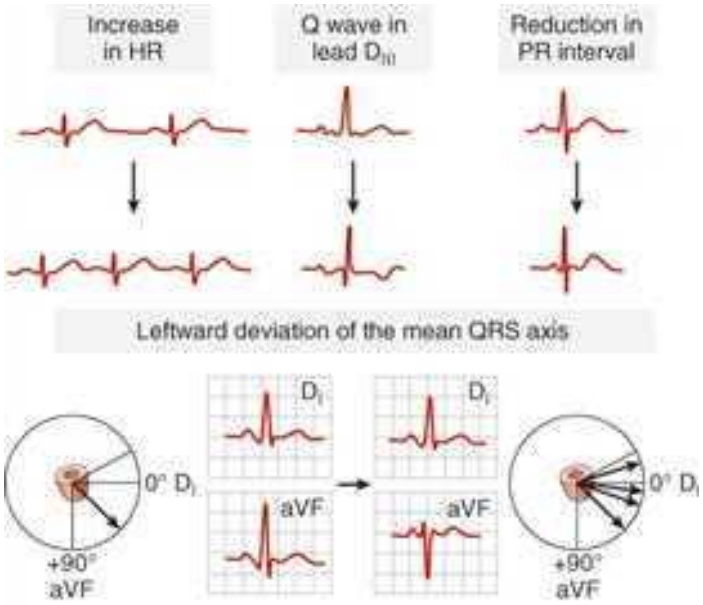


Diagnostic Studies

Noninvasive cardiovascular studies such as electrocardiography, chest radiography, and echocardiography will provide the data necessary for evaluation in most women.

In the *electrocardiogram (ECG)*, an average 15-degree left-axis deviation is found as the diaphragm is elevated in advancing pregnancy. Other findings, depicted in Figure 49-2, include a reduced PR interval, inverted or flattened T waves, and a Q wave in lead D_{III} (Angeli, 2014). Pregnancy does not alter voltage findings. Atrial and ventricular premature contractions are relatively frequent (Carruth, 1981).

FIGURE 49-2
Normal electrocardiograph (ECG) adaptations during pregnancy, including a reduced mean PR interval, increased heart rate, left axis deviation, inverted or flattened T waves and a Q wave in lead D_{III}. (Reproduced with permission from Angeli F, Angeli E, Verdecchia P: Electrocardiographic changes in hypertensive disorders of pregnancy, Hypertens Res. 2014 Nov;37(11):973–975.)



With *radiography*, anteroposterior (AP) and lateral chest radiographs are useful, and when a lead apron shield is used, fetal radiation exposure is minimal. Gross cardiomegaly can usually be excluded, but slight heart enlargement cannot be detected accurately because the heart silhouette normally is larger in pregnancy. This is accentuated further with a portable AP chest radiograph.

Echocardiography is now widely used and permits accurate diagnosis of most heart diseases during pregnancy. Some normal pregnancy-induced changes include a small increase in the dimensions of all cardiac chambers, a slight but significant growth in left ventricular mass, and greater tricuspid and mitral valve regurgitation (Grewal, 2014). Of note, systolic function normally does not change. Savu (2012) and Vitarelli (2011) and their colleagues have provided normal echocardiographic parameters for pregnancy, which are listed in the Appendix (Maternal Echocardiographic Measurements). In some situations, such as complex congenital heart disease, transesophageal echocardiography may be useful.

Cardiovascular MR imaging, compared with echocardiography, is associated with higher reproducibility and is less hindered by ventricular geometry and body habitus. The right ventricle can also be assessed (Nelson, 2017). Ducas and associates (2014) have published normal reference values for pregnancy.

Of other studies, albumin or red cells tagged with technetium-99m are rarely needed during pregnancy to evaluate ventricular function. That said, the estimated fetal radiation exposure from nuclear medicine studies of myocardial perfusion is negligible. It is safe to perform cardiac catheterization with limited fluoroscopy time. During coronary angiography, the mean radiation exposure to the unshielded abdomen is 1.5 mGy, and less than 20 percent of this reaches the fetus (European Society of Cardiology, 2011). Shortening the fluoroscopic time may help to minimize radiation exposure (Raman, 2015; Tuzcu, 2015). In women with clear indications, any minimal theoretical fetal risk is outweighed by maternal benefits (Chap. 46, X-Ray Dosimetry).

Classification of Functional Heart Disease

No clinically applicable test accurately measures functional cardiac capacity. The clinical classification of the New York Heart Association (NYHA) is based on past and present disability and is uninfluenced by physical signs:

Class I. *Uncompromised—no limitation of physical activity:* These women do not have symptoms of cardiac insufficiency or experience anginal pain.

Class II. *Slight limitation of physical activity:* These women are comfortable at rest, but if ordinary physical activity is undertaken, discomfort in the form of excessive fatigue, palpitation, dyspnea, or anginal pain results.

Class III. *Marked limitation of physical activity:* These women are comfortable at rest, but less than ordinary activity causes excessive fatigue, palpitation, dyspnea, or anginal pain.

Class IV. *Severely compromised—inability to perform any physical activity without discomfort*: Symptoms of cardiac insufficiency or angina may develop even at rest. If any physical activity is undertaken, discomfort is increased.

Siu and associates (2001b) expanded the NYHA classification and developed a scoring system for predicting cardiac complications during pregnancy. The system derives from a Canadian prospective analysis of 562 pregnant women with heart disease during 617 pregnancies. Predictors of cardiac complications included: (1) prior heart failure, transient ischemic attack, arrhythmia, or stroke; (2) baseline NYHA class III or IV or cyanosis; (3) left-sided obstruction defined as mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, or peak left ventricular outflow tract gradient >30 mm Hg; and (4) ejection

fraction <40 percent. The risk of pulmonary edema, sustained arrhythmia, stroke, cardiac arrest, or cardiac death was substantially elevated with one of these factors and even more so with two or more. Khairy and colleagues (2006) reported similar findings.

An even more comprehensive risk stratification system is the modified World Health Organization (WHO) Risk Classification of Cardiovascular Disease and Pregnancy (Table 49-3). It is especially useful for assessing maternal risk and for preconceptional counseling. Lu (2015) and Pijuan-Domènech (2015) and their associates in their analyses concluded that the modified WHO classification provides the greatest predictive accuracy for cardiac complications during pregnancy.

TABLE 49-3

World Health Organization (WHO) Risk Classification of Cardiovascular Disease and Pregnancy with Management Recommendations

Risk Category	Associated Conditions
WHO 1—Risk no higher than general population	Uncomplicated, small, or mild: Pulmonary stenosis Ventricular septal defect Patent ductus arteriosus Mitral valve prolapse with no more than trivial mitral regurgitation Successfully repaired simple lesions: Ostium secundum atrial septal defect Ventricular septal defect Patent ductus arteriosus Total anomalous pulmonary venous drainage Isolated ventricular extrasystoles and atrial ectopic beats
• Cardiology consultation once or twice during pregnancy	
WHO 2—Small increase in risk of maternal mortality and morbidity	If otherwise uncomplicated: Unoperated atrial septal defect Repaired Fallot tetralogy Most arrhythmias
• Cardiology consultation each trimester	
WHO 2 or 3—Depends on individual case	Mild left ventricular impairment Hypertrophic cardiomyopathy Native or tissue valvular heart disease not considered WHO 4 Marfan syndrome without aortic dilation Heart transplantation
• Individualized care similar to WHO categories 2 or 3 depending on lesion and disease severity	
WHO 3—Significantly increased risk of maternal mortality or expert cardiac and obstetrical care required	Mechanical valve Systemic right ventricle—congenitally corrected transposition, simple transposition post Mustard or Senning repair Post-Fontan operation Cyanotic heart disease Other complex congenital heart disease
• Care directed by multispecialty team; monthly or bimonthly cardiac and obstetrical monitoring	
WHO 4—Very high risk of maternal mortality or severe morbidity; pregnancy contraindicated and termination discussed	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (NYHA III-IV or LVEF <30%) Previous peripartum cardiomyopathy with any residual impairment of left ventricular function Severe left heart obstruction Marfan syndrome with aorta dilated >40 mm
• Pregnancy contraindicated. • If pregnancy occurs, monthly or bimonthly cardiac and obstetrical monitoring	

Summarized from European Society of Gynecology, 2011; Nanna, 2014; Thorne, 2006; World Health Organization, 2010.

Preconceptional Counseling

Women with severe heart disease will benefit immensely from counseling before pregnancy, and they usually are referred for maternal-fetal medicine or cardiology consultation (Clark, 2012; Seshadri, 2012). Maternal mortality rates generally correlate directly with functional classification, and this relationship may change as pregnancy progresses. From the previously described Canadian study, Siu and colleagues (2001b) observed significant worsening of NYHA class in 4.4 percent of 579 pregnancies in which the baseline class was I or II. As described later, some women have life-threatening cardiac abnormalities that can be reversed by corrective surgery, and subsequent pregnancy becomes less dangerous. In other cases, such as women with mechanical valves taking warfarin, fetal teratogenic concerns predominate. Last, many congenital heart lesions are inherited as polygenic characteristics (Chap. 13, Imprinting). Because of this, some women with congenital heart lesions give birth to similarly affected neonates, and the risk varies widely (Table 49-4).

TABLE 49-4

Risks for Fetal Heart Lesions Related to Affected Family Members

	Congenital Heart Disease in Fetus (%)		
Cardiac Lesion	**Previous Sibling Affected**	**Father Affected**	**Mother Affected**
Marfan syndrome	NS	50	50
Aortic stenosis	2	3	15–18
Pulmonary stenosis	2	2	6–7
Ventricular septal defect	3	2	10–16
Atrial septal defect	2.5	1.5	5–11
Patent ductus arteriosus	3	2.5	4
Coarctation of the aorta	NS	NS	14
Fallot tetralogy	2.5	1.5	2–3

NS = not stated.

Data from Lupton, 2002.

PERIPARTUM MANAGEMENT CONSIDERATIONS

In most instances, management involves a team approach with an obstetrician, cardiologist, anesthesiologist, and other specialists as needed. With complex lesions or other high-risk cases, evaluation by a multidisciplinary team is recommended early in pregnancy. Within this framework, both prognosis and management are influenced by the type and severity of the specific lesion and by the maternal functional classification. In some, pregnancy termination may be advisable.

With rare exceptions, women in NYHA class I and most in class II negotiate pregnancy without morbidity. Special attention is directed toward both prevention and early recognition of heart failure. Of specific risks, infection with sepsis syndrome can precipitate this. Moreover, bacterial endocarditis is a deadly complication of valvular heart disease (Infective Endocarditis). Each woman is instructed to avoid contact with persons who have respiratory infections, including the common cold, and to report at once any evidence for infection. Pneumococcal and influenza vaccines are recommended (Chap. 9, Immunization).

Cigarette smoking is prohibited. Illicit drug use may be particularly harmful, an example being the cardiovascular effects of cocaine or amphetamines. In addition, intravenous drug use raises the risk of infective endocarditis.

Fortunately, women in NYHA class III and IV are uncommon today. In the prior Canadian study, only 3 percent of the approximately 600 pregnancies were complicated by NYHA class III heart disease, and no women had class IV when first seen (Siu, 2001b). If a woman chooses pregnancy, she must understand the risks and is encouraged to be compliant with planned care. In some women, prolonged hospitalization or bed rest is often necessary.

Labor and Delivery

In general, vaginal delivery is preferred, and labor induction is usually safe (Thurman, 2017). From the large Registry on Pregnancy and Cardiac Disease, Ruys and coworkers (2015) compared pregnancy outcomes between 869 women who had a planned vaginal delivery and 393 gravidas who had a planned cesarean delivery. Planned cesarean delivery conferred no advantage for maternal or neonatal outcome.

Cesarean delivery is usually limited to obstetrical indications, and considerations are given for the specific cardiac lesion, overall maternal condition, and availability of experienced anesthesia personnel and hospital capabilities. Some of these women tolerate major surgical procedures poorly and are best delivered in a unit experienced with management of complicated cardiac disease. Occasionally, pulmonary artery catheterization may be needed for hemodynamic monitoring (Chap. 47, Obstetrical Critical Care). In our experiences, however, invasive monitoring is rarely indicated.

Based on her review, Simpson (2012) recommends cesarean delivery for women with the following: (1) dilated aortic root >4 cm or aortic aneurysm; (2) acute severe congestive heart failure; (3) recent myocardial infarction; (4) severe symptomatic aortic stenosis; (5) warfarin administration within 2 weeks of delivery; and (6) need for emergency valve replacement immediately after delivery. Although we agree with most of these, we have some caveats. For example, we prefer aggressive medical stabilization of pulmonary edema followed by vaginal delivery if possible. Also, warfarin anticoagulation can be reversed with vitamin K, plasma, or prothrombin concentrates.

During labor, the mother with significant heart disease should be kept in a semirecumbent position with a lateral tilt. Vital signs are taken frequently between contractions. Increases in pulse rate much above 100 beats per minute (bpm) or respiratory rate above 24 per minute, particularly when associated with dyspnea, may suggest impending ventricular failure. For evidence of cardiac decompensation, intensive medical management must be instituted immediately. Delivery itself does not necessarily improve the maternal condition and, in fact, may worsen it. Moreover, emergency cesarean delivery may be particularly hazardous. Clearly, both maternal and fetal status must be considered in the decision to hasten delivery under these circumstances.

Analgesia and Anesthesia

Relief from pain and from apprehension is important. Although intravenous analgesics provide satisfactory pain relief for some women, continuous epidural analgesia is recommended for most. The major problem with conduction analgesia is maternal hypotension (Chap. 25, Cesarean Delivery). This is especially dangerous in women with intracardiac shunts in whom flow may be reversed. Hypotension can also be life-threatening if there is pulmonary arterial hypertension or aortic stenosis because ventricular output is dependent on adequate preload. In women with these conditions, narcotic regional analgesia or general anesthesia may be preferable.

For vaginal delivery in women with only mild cardiovascular compromise, epidural analgesia given with intravenous sedation often suffices. This has been shown to minimize intrapartum cardiac output fluctuations and allows forceps or vacuum-assisted delivery. Subarachnoid blockade is not generally recommended in women with significant heart disease due to associated hypotension. For cesarean delivery, epidural analgesia is preferred by most clinicians with caveats for its use with pulmonary arterial hypertension (Cardiomyopathies).

Intrapartum Heart Failure

Cardiovascular decompensation during labor may manifest as pulmonary edema with hypoxia or as hypotension, or both. The proper therapeutic approach depends on the specific hemodynamic status and the underlying cardiac lesion. For example, decompensated mitral stenosis with pulmonary edema due to fluid overload is often best treated with aggressive diuresis. If precipitated by tachycardia, heart rate control with β-blocking agents is preferred. Conversely, the same treatment in a woman suffering decompensation and hypotension due to aortic stenosis could prove fatal. Unless the underlying pathophysiology is understood and the cause of the decompensation is clear, empirical therapy may be hazardous.

Puerperium

Women who have shown little or no evidence of cardiac compromise during pregnancy, labor, or delivery may still decompensate postpartum. Fluid mobilized into the intravascular compartment and reduced peripheral vascular resistance place higher demands on myocardial performance. Therefore, meticulous care is continued into the puerperium (Keizer, 2006; Zeeman, 2006). Postpartum hemorrhage, anemia, infection, and thromboembolism are much more serious complications with heart disease. Indeed, these factors often act in concert to precipitate postpartum heart failure. In addition, sepsis and severe preeclampsia cause or worsen pulmonary edema because of endothelial activation and capillary-alveolar leakage (Chap. 47, Acute Pulmonary Edema).

For puerperal tubal sterilization after vaginal delivery, the procedure can be delayed up to several days to ensure that the mother has normalized hemodynamically and that she is afebrile, not anemic, and ambulating normally. Alternatively, for those desiring future fertility, detailed contraceptive advice is available in the *U.S. Medical Eligibility Criteria for Contraceptive Use* guidelines (Curtis, 2016).

SURGICALLY CORRECTED HEART DISEASE

Most clinically significant congenital heart lesions are repaired during childhood. Examples of those frequently not diagnosed until adulthood include atrial septal defects, pulmonic stenosis, bicuspid aortic valve, and aortic coarctation (Brickner, 2014). In some cases, the defect is mild and surgery is not required. In others, a significant anomaly is amenable to corrective surgery, performed ideally before pregnancy. In rare instances, surgical corrections are necessary during pregnancy.

Valve Replacement before Pregnancy

Numerous reports describe subsequent pregnancy outcomes in women who have a prosthetic mitral or aortic valve. The type of valve, either mechanical or biological, is paramount. From one review, the overall estimated maternal mortality rate was 1.2 percent. The rate was 1.8 percent in the mechanical valve subgroup and 0.7 percent in the bioprosthetic subgroup (Lawley, 2015). Using the Registry of Pregnancy and Cardiac Disease, the maternal mortality rate was 1.4 percent in women with a mechanical heart valve and 1.5 percent in women with a tissue heart valve (van Hagen, 2015). Mechanical heart valve thrombosis complicated 4.7 percent. In total, only 58 percent with a mechanical heart valve had a pregnancy free of serious adverse events compared with 79 percent of patients with a tissue heart valve (Table 49-5). Because of thrombosis risks, anticoagulation may be requisite, but its complications are described in the next section. Thus, pregnancy is undertaken only after serious consideration for women with a prosthetic mechanical valve.

TABLE 49-5

Selected Outcomes in Pregnancies Complicated by Heart-Valve Replacement[a]

Outcome	Mechanical Valve (n = 212)	Tissue Valve (n = 134)
Maternal mortality	3 (1.4)	2 (1.5)
Heart failure	162 (7.5)	1 (8.2)
Thrombotic complication	13 (6.1)	1 (0.7)
Hemorrhagic complication	49 (23)	7 (5.1)
Pregnancy loss <24 weeks	33 (15.6)	2 (1.5)
Stillbirth	6 (2.8)	0 (0)
Preterm birth <37 weeks	29 (18)	24 (19)

Data presented as n (%).

[a]Data from the Registry of Pregnancy and Cardiac Disease.

Data from van Hagen, 2015.

Bouhout and coworkers (2014) reported the outcomes of 27 pregnancies in 14 women who underwent an *aortic valve* replacement prior to pregnancy. Seven of the 27 pregnancies occurred in five women with a mechanical prosthesis. Complications in this group included two embolic myocardial infarctions and one each of miscarriage, postpartum hemorrhage, placental abruption, and preterm birth. In the bioprosthetic group, nine miscarriages, two hospitalizations for syncope, and one preterm birth were noted.

Porcine tissue valves are safer during pregnancy, primarily because thrombosis is rare and anticoagulation is not required (see Table 49-5). Despite this, valvular dysfunction with cardiac deterioration poses a serious risk. Another drawback is that bioprostheses are less durable than mechanical ones, and valve replacement longevity averages 10 to 15 years. Cleuziou and colleagues (2010) concluded that pregnancy does not accelerate the risk for replacement. But, Nappi and associates (2014) found an association between pregnancy and valve deterioration in women with cryopreserved mitral homograft valves.

Anticoagulation

This is critical for women with mechanical prosthetic valves. Unfortunately, warfarin is the most effective anticoagulant for preventing maternal thromboembolism but causes harmful fetal effects (Chap. 12, Warfarin). Anticoagulation with heparin is less hazardous for the fetus, however, the risk of maternal thromboembolic complications is much higher (McLintock, 2011).

Warfarin is teratogenic and causes miscarriage, stillbirths, and fetal malformations. In one study of 71 women given warfarin throughout pregnancy, the rates of miscarriage were 32 percent; stillbirth, 7 percent; and embryopathy, 6 percent (Cotrufo, 2002). The risk was highest when the mean daily dose of warfarin exceeded 5 mg. Similarly, the American College of Cardiology and the American Heart Association estimate that the risk of embryopathy is dose dependent, with a lower risk—less than 3 percent—if the dose of warfarin is ≤5 mg/d (Nishimura, 2014). If the dosage is >5 mg/d, the risk of embryopathy exceeds 8 percent.

Anticoagulation for mechanical valves using *low-dose* unfractionated heparin is definitely inadequate and carries a high associated maternal mortality rate (Chan, 2000; Iturbe-Alessio, 1986). Even *full* anticoagulation with either unfractionated heparin (UFH) or one of the low-molecular-weight heparins (LMWH) is associated with valvular thrombosis (Leyh, 2002, 2003; Rowan, 2001). But, compliance with twice-daily dosing and therapeutic monitoring may have contributed (McLintock, 2014). Thus, if full anticoagulation with dose-adjusted UFH or LMWH is used, meticulous monitoring is recommended. The activated partial thromboplastin time (aPTT) should be at least 2 times control or anti-Xa levels should be 0.8 to 1.2 U/mL at 4 to 6 hours postdose (Nishimura, 2014).

Recommendations for Anticoagulation

Several different treatment options—none of which are completely ideal—are principally based on consensus opinion. Two are from the American College of Chest Physicians and the other jointly from the American College of Cardiology and the American Heart Association (Bates, 2012; Nishimura, 2014). Any of four regimens is recommended. First, adjusted-dose LMWH is given twice daily, with a peak anti-Xa level drawn 4 hours after dosing. In another, adjusted UFH is dosed every 12 hours to keep the midinterval aPTT twice control or anti Xa level between 0.35–0.70 U/mL. As a third option, LMWH or UFH is given as just described until 13 weeks, and then warfarin is substituted until near delivery, at which time it is replaced by LMWH or UFH. Last, in women judged to carry a high risk of thrombosis and for whom the efficacy and safety of heparins are concerns, warfarin is suggested throughout pregnancy. Heparin is then substituted close to delivery. In addition, aspirin, 75 to 100 mg, is given daily.

Heparin is discontinued just before delivery. If delivery supervenes while the anticoagulant is still effective, and extensive bleeding is encountered, then protamine sulfate is given intravenously. Anticoagulant therapy with warfarin or heparin may be restarted 6 hours following vaginal delivery, usually with no problems. Following cesarean delivery, full anticoagulation is withheld, but the optimal duration is not exactly known. The American College of Obstetricians and Gynecologists (2017) advises resuming unfractionated or low-molecular-weight heparin 6 to 12 hours after cesarean delivery. It is our practice, however, to wait at least 24 hours following a major surgical procedure.

Because warfarin, LMWH, and UFH do not accumulate in breast milk, they do not induce an anticoagulant effect in the newborn. These anticoagulants are compatible with breastfeeding (American College of Obstetricians and Gynecologists, 2017).

Cardiac Surgery During Pregnancy

Although usually postponed until after delivery, valve replacement or other cardiac surgery during pregnancy may be lifesaving. Several reviews confirm that such surgery is associated with major maternal and fetal morbidity and mortality. At the Mayo Clinic between 1976 and 2009, 21 pregnant women underwent cardiothoracic surgery requiring cardiopulmonary bypass (John, 2011). The procedures included valve replacements, myxoma excisions, aneurysm repairs, patent foramen ovale closure, prosthetic aortic valve thrombectomy, and septal myectomy. Median cardiopulmonary bypass time was 53 minutes, with a range of 16 to 185 minutes. One woman died 2 days after surgery, three fetuses died, and 52 percent were delivered before 36 weeks' gestation. Elassy and associates (2014) described 23 women who underwent urgent open cardiac surgery for severe valve malfunction. Two women and 10 fetuses—all at a gestational age below 28 weeks—died before hospital discharge. Only six fetuses were delivered at term. To optimize outcomes, Chandrasekhar and coworkers (2009) recommend that surgery be elective when possible, pump flow rate should remain >2.5 L/min/m^2, normothermic perfusion pressure should exceed 70 mm Hg, and hematocrit should be kept >28 volumes percent.

Pregnancy after Heart Transplantation

Many successful pregnancies have followed cardiac transplantation (Abdalla, 2014; Vos, 2014). The current recommendations from The International Society of Heart and Lung Transplantation do not discourage pregnancy in stable heart transplant recipients who are more than 1 year posttransplant (Costanzo, 2010). Obviously, a highly specialized level of care with a multidisciplinary team is necessary.

The transplanted heart appears to responds normally to pregnancy-induced alterations (Key, 1989; Kim, 1996). Despite this, complications are common during pregnancy (Dashe, 1998). Of 53 pregnancies in 37 heart recipients, almost half developed hypertension, and 22 percent suffered at least one rejection episode during pregnancy (Armenti, 2002; Miniero, 2004). They were delivered—usually by cesarean—at a mean of 37 to 38 weeks' gestation. Three fourths of neonates were liveborn. At follow-up, at least five women had died more than 2 years postpartum. Another analysis of 25 such women with 42 pregnancies found no maternal deaths. Major complications included two rejections during the early puerperium, two cases of renal failure, and 11 spontaneous abortions (Estensen, 2011). Five women died 2 to 12 years after delivery. And from the United Kingdom, Mohamed-Ahmed and colleagues (2014) identified 14 women with transplants between 2007 and 2011. Graft rejections occurred in two women, one of whom died.

VALVULAR HEART DISEASE

Rheumatic fever is uncommon in the United States because of less crowded living conditions, penicillin availability, and evolution of nonrheumatogenic streptococcal strains. Still, it remains the chief cause of serious mitral valvular disease in women of childbearing age in the nonindustrialized world (Nanna, 2014; Roeder, 2011).

Mitral Stenosis

Rheumatic endocarditis causes most mitral stenosis lesions. The normal mitral valve surface area is 4.0 cm^2, and when stenosis narrows this to <2.5 cm^2, symptoms usually develop (Desai, 2000). The contracted valve impedes blood flow from the left atrium to the ventricle.

With more severe stenosis, the left atrium dilates, left atrial pressure is chronically elevated, and significant passive pulmonary hypertension develops (Table 49-6). These women have a relatively fixed cardiac output, and thus the increased preload of normal pregnancy and other factors that raise cardiac output may cause ventricular failure and pulmonary edema. Indeed, a fourth of women with mitral stenosis have cardiac failure for the first time during pregnancy (Caulin-Glaser, 1999). The resulting pulmonary venous hypertension and pulmonary edema create symptoms of dyspnea, fatigue, palpitations, cough, and hemoptysis. The classic murmur may not be heard in some women, and this clinical picture at term may be confused with idiopathic peripartum cardiomyopathy (Cunningham, 1986, 2012).

TABLE 49-6

Major Cardiac Valve Disorders

Type	Cause	Pathophysiology	Pregnancy
Mitral stenosis	Rheumatic valvulitis	LA dilation and passive pulmonary hypertension Atrial fibrillation	Heart failure from fluid overload, tachycardia
Mitral insufficiency	Rheumatic valvulitis Mitral valve prolapse LV dilation	LV dilation and eccentric hypertrophy	Ventricular function improves with afterload decrease
Aortic stenosis	Congenital bicuspid valve	LV concentric hypertrophy, decreased cardiac output	Moderate stenosis is tolerated; severe is life-threatening with decreased preload, e.g., obstetrical hemorrhage or regional analgesia
Aortic insufficiency	Rheumatic valvulitis Connective tissue disease Congenital	LV hypertrophy and dilation	Ventricular function improves with afterload decrease
Pulmonary stenosis	Rheumatic valvulitis Congenital	Severe stenosis associated with RA and RV enlargement	Mild stenosis usually well tolerated; severe stenosis associated with right heart failure and atrial arrhythmias

LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Also with significant stenosis, tachycardia shortens ventricular diastolic filling time and elevates the mitral gradient. This too may lead to pulmonary edema. Thus, sinus tachycardia is often treated prophylactically with β-blocking agents. Atrial tachyarrhythmias, including fibrillation, are common in mitral stenosis and are treated aggressively. Atrial fibrillation also predisposes to mural thrombus formation and cerebrovascular embolization that can cause stroke (Chap. 60, Ischemic Stroke). Atrial thrombosis can develop despite a sinus rhythm (Hameed, 2005).

Pregnancy Outcomes

In general, complications are directly associated with the degree of valvular stenosis. Women with a mitral-valve area <2 cm^2 are at greatest risk (Siu, 2001b). In one study of 46 gravidas with mitral stenosis, 43 percent developed heart failure, and 20 percent developed arrhythmias (Hameed, 2001). Fetal-growth restriction was more common in women with a mitral valve area <1.0 cm^2.

Prognosis is also related to maternal functional capacity. Among 486 pregnancies complicated by rheumatic heart disease—predominantly mitral stenosis—8 of 10 maternal deaths were in women in NYHA classes III or IV (Sawhney, 2003).

Management

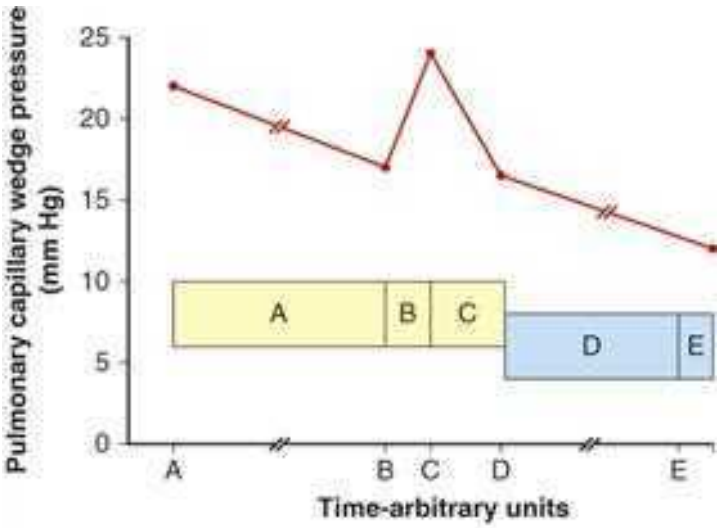
Limited physical activity is generally recommended in women with mitral stenosis. If symptoms of pulmonary congestion develop, activity is further reduced, dietary sodium is restricted, and diuretics are given (Siva, 2005). Also, β-blocker drug therapy slows the ventricular response to activity. If new-onset atrial fibrillation develops, intravenous verapamil, 5 to 10 mg, is given, or electrocardioversion is performed. For chronic fibrillation, digoxin, a β-blocker, or a calcium-channel blocker can slow ventricular response. Therapeutic anticoagulation is indicated with persistent fibrillation, left atrial thrombus, and/or a history of embolism (Nanna, 2014).

Surgical intervention is considered for women with symptomatic severe mitral stenosis and in those with lesser degrees of mitral stenosis—mitral-valve area 1.5 to 2.0 cm^2—complicated by recurrent systemic embolization or severe pulmonary hypertension. Balloon valvuloplasty is preferred if the valve is pliable (Bui, 2014). In one review of 71 pregnant women with tight mitral stenosis and heart failure who underwent percutaneous valvuloplasty, 98 percent were either NYHA class I or II at delivery (Esteves, 2006). At a mean of 44 months, the total event-free maternal survival rate was 54 percent. However, eight women required another surgical intervention. All of the 66 newborns who were delivered at term had normal growth and development.

Labor and delivery are particularly stressful for women with symptomatic mitral stenosis (Fig. 49-3). Uterine contractions increase cardiac output by increasing circulating blood volume. Pain, exertion, and anxiety cause tachycardia with possible rate-related heart failure. Epidural analgesia for labor is ideal, but fluid overload is avoided. Abrupt expansion in preload may raise pulmonary capillary wedge pressure and cause pulmonary edema. Wedge pressures rise immediately postpartum. One hypothesis for this suggests that the loss of the low-resistance placental circulation couples with venous "autotransfusion" from a now-empty, contracted uterus and from the lower extremities and pelvis (Clark, 1985).

FIGURE 49-3

Mean pulmonary capillary wedge pressure measurements (*red graph line*) in eight women with mitral valve stenosis. Shaded yellow and blue boxes are mean (± 1 SD) pressures in nonlaboring normal women at term. **A.** First-stage labor. **B.** Second-stage labor 15 to 30 minutes before delivery. **C.** Postpartum 5 to 15 minutes. **D.** Postpartum 4 to 6 hours. **E.** Postpartum 18 to 24 hours. (Data from Clark, 1985, 1989.)



Most prefer vaginal delivery in women with mitral stenosis. Elective induction is reasonable so that labor and delivery are attended by a scheduled, experienced team. With severe stenosis and chronic heart failure, insertion of a pulmonary artery catheter may help guide management.

Mitral Insufficiency

A trivial degree of mitral insufficiency is found in most normal patients. But if mitral valve leaflets align improperly during systole, abnormal degrees of mitral regurgitation can develop. This is eventually followed by left ventricular dilation and eccentric hypertrophy (see Table 49-6). *Acute mitral insufficiency* is caused by chordae tendineae rupture, papillary muscle infarction, or leaflet perforation from infective endocarditis. *Chronic mitral regurgitation*, in contrast, may derive from rheumatic fever, connective tissue diseases, mitral valve prolapse, or left ventricular dilation of any etiology—for example, dilated cardiomyopathy. Less common causes include a calcified mitral annulus, possibly some appetite suppressants, and in older women, ischemic heart disease. Mitral valve vegetations—*Libman-Sacks endocarditis*—are relatively common in women with antiphospholipid antibodies (Shroff, 2012). These sometimes coexist with systemic lupus erythematosus.

In nonpregnant patients, symptoms from mitral valve insufficiency are rare, and valve replacement is seldom indicated unless infective endocarditis develops. During pregnancy, mitral regurgitation is similarly well tolerated, probably because the lowered systemic vascular resistance yields less regurgitation. Heart failure rarely develops during pregnancy, and occasionally tachyarrhythmias or severely depressed systolic function require treatment.

Mitral Valve Prolapse

This diagnosis implies the presence of a pathological connective tissue disorder—often termed *myxomatous degeneration*—which may involve the valve leaflets themselves, the annulus, or the chordae tendineae. Mitral insufficiency may develop. Most women with mitral valve prolapse are asymptomatic and are diagnosed during routine examination or echocardiography. The few women with symptoms have anxiety, palpitations, atypical chest pain, dyspnea with exertion, and syncope (Guy, 2012).

Pregnant women with mitral valve prolapse rarely have cardiac complications. Hypervolemia may even improve alignment of the mitral valve, and women without pathological myxomatous degeneration generally have excellent pregnancy outcomes (Leśniak-Sobelga, 2004). For women who are symptomatic, β-blocking drugs diminish sympathetic tone, relieve chest pain and palpitations, and reduce the risk of life-threatening arrhythmias.

Aortic Stenosis

Usually a disease of aging, aortic stenosis in younger women is most likely a congenital lesion. Since the decline in rheumatic disease incidence, aortic stenosis is less common, and the most frequent cause in the United States is a bicuspid valve (Friedman, 2008). A normal aortic valve has an area of 3 to 4 cm^2, with a pressure gradient <5 mm Hg. If the valve area is <1 cm^2, there is severe obstruction to flow and a progressive pressure overload on the left ventricle (Roeder, 2011). Concentric left ventricular hypertrophy follows, and if it is severe, end-diastolic pressures become elevated, ejection fraction declines, and cardiac output is reduced (see Table 49-6). Characteristic manifestations develop late and include chest pain, syncope, heart failure, and sudden death from arrhythmias. Life expectancy averages only 5 years after exertional chest pain develops, and valve replacement is indicated for symptomatic patients.

Pregnancy

Clinically significant aortic stenosis is infrequent during pregnancy. Mild-to-moderate degrees of stenosis are well tolerated, however, severe disease is life-threatening. The principal underlying hemodynamic problem is the fixed cardiac output associated with severe stenosis. During pregnancy, several common events acutely lower preload further and thus aggravate the fixed cardiac output. These include vena caval occlusion from the gravid uterus, regional analgesia, and hemorrhage. Importantly, these also decrease cardiac, cerebral, and uterine perfusion. It follows that severe aortic stenosis may be extremely dangerous during pregnancy. From the earlier-cited Canadian study, complication rates were higher if the aortic valve area measured <1.5 cm^2 (Siu, 2001b). And in the report by Hameed and associates (2001), the maternal mortality rate with aortic stenosis was 8 percent. Women with valve pressure gradients >100 mm Hg appear to be at greatest risk.

Management

For asymptomatic women with aortic stenosis, no treatment except close observation is required. Management of a symptomatic woman includes strict limitation of activity and prompt treatment of infections. If symptoms persist despite bed rest, surgical intervention may be considered. Catheter-based valvuloplasty is associated with risks to both the mother and fetus and is not very effective in the long term (Pessel, 2014; Reich, 2004). The aortic valve can again narrow or new aortic regurgitation may develop. The alternative surgical approach—valve replacement—is associated with significant risk of fetal demise due to the effects of cardiac bypass (Datt, 2010). Accordingly, the American College of Cardiology, the American Heart Association, and the European Society of Cardiology recommend delaying conception until after surgical correction for severe aortic stenosis (Bonow, 2008).

For women with critical aortic stenosis, intensive monitoring during labor is essential. Pulmonary artery catheterization may be helpful because of the narrow margin separating fluid overload from hypovolemia. Women with aortic stenosis are dependent on adequate end-diastolic ventricular filling pressures to maintain cardiac output and systemic perfusion. Abrupt drops in end-diastolic volume may result in hypotension, syncope, myocardial infarction, and sudden death. Thus, avoiding diminished ventricular preload and maintaining cardiac output are key. During labor and delivery, affected women are best managed on the “wet” side. This provides a margin of safety in intravascular volume in anticipation of possible hemorrhage. In women with a competent mitral valve, pulmonary edema is rare.

During labor, narcotic epidural analgesia seems ideal and avoids potentially hazardous hypotension. Easterling and coworkers (1988) studied the effects of epidural analgesia in five women with severe stenosis and demonstrated immediate and profound effects from decreased filling pressures. Xia and associates (2006) emphasize slow administration of dilute local anesthetic agents into the epidural space. In hemodynamically stable women, forceps or vacuum delivery is used for standard obstetrical indications.

Aortic Insufficiency

Aortic valve regurgitation or insufficiency allows diastolic flow of blood from the aorta back into the left ventricle. Frequent causes of abnormal insufficiency are rheumatic fever, connective tissue abnormalities, and congenital lesions. With Marfan syndrome, the aortic root may dilate and create regurgitation (Diseases of the Aorta). Acute insufficiency may also develop with bacterial endocarditis or aortic dissection (Infective Endocarditis and Diseases of the Aorta). Last, aortic and mitral valve insufficiency have both been linked to the appetite suppressants fenfluramine and dexfenfluramine and to the ergot-derived dopamine agonists cabergoline and pergolide (Gardin, 2000; Schade, 2007; Zanettini, 2007). With chronic insufficiency, left ventricular hypertrophy and dilation develop and are followed by slow-onset fatigue, dyspnea, and pulmonary edema, although rapid deterioration usually follows (see Table 49-6).

Aortic insufficiency is generally well tolerated during pregnancy. Like mitral valve insufficiency, diminished vascular resistance is thought to improve hemodynamic function. If symptoms of heart failure develop, diuretics are given and bed rest is encouraged.

Pulmonic Stenosis

This lesion is usually congenital and also may be associated with Fallot tetralogy or Noonan syndrome. The greater hemodynamic burden of pregnancy can precipitate right-sided heart failure or atrial arrhythmias in women with severe stenosis. Surgical correction ideally is done before pregnancy, but if symptoms progress, a balloon valvuloplasty may be necessary antepartum (Galal, 2015; Siu, 2001a).

In studying pregnancy outcomes, Drenthen and colleagues (2006) found infrequent cardiac complications in a group of 81 pregnancies in 51 Dutch women with pulmonic stenosis. The NYHA classification worsened in two women, and nine experienced palpitations or arrhythmias. No changes in pulmonary valvular function or other adverse cardiac events were reported. However, noncardiac complication rates were significant—17 percent had preterm delivery, 15 percent had hypertension, and 4 percent developed thromboembolism.

CONGENITAL HEART DISEASE

The incidence of congenital heart disease in the United States approximates 11 per 1000 liveborn neonates (Egbe, 2014). With modern surgeries, approximately 90 percent of those born with congenital heart disease survive to childbearing age, and it is now the most common type of heart disease encountered during pregnancy (Brickner, 2014; Lindley, 2015). Specifically, analysis from the United States Nationwide Inpatient Sample database shows a linear rise in the prevalence of congenital heart disease between 2000 and 2010—from 6.4 to 9.0 per 10,000 women admitted for delivery (Thompson, 2015).

Of pregnancy outcomes in women with congenital heart disease compared with those without, the odds of cardiovascular and obstetrical complications were 10.5 to 35.5 and 1.2 to 2.1 times higher, respectively (Thompson, 2015). Moreover, maternal mortality rates were greater for women with congenital heart disease than for unaffected gravidas—17.8 and 0.7 per 10,000 deliveries, respectively. Opotowsky and coworkers (2012) reported similar risks.

Atrial Septal Defects

Approximately one fourth of all adults has a patent foramen ovale (Miller, 2015). Most atrial septal defects (ASDs) are asymptomatic until the third or fourth decade. The secundum-type defect accounts for 70 percent, and associated mitral valve myxomatous abnormalities with prolapse are common. Most recommend repair if ASD is discovered in adulthood. Pregnancy is well tolerated unless pulmonary hypertension has developed, but this is uncommon (Geva, 2014). Treatment of ASD during pregnancy is indicated for congestive heart failure or an arrhythmia. Based on their review, Aliaga and colleagues (2003) concluded that the risk of endocarditis with an ASD is negligible.

With the potential to shunt blood from right to left, a *paradoxical embolism,* that is, entry of a venous thrombus through the septal defect and into the systemic arterial circulation, is possible and may cause an embolic stroke (Erkut, 2006; Miller, 2015). In asymptomatic women with ASD, thromboembolism prophylaxis is problematic, and the heterogeneous recommendations have been summarized by Kizer and Devereux (2005). Compression stockings and prophylactic heparin have also been recommended for a pregnant woman with an ASD who is immobile or has another risk factor for thromboembolism (Head, 2005).

Ventricular Septal Defects

These lesions close spontaneously during childhood in 90 percent of cases. Most defects are paramembranous, and the degree of left-to-right shunt and associated physiological derangements are related to lesion size. In general, if the defect measures <1.25 cm^2, pulmonary hypertension and heart failure do not develop. If the effective defect size exceeds that of the aortic valve orifice, symptoms rapidly develop. For these reasons, most children undergo surgical repair before pulmonary hypertension develops. Adults with unrepaired large defects develop left ventricular failure and pulmonary hypertension and have a high incidence of bacterial endocarditis (Brickner, 2000, 2014).

Pregnancy is well tolerated with small-to-moderate sized shunts. If pulmonary arterial pressures reach systemic levels, however, there is reversal or bidirectional flow—*Eisenmenger syndrome* (Pulmonary Hypertension). When this develops, the maternal and fetal mortality rates are significantly higher,

and thus, pregnancy is not generally advisable. Bacterial endocarditis is more common with unrepaired defects, and antimicrobial prophylaxis is often required (Infective Endocarditis). As shown in Table 49-4, 10 to 16 percent of offspring born to these women also have a ventricular septal defect.

Atrioventricular Septal Defects

These account for approximately 3 percent of all congenital cardiac malformations and are distinct from isolated atrial or ventricular septal defects. An atrioventricular (AV) septal defect is characterized by a common, ovoid AV junction. This defect is associated with aneuploidy, Eisenmenger syndrome, and other malformations (Altin, 2015). Compared with simple septal defects, complications are more frequent during pregnancy. In a review of 48 pregnancies in 29 affected women, complications included persistent deterioration of NYHA class in 23 percent, significant arrhythmias in 19 percent, and heart failure in 2 percent (Drenthen, 2005b). Congenital heart disease was identified in 15 percent of the offspring.

Persistent (Patent) Ductus Arteriosus

The ductus connects the proximal left pulmonary artery to the descending aorta just distal to the left subclavian artery. Functional closure of the ductus from vasoconstriction occurs shortly after term birth. The physiological consequences with its persistence are related to its size. Most significant lesions are repaired in childhood, but for individuals who do not undergo repair, the mortality rate is high after the fifth decade (Brickner, 2014). In some younger women with an unrepaired ductus during pregnancy, however, pulmonary hypertension, heart failure, or cyanosis will develop if systemic blood pressure falls and leads to shunt reversal of blood from the pulmonary artery into the aorta (Vashisht, 2015). A sudden blood pressure decline at delivery—such as with regional analgesia or hemorrhage—may lead to fatal collapse. Accordingly, hypotension is ideally avoided but treated vigorously if it develops. Prophylaxis for bacterial endocarditis is indicated at delivery for unrepaired defects (Infective Endocarditis). As shown in Table 49-4, the incidence of inheritance approximates 4 percent.

Cyanotic Heart Disease

When congenital heart lesions produce right-to-left shunting of blood past the pulmonary capillary bed, cyanosis develops. The classic and most commonly encountered lesion in adults and during pregnancy is the *Fallot tetralogy* (Lindley, 2015). This is characterized by a large ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy, and an overriding aorta that receives blood from both the right and left ventricles. The magnitude of the shunt varies inversely with systemic vascular resistance. Hence, during pregnancy, when peripheral resistance declines, the shunt increases and cyanosis worsens.

Generally, women with cyanotic heart disease do poorly during pregnancy. With uncorrected Fallot tetralogy, maternal mortality rates approach 10 percent. There is a relationship between chronic hypoxemia, polycythemia, and pregnancy outcomes such as miscarriage and perinatal morbidity. When hypoxemia is intense enough to stimulate a rise in hematocrit above 65 volumes percent, pregnancy wastage is virtually 100 percent.

Although not all cyanotic lesions are repairable, with satisfactory surgical correction before pregnancy, maternal and fetal outcomes are much improved. In a review of 197 pregnancies in 99 women with surgically corrected Fallot tetralogy, pregnancy was usually well tolerated, and no mothers died. Still, almost 9 percent of pregnancies were complicated by adverse cardiac events including new-onset or worsening arrhythmias and heart failure (Balci, 2011; Kamiya, 2012). For women with a pulmonary valve replacement, pregnancy does not adversely affect graft function (Oosterhof, 2006). Prior to or after conception, women with Fallot tetralogy are offered genetic counseling and evaluation for 22q11 deletion syndrome (Lindley, 2015).

Some women with *Ebstein anomaly,* characterized by a malpositioned and malformed tricuspid valve, may reach reproductive age. Right ventricular failure from volume overload and cyanosis are common during pregnancy. In the absence of cyanosis, heart failure, or significant arrhythmias, affected women usually tolerate pregnancy well (Brickner, 2014).

Pregnancy after Surgical Repair

Transposition of the Great Vessels

Pregnancy following surgical correction of transposition has prominent risks. Canobbio (2006) and Drenthen (2005a), each with their colleagues, described outcomes of 119 pregnancies in 68 women—90 percent had a prior Mustard procedure and 10 percent a previous Senning procedure. During pregnancy, one fourth had arrhythmias, 12 percent developed heart failure, and one subsequently required cardiac transplantation. One woman died suddenly a month after delivery, and another died 4 years later. A third of the newborns were delivered preterm. In another report of 60 pregnancies in 34 women who had undergone transposition repair, approximately a fourth ended in miscarriage or abortion, and another fourth delivered preterm (Trigas, 2014). Deterioration in functional class occurred in seven women, and documented deterioration in systolic function occurred in four women. Finally, two women required resuscitation during delivery, and one experienced supraventricular tachycardia during labor. Of other defects, in women with previously repaired *truncus arteriosus* and *double-outlet right ventricle,* successful—although eventful—pregnancies have also been described (Drenthen, 2008; Hoendermis, 2008).

Single Functional Ventricle

With *hypoplastic left heart syndrome,* almost 70 percent of affected women are now expected to survive into adulthood and frequently become pregnant (Feinstein, 2012). Those who have undergone a *Fontan repair* are at particularly high risk for complications. In brief, this procedure involves diverting blood via a surgical anastomosis from the vena cava to the pulmonary artery without passing through the right ventricle. Blood flows passively to the pulmonary vasculature. Thus, patients with a Fontan palliation are very preload dependent (Lindley, 2015).

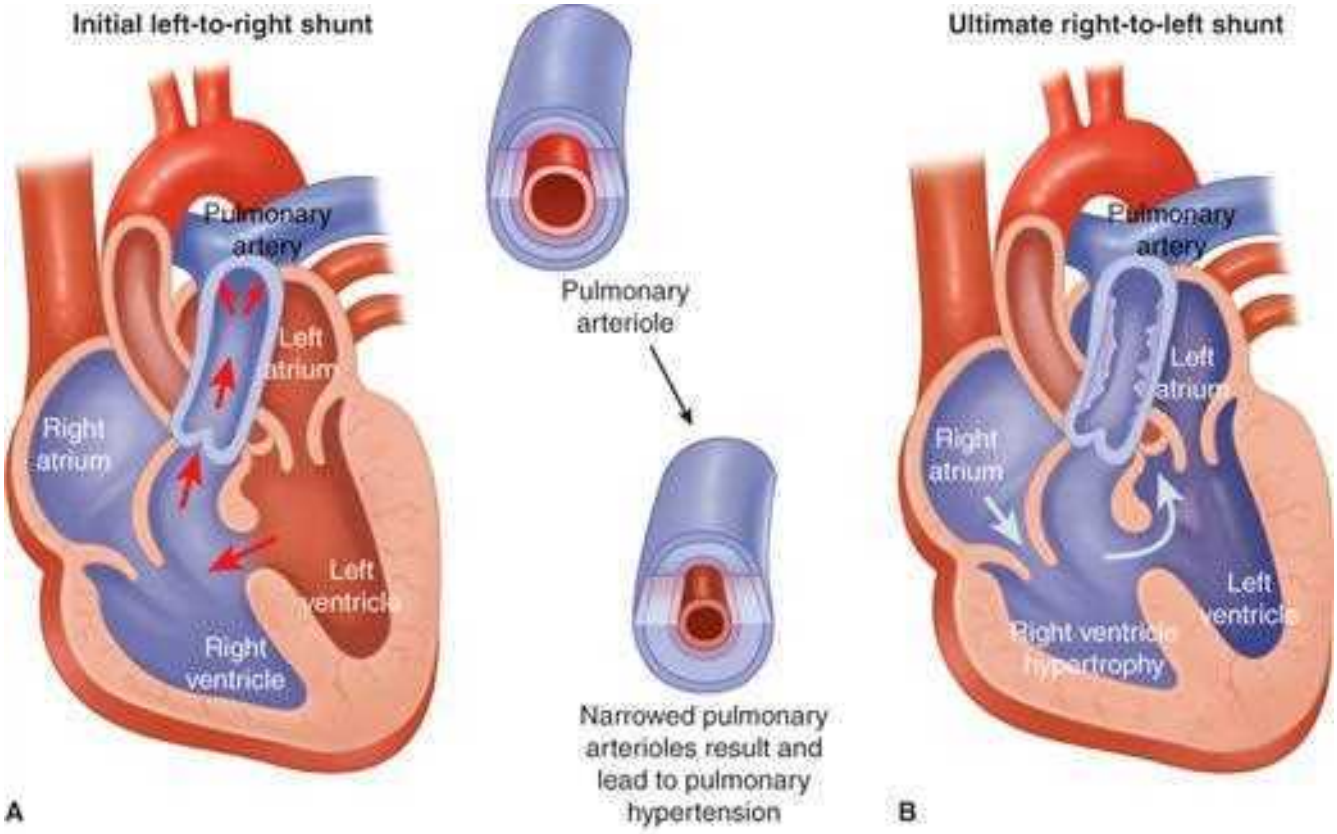
Of outcomes, one review of 14 women conceiving after a Fontan repair found that six spontaneously aborted all pregnancies, and eight others carried 14 pregnancies to viability (Cauldwell, 2016). Cardiac complications included arrhythmias and thromboembolism. Ten newborns delivered preterm, and eight neonates were small for gestational age. Similar complications attend a maternal systemic right ventricle, that is, one in which the right ventricle rather than the left pumps blood to the systemic circulation (Khan, 2015).

Eisenmenger Syndrome

This describes secondary pulmonary hypertension that arises from any cardiac lesion. The syndrome develops when pulmonary vascular resistance exceeds systemic resistance and leads to concomitant right-to-left shunting. The most common underlying defects are atrial or ventricular septal defects and persistent ductus arteriosus (Fig. 49-4). Patients are asymptomatic for years, but eventually pulmonary hypertension becomes severe enough to cause this shunting (Greutmann, 2015).

FIGURE 49-4

Eisenmenger syndrome due to a ventricular septal defect (VSD). **A.** Substantial left-to-right shunting through the VSD leads to morphological changes in the smaller pulmonary arteries and arterioles. Specifically, medial hypertrophy, intimal cellular proliferations, and fibrosis lead to narrowing or closure of the vessel lumen. These vascular changes create pulmonary hypertension and a resultant reversal of the intracardiac shunt **(B)**. With sustained pulmonary hypertension, extensive atherosclerosis and calcification often develop in the large pulmonary arteries. Although a VSD is shown here, Eisenmenger syndrome may also develop in association with a large atrial septal defect or patent ductus arteriosus.



Pregnant women with Eisenmenger syndrome tolerate hypotension poorly, and death usually is caused by right ventricular failure with cardiogenic shock. In a review of 44 cases through 1978, maternal and perinatal mortality rates approximated 50 percent (Gleicher, 1979). In a later review of 73 pregnancies, Weiss and associates (1998) cited a 36-percent maternal death rate. Three of 26 deaths were antepartum, and the remainder of women died intrapartum or within a month of delivery. In a subsequent study of 13 gravidas, one mother died 17 days after delivery, and there were five perinatal deaths (Wang, 2011). *Given such poor outcomes for both mother and fetus, Eisenmenger syndrome is considered to be an absolute contraindication to pregnancy* (Brickner, 2014; Lindley, 2015; Meng, 2017; Warnes, 2015). Management of those who do become pregnant has recently been detailed by Broberg (2016) and is discussed in the next section.

PULMONARY HYPERTENSION

Normal resting mean pulmonary artery pressure is 12 to 16 mm Hg. Pulmonary vascular resistance in late pregnancy approximates 80 dyne/sec/cm^{-5}, which is 34-percent less than the nonpregnant value of 120 dyne/sec/cm^{-5} (Clark, 1989). *Pulmonary hypertension* is defined in nonpregnant individuals as a resting mean pulmonary pressure >25 mm Hg.

The current clinical classification system, shown in Table 49-7, includes five groups of disorders that cause pulmonary hypertension (Galiè, 2016). There are important prognostic and therapeutic distinctions between group 1 pulmonary arterial hypertension and the other groups. Group 1 indicates that a specific disease affects pulmonary arterioles. It includes idiopathic or primary pulmonary arterial hypertension as well as those cases secondary to a known cause such as connective tissue disease. For example, approximately one third of women with scleroderma and 10 percent with systemic lupus erythematosus have pulmonary hypertension (Rich, 2005). Other causes in young women are human immunodeficiency virus (HIV) infection, sickle-cell disease, and thyrotoxicosis (Newman, 2015; Sheffield, 2004).

TABLE 49-7

Comprehensive Clinical Classification of Pulmonary Hypertension

1. **Pulmonary arterial hypertension**
   - Idiopathic
   - Heritable
   - Drug and toxin induced
   - Associated with connective tissue disease, HIV infections, portal hypertension, congenital heart diseases, schistosomiasis
   - **I' Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis**
   - Idiopathic
   - Heritable
   - Drugs, toxins and radiation induced
   - Associated with connective tissue disease, HIV infection
   - **I" Persistent pulmonary hypertension of the newborn**
2. **Pulmonary hypertension due to left heart disease**
   - Left ventricular systolic dysfunction
   - Left ventricular diastolic dysfunction
   - Valvular disease
   - Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
   - Congenital/acquired pulmonary vein stenosis
3. **Pulmonary hypertension due to lung diseases and/or hypoxia**
   - Chronic obstructive pulmonary disease
   - Interstitial lung disease
   - Other pulmonary diseases with mixed restrictive and obstructive pattern
   - Sleep-disoriented breathing
   - Alveolar hypoventilation disorder
   - Chronic exposure to high altitude
   - Developmental lung diseases
4. **Chronic thromboembolic pulmonary hypertension/other pulmonary artery obstructions**
   - Chronic thromboembolic pulmonary hypertension
   - Other pulmonary artery obstructions, i.e., tumors, arteritis, pulmonary stenosis, parasites
5. **Pulmonary hypertension with unclear and/or multifactorial mechanisms**
   - Hematological disorders: chronic hemolysis, myeloproliferative disorders, splenectomy
   - Systemic disorders: sarcoidosis, pulmonary histiocytosis, neurofibromatosis
   - Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - Others: fibrosing mediastinitis, chronic renal failure

HIV = human immunodeficiency virus.

Adapted from Galiè, 2016.

In pregnant women, group 2 disorders are the most common. These are secondary to pulmonary *venous* hypertension caused by left-sided atrial, ventricular, or valvular disorders. A typical example is mitral stenosis discussed earlier (Valvular Heart Disease). In contrast, groups 3 through 5 are seen

infrequently in young healthy women.

Diagnosis

Symptoms may be vague, and dyspnea with exertion is the most frequent. With group 2 disorders, orthopnea and nocturnal dyspnea are also usually present. Angina and syncope occur when right ventricular output is fixed, and they suggest advanced disease. Chest radiography often shows enlarged pulmonary hilar arteries and attenuated peripheral markings. It also may disclose parenchymal causes of hypertension. Noninvasive echocardiography can provide an estimate of pulmonary artery pressures, although cardiac catheterization remains the standard for measurement. In two studies with a combined 51 pregnant women who underwent both echocardiography and cardiac catheterization, pulmonary artery pressures were significantly overestimated by echocardiography in approximately one third of cases (Penning, 2001; Wylie, 2007).

Prognosis

Regardless of the etiology, the final common pathway of pulmonary hypertension is right heart failure and death. The average survival length after diagnosis is <4 years (Krexi, 2015). That said, longevity depends on the severity and cause of pulmonary hypertension at discovery. As discussed later, some disorders respond to medical interventions, which may improve quality of life. Preconceptional and contraceptive counseling are imperative (Gei, 2014).

Pregnancy

The maternal mortality rate is appreciable in affected women, and this is especially so with idiopathic pulmonary hypertension. In the past, there were frequently poor distinctions in identifying both causes and severity of hypertension. Thus, although most severe cases of idiopathic pulmonary arterial hypertension had the worst prognosis, it was erroneously assumed that all types of pulmonary hypertension were equally dangerous. With widespread use of echocardiography, less-severe lesions with a better prognosis are now discernible. Bédard and coworkers (2009) reported that maternal mortality rate statistics improved during the decade ending in 2007 (25 percent) compared with those for the decade ending in 1996 (38 percent). Importantly, almost 80 percent of the deaths were during the first month postpartum. More recently, Meng and associates (2017) reported mortality rates of 23 percent with group 1 and 5 percent with the other groups. Mortality was related to pulmonary hypertension severity.

As discussed, pregnancy is contraindicated with severe disease, especially in women with pulmonary arterial changes—most cases in group 1. With milder disease from other causes—group 2 being the most common—the prognosis is better (Meng, 2017). With the more frequent use of echocardiography and pulmonary artery catheterization in young women with heart disease, we have identified women with mild-to-moderate pulmonary hypertension who tolerate pregnancy, labor, and delivery well. One example described by Sheffield and Cunningham (2004) is that of pulmonary hypertension that develops with thyrotoxicosis but is reversible with treatment. Similarly, Boggess and colleagues (1995) described nine women with interstitial and restrictive lung disease with varying degrees of pulmonary hypertension, and all tolerated pregnancy reasonably well.

Management

Treatment of symptomatic pregnant women includes activity limitation and avoidance of the supine position later in gestation. Diuretics, supplemental oxygen, and pulmonary vasodilator drugs are standard therapy for symptoms. Some recommend anticoagulation (Hsu, 2011). Several reports describe the successful use of intravenous pulmonary artery vasodilators (Badalian, 2000; Garabedian, 2010; Goya, 2014). Prostacyclin analogues that can be administered parenterally include epoprostenol and treprostinil, whereas iloprost is inhaled. Each has been used in gravidas. Inhaled nitric oxide is an option that has been employed in cases of acute cardiopulmonary decompensation (Lane, 2011). As reviewed by Običan and Cleary (2014), phosphodiesterase-5 inhibitors, such as sildenafil, cause vasodilation of both the pulmonary and systemic vascular beds and have an inotropic effect on the hypertrophic right ventricle. This also has been used to advantage during pregnancy (Goland, 2010; Hsu, 2011; Meng, 2017). Bosentan, an endothelin-receptor antagonist, is teratogenic in mice and contraindicated in pregnancy (Običan, 2014).

During labor and delivery, these women are at greatest risk when venous return and right ventricular filling are diminished. To avoid hypotension, assiduous attention is given to epidural analgesia induction and to blood loss prevention and treatment at delivery (Meng, 2017).

CARDIOMYOPATHIES

The American Heart Association defines these as a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction. Affected women usually—but not invariably—have inappropriate ventricular hypertrophy or dilation. Cardiomyopathies stem from varied causes, some of which are genetic (Maron, 2006). Of the two major divisions, *primary cardiomyopathies* are solely or predominantly confined to heart muscle. Examples are hypertrophic cardiomyopathy, dilated cardiomyopathies, and peripartum cardiomyopathy. *Secondary cardiomyopathies* result from generalized systemic disorders that produce pathological myocardial involvement. Diabetes, systemic lupus erythematosus, chronic hypertension, and thyroid disorders are representative conditions.

Hypertrophic Cardiomyopathy

Epidemiological studies suggest that this disorder is common, affecting approximately 1 in 500 adults (Herrey, 2014; Maron, 2004). Characterized by cardiac hypertrophy, myocyte disarray, and interstitial fibrosis, the condition is caused by mutations in any one of more than a dozen genes that encode cardiac sarcomere proteins in up to 60 percent of affected patients. In such cases, inheritance is autosomal dominant, and genetic screening is complex (Elliott, 2014). Other genetic and nongenetic causes account for 5 to 10 percent of cases, and the cause is unknown in approximately 25 percent. The myocardial muscle abnormality is typified by left ventricular myocardial hypertrophy with a pressure gradient against left ventricular outflow. Diagnosis is established by echocardiographic identification of a hypertrophied and nondilated left ventricle in the absence of other cardiovascular conditions.

Most affected women are asymptomatic, but dyspnea, anginal or atypical chest pain, syncope, and arrhythmias may develop. Complex arrhythmias may progress to sudden death, which is the most frequent cause of death. Asymptomatic patients with runs of ventricular tachycardia are especially prone to sudden death. Symptoms usually worsen with exercise.

Although limited reports suggest that pregnancy is well tolerated, adverse cardiac events are frequent. In one analysis of 271 pregnancies in 127 affected women, there were no maternal deaths. However, more than a fourth had at least one adverse cardiac symptom—including dyspnea, chest pain, or palpitations (Thaman, 2003). Based on one systematic review that included 237 women with hypertrophic cardiomyopathy who had a combined 408 pregnancies, Schinkel (2014) calculated a maternal mortality rate of 0.5 percent. Worsening of symptoms or other complications occurred in 29 percent, and 26 percent delivered preterm.

Management is similar to that for aortic stenosis. Strenuous exercise is prohibited during pregnancy. Abrupt positional changes are avoided to prevent reflex vasodilation and decreased preload. Likewise, drugs that evoke diuresis or diminish vascular resistance are generally not used. If symptoms develop, especially angina, β-adrenergic or calcium-channel blocking drugs are given. The delivery route of the fetus is determined by obstetrical indications. Choice of anesthesia is controversial, and some authors consider general anesthesia the safest (Pitton, 2007). Neonates rarely demonstrate inherited lesions at birth.

Dilated Cardiomyopathy

This is characterized by left and/or right ventricular enlargement and reduced systolic function in the absence of coronary, valvular, congenital, or systemic disease known to cause myocardial dysfunction. Although there are many known causes of dilated cardiomyopathy—both inherited and acquired, the etiology remains undefined in approximately half of cases (Stergiopoulos, 2011). Some result from viral infections, including myocarditis and HIV (Barbaro, 1998; Felker, 2000). Other causes, which are potentially reversible, include alcoholism, cocaine abuse, and thyroid disease. Watkins and coworkers (2011) reviewed the many complex genetic mutations associated with inherited forms of dilated cardiomyopathy.

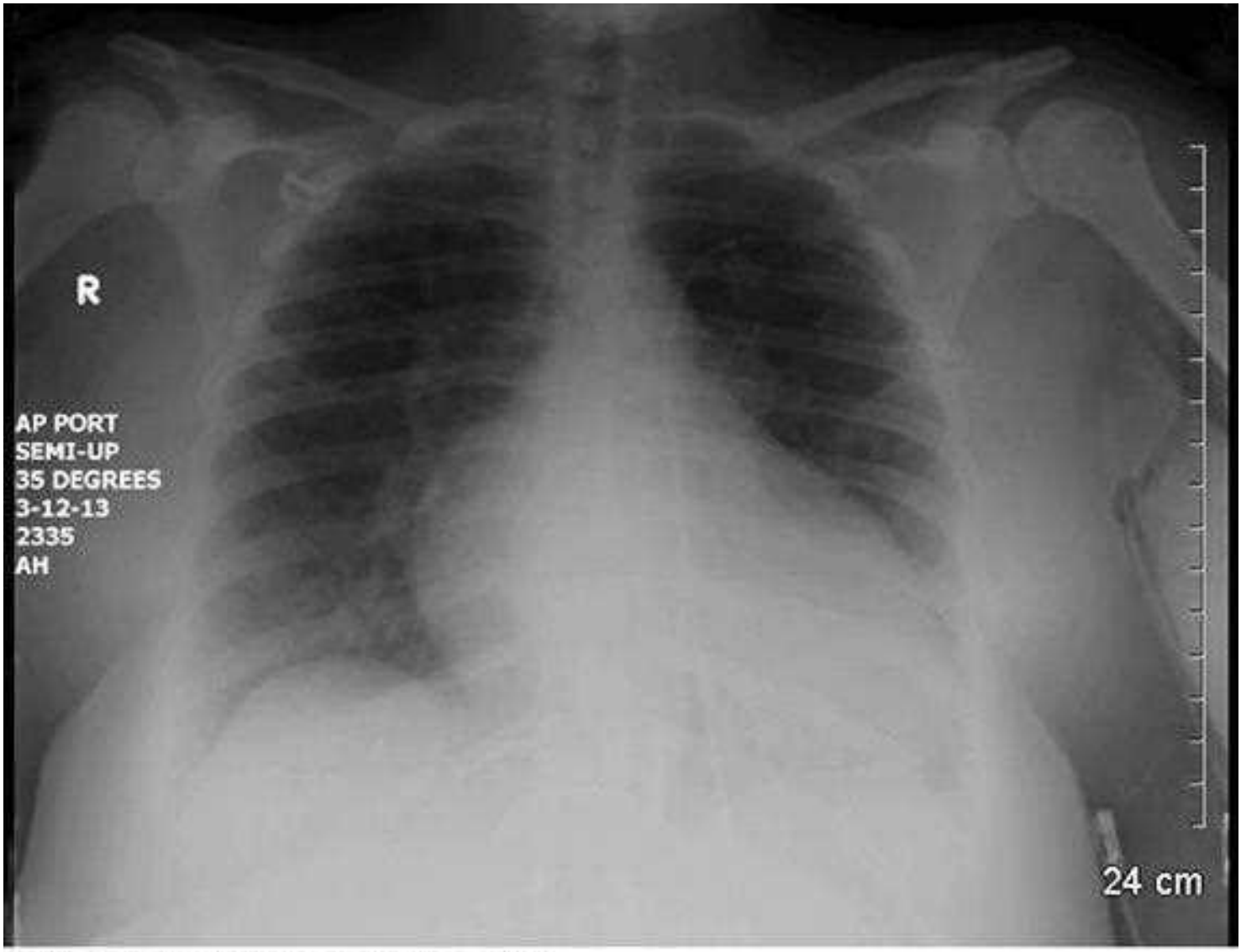
Peripartum Cardiomyopathy

This disorder is similar to other forms of nonischemic dilated cardiomyopathy except for its unique relationship with pregnancy (Pyatt, 2011). Indeed, peripartum cardiomyopathy shares a genetic predisposition with both familial and sporadic idiopathic dilated cardiomyopathy (Ware, 2016). Currently, it is a diagnosis of exclusion following a concurrent evaluation for peripartum heart failure.

Although the term peripartum cardiomyopathy has been used widely, at least until recently, little evidence supported a unique pregnancy-induced cardiomyopathy. Pearson (2000) reported findings of a workshop of the National Heart, Lung, and Blood Institute that established the following diagnostic criteria:

1. Development of cardiac failure in the last month of pregnancy or within 5 months after delivery,
2. Absence of an identifiable cause for the cardiac failure,
3. Absence of recognizable heart disease prior to the last month of pregnancy, and
4. Left ventricular systolic dysfunction demonstrated by classic echocardiographic criteria, such as depressed ejection fraction or fractional shortening along with a dilated left ventricle (Fig. 49-5).

FIGURE 49-5
Peripartum cardiomyopathy with mild pulmonary edema. Anterior-posterior projection chest radiograph of a woman with an abnormally enlarged heart and mild perihilar opacification consistent with dilated cardiomyopathy.



The etiology of peripartum cardiomyopathy remains unknown, and proposed causes include viral myocarditis, abnormal immune response to pregnancy, aberrant response to the greater hemodynamic burden of pregnancy, hormonal interactions, malnutrition, inflammation, and apoptosis (Elkayam, 2011). Another suggests that oxidative stress during late pregnancy leads to the proteolytic cleavage of prolactin (Hilfiker-Kleiner, 2014). The resulting 16-kDa prolactin fragment is cardiotoxic and can impair cardiomyocyte metabolism and contractility. Bromocriptine therapy has been suggested because it inhibits prolactin secretion. In one preliminary study, bromocriptine improved recovery of affected women, and a randomized trial is currently recruiting patients (Haghikia, 2015; Sliwa, 2010).

Hypertensive disorders frequently coexist with peripartum cardiomyopathy, and another proposed mechanism links peripartum cardiomyopathy to preeclampsia (Cunningham, 2012; Fong, 2014; Patten, 2012). Antiangiogenic factors—already known to be associated with preeclampsia—can induce peripartum cardiomyopathy in susceptible mice. Thus, cardiomyopathy may be precipitated by antiangiogenic factors in a host made susceptible because of insufficient proangiogenic factors.

Several investigators describe a common pathway linking these suggested etiologies (Arany, 2016; Hilfiker-Kleiner, 2014). Specifically, unbalanced oxidative stress and a high level of prolactin leads to production of the 16-kDa prolactin fragment that seems to both initiate and propagate the disease. The fragment, which mainly affects the endothelium, together with additional antiangiogenic factors might disturb the angiogenic balance during the puerperium and thereby impair cardiac function.

With no proven etiology, the diagnosis of peripartum cardiomyopathy currently requires that other causes of cardiac dysfunction be excluded. Bültmann and coworkers (2005) studied endomyocardial biopsy specimens from 26 women with peripartum cardiomyopathy and reported that more than half had histological evidence of “borderline myocarditis.” They noted viral genomic material for parvovirus B19, human herpesvirus 6, Epstein-Barr virus, and cytomegalovirus. From Parkland Hospital, otherwise “idiopathic” heart failure was found to be caused by hypertensive heart disease, clinically silent mitral stenosis, obesity, or viral myocarditis (Cunningham, 1986). Indeed, 20 percent of women with treated chronic hypertension in pregnancy have concentric hypertrophy (Ambia, 2017).

Ntusi and associates (2015) analyzed the clinical features of 30 women with peripartum cardiomyopathy compared with 53 women with hypertensive heart failure. With cardiomyopathy, the symptoms began postpartum in all women, whereas symptoms began antepartum in 85 percent of women with hypertensive heart failure. Peripartum cardiomyopathy was significantly linked with twin gestation, smoking, and echocardiographic abnormalities. In contrast, hypertensive heart failure patients more often had a family history of hypertension, hypertension and preeclampsia in a prior pregnancy, tachycardia, and left ventricular hypertrophy on echocardiography.

The incidence of peripartum cardiomyopathy varies considerably and depends on the diligence for the search of a cause. In a review of the Nationwide Inpatient Sample database, the incidence rose from 1 in 1181 live births in 2004 to 1 in 849 in 2011 (Kolte, 2014). Two other large population-based studies cite a frequency of 1 in 2000 to 2800 live births (Gunderson, 2011; Harper, 2012). In an earlier study from Parkland Hospital, we identified idiopathic cardiomyopathy in only approximately 1 in 15,000 deliveries—an incidence similar to that of idiopathic cardiomyopathy in young nonpregnant women (Cunningham, 1986).

Prognosis

Approximately half of women suffering from peripartum cardiomyopathy recover baseline ventricular function within 6 months of delivery. But in those with persistent cardiac failure, the mortality rate approaches 85 percent over 5 years (Moioli, 2010). In a group of 100 women with newly diagnosed peripartum cardiomyopathy, 72 percent had a left ventricular ejection fraction ≥50 percent, and 93 percent had event-free survival (McNamara, 2015). However, six women experienced nine major events that included four deaths, four left ventricular assist device implantations, and one heart transplantation. Recovery to a left ventricular ejection fraction ≥50 percent occurred in almost 90 percent of women whose baseline ejection fraction was at least 30 percent. This compared with <40 percent in women whose baseline ventricular ejection fraction was <30 percent. Recovery was also related to the baseline left ventricular end-diastolic diameter. Li and colleagues (2016) also found that a baseline left ventricular ejection fraction <34 percent and a brain natriuretic peptide (BNP) level >1860 pg/mL were associated with an approximately threefold greater risk of persistent left ventricular systolic dysfunction.

Subsequent Pregnancy

From the largest studies on the topic, approximately one third of women with a history of peripartum cardiomyopathy will suffer relapse with worsening of symptoms and deterioration of left ventricular function during another pregnancy (Elkayam, 2014a). The risk of relapse in women with persistent left ventricular dysfunction is substantially higher than in those who have developed normal ventricular function before a subsequent pregnancy (Hilfiker-Kleiner, 2017). But, normalization of left ventricular function does not guarantee an uncomplicated pregnancy, because approximately 20 percent of these women are at risk for deterioration in left ventricular function.

Other Cardiomyopathy Types

Arrhythmogenic right ventricular dysplasia is a unique cardiomyopathy defined histologically by progressive replacement of right ventricular myocardium with adipose and fibrous tissue. It has an estimated population prevalence of 1 in 5000, predisposes to ventricular tachyarrhythmias, and is a cause of sudden death, particularly in younger individuals (Agir, 2014; Elliott, 2008). The additional risk of pregnancy in women with arrhythmogenic right ventricular cardiomyopathy is unknown, however, based on their systematic review, Krul and coworkers (2011) counsel against pregnancy.

Restrictive cardiomyopathy is probably the least common type. This inherited cardiomyopathy is characterized by a ventricular filling pattern in which worsening myocardial stiffness raises ventricular pressure precipitously and allows only a small filling volume (Elliott, 2008). Because of the severe clinical course and poor prognosis in general, pregnancy is not advised (Krul, 2011). *Takotsubo cardiomyopathy* is a rare form of acute reversible left ventricular apical wall ballooning (Kraft, 2017).

HEART FAILURE

Regardless of the underlying condition that causes cardiac dysfunction, women who develop peripartum heart failure almost always have obstetrical complications that either contribute to or precipitate heart failure. For example, preeclampsia is common and may precipitate afterload failure. Indeed, findings from the Registry on Pregnancy and Cardiac Disease indicate that women with preexisting heart disease who develop preeclampsia have a 30-percent risk of developing heart failure during pregnancy (Ruys, 2014). Moreover, high-output states caused by hemorrhage and acute anemia elevate cardiac workload and magnify the physiological effects of compromised ventricular function. Similarly, infection and sepsis syndrome raise cardiac output and oxygen utilization and depress myocardial function.

In many populations, chronic hypertension with superimposed preeclampsia is the most frequent cause of heart failure in pregnancy. Many of these women have concentric left ventricular hypertrophy (Ambia, 2017). In some, mild antecedent undiagnosed hypertension causes covert cardiomyopathy, and when superimposed preeclampsia develops, together they may cause otherwise inexplicable peripartum heart failure. Obesity is a frequent cofactor with chronic hypertension, and it too is associated with ventricular hypertrophy (Kenchaiah, 2002).

Diagnosis

Congestive heart failure can have a gradual onset or may present as acute “flash” pulmonary edema. Heart failure onset is most likely at the end of the second/beginning of the third trimester and peripartum (Ruys, 2014). Of symptoms, dyspnea is universal and others are orthopnea, palpitations, substernal chest pain, a sudden decline in the ability to complete usual duties, and nocturnal cough. Clinical findings include persistent basilar rales, hemoptysis, progressive edema, tachypnea, and tachycardia (Sheffield, 1999). Hallmark radiographic findings usually are cardiomegaly and pulmonary edema (see Fig. 49-5). Acutely, there is usually systolic failure, and echocardiography shows an ejection fraction <0.45 or a fractional shortening <30 percent, or both, and an end-diastolic dimension >2.7 cm/m^2 (Hibbard, 1999). Coincidental diastolic failure may also be found, depending on the underlying cause (Redfield, 2016).

Management

Pulmonary edema from heart failure usually responds promptly with diuretic administration to reduce preload. Hypertension is common, and afterload reduction is accomplished with hydralazine or another vasodilator. Because of marked fetal effects, angiotensin-converting enzyme inhibitors are withheld until after delivery. With chronic heart failure, the incidence of associated thromboembolism is high, and thus prophylactic heparin is often recommended.

Left ventricular assist devices are now employed more frequently for acute and chronic heart failure treatment. A few reports describe their use during pregnancy (LaRue, 2011; Sims, 2011). *Extracorporeal membrane oxygenation (ECMO)* was reported to be lifesaving in a woman with fulminating peripartum cardiomyopathy, and it may be used in women with pulmonary hypertension (Meng, 2017; Smith, 2009).

INFECTIVE ENDOCARDITIS

In the United States, those at greatest risk for endocarditis are those with congenital heart lesions, intravenous drug use, degenerative valve disease, and intracardiac devices (Karchmer, 2015). *Subacute bacterial endocarditis* usually stems from a low-virulence bacterial infection superimposed on an underlying structural lesion. These are usually native valve infections. Organisms that cause indolent endocarditis are most often viridans-group streptococci or *Staphylococcus* or *Enterococcus* species. Among intravenous drug abusers and those with catheter-related infections, *Staphylococcus aureus* predominates. With prosthetic valve infections, *Staphylococcus epidermidis* is a frequent cause. *Streptococcus pneumoniae* and *Neisseria gonorrhoeae* may occasionally cause acute, fulminating disease. Others have reported *Neisseria sicca* and *N mucosa*, group B streptococcus, and *Escherichia coli* endocarditis during pregnancy or peripartum (Cox, 1988; Deger, 1992; Kangavari, 2000; Kulaš, 2006).

Diagnosis and Management

Infective endocarditis symptoms vary and often develop insidiously. Fever, often with chills, is seen in 80 to 90 percent of cases, a murmur is heard in up to 85 percent, and anorexia, fatigue, and other constitutional symptoms are common (Karchmer, 2015). Clinical clues are anemia, proteinuria, and manifestations of embolic lesions that include petechiae, focal neurological changes, chest or abdominal pain, and ischemia in an extremity. In some cases, heart failure develops. Symptoms may persist for several weeks before the diagnosis is found, and a high index of suspicion is necessary.

Diagnosis is made using the *Duke criteria,* which include positive blood cultures for typical organisms and evidence of endocardial involvement (Hoen, 2013; Pierce, 2012). Echocardiography may be diagnostic, but lesions <2 mm or those on the tricuspid valve may be missed. If uncertain, transesophageal echocardiography is accurate and informative. Importantly, a negative echocardiographic study does not exclude endocarditis.

Treatment is primarily medical, and ascertainment of the infecting organism and its sensitivities is imperative for antimicrobial selection. Guidelines for appropriate antibiotic treatment are published by professional societies and updated regularly (Habib, 2015; Karchmer, 2015). Recalcitrant bacteremia and heart failure due to valvular dysfunction are but a few reasons that persistent valvular infection may require replacement.

Pregnancy

Infective endocarditis is uncommon during pregnancy and the puerperium. During a 7-year period, the incidence of endocarditis at Parkland Hospital approximated 1 in 16,000 births, and two of seven women died (Cox, 1988). Maternal and fetal mortality rates range from 25 to 35 percent (Habib, 2015; Seaworth, 1986). In a systematic review of infective endocarditis during pregnancy, risk factors were intravenous drug use (14 percent), congenital heart disease (12 percent), and rheumatic heart disease (12 percent) (Kebed, 2014). The most common pathogens were streptococcal (43 percent) and staphylococcal (26 percent) species. Among 51 pregnancies, the maternal mortality rate was 11 percent.

Endocarditis Prophylaxis

For years, patients with heart valve problems were given periprocedural antibiotics for endocarditis prophylaxis. Currently, however, recommendations are more stringent. The American Heart Association recommends prophylaxis for dental procedures in those with: (1) a prosthetic valve or prosthetic material used in a valve repair, (2) prior endocarditis, (3) unrepaired cyanotic heart defect or repaired lesion with residual defect at prosthetic sites, and (4) valvulopathy after heart transplantation (Nishimura, 2017). The American College of Obstetricians and Gynecologists (2016) does not recommend endocarditis prophylaxis for either vaginal or cesarean delivery in the absence of pelvic infection except with the lesions cited above. Women at highest

risk for endocarditis are those with cyanotic cardiac disease, prosthetic valves, or both. When indicated, and for women not already receiving intrapartum antimicrobial therapy for another indication that would also provide coverage against endocarditis, prophylactic regimens are shown in Table 49-8. These are administered as close to 30 to 60 minutes before the anticipated delivery time as is feasible.

TABLE 49-8

Antibiotic Prophylaxis for Infective Endocarditis in High-Risk Patients

American College of Obstetricians and Gynecologist (2016) Standard (IV): ampicillin 2 g ***or*** cefazolin or ceftriaxone 1 g Penicillin-allergic (IV): cefazolin or ceftriaxone 1 g ***or*** clindamycin 600 mg Oral: amoxicillin 2 g
American Heart Association/European Society of Cardiology (Karchmer, 2015)[a] Standard: amoxicillin 2 g PO ***or*** ampicillin 2 g IV or IM Penicillin-allergic: clarithromycin or azithromycin 500 mg PO; cephalexin 2 g PO; clindamycin 600 mg PO, IV, or IM; ***or*** cefazolin or ceftriaxone 1 g IV or IM

IM = intramuscularly; IV = intravenously.

[a]Cefazolin or ceftriaxone given 30 minutes and all others given 1 hour prior to procedure.

ARRHYTHMIAS

Both preexisting and new-onset cardiac arrhythmias are often encountered during pregnancy, labor, delivery, and the puerperium (Joglar, 2014; Knotts, 2014). In a study of 73 women with a history of supraventricular tachycardia (SVT), paroxysmal atrial flutter or fibrillation, or ventricular tachycardia, recurrence rates during pregnancy were 50, 52, and 27 percent, respectively (Silversides, 2006). The mechanism(s) responsible for the higher incidence of arrhythmias during pregnancy are not well elucidated. From some studies, estradiol and progesterone are proarrhythmic. Estrogen augments the number of adrenergic receptors in the myocardium, and adrenergic responsiveness seems to be greater in pregnancy (Enriquez, 2014). Perhaps the normal but mild hypokalemia of pregnancy and/or the physiological rise in heart rate serves to induce arrhythmias. Alternatively, detection of arrhythmias may be greater because of the frequent visits typical of routine prenatal care.

Bradyarrhythmias

Slow heart rhythms, including complete heart block, are compatible with a successful pregnancy outcome (Keepanasseril, 2015). Some women with complete heart block have syncope during labor and delivery, and occasionally temporary cardiac pacing is necessary (Hidaka, 2006). In our experiences and from others, women with permanent artificial pacemakers usually tolerate pregnancy well (Hidaka, 2011; Jaffe, 1987). With fixed-rate devices, cardiac output apparently is increased by augmented stroke volume.

Patients with pacemakers or other electrical implants require special precautions during surgery. Stray current may be interpreted as an intracardiac signal by the implanted device and lead to pacing changes. In addition, myocardial burns may result from conduction of current through the pacing electrode rather than through the grounding pad (Pinski, 2002). With these devices, preventive steps include cardiology consultation; bipolar electrosurgery or Harmonic scalpel use rather than monopolar current; if needed, minimal monopolar settings; continuous cardiac and pulse oximetry monitoring; contingency plans for arrhythmias; and close proximity of electrosurgery active and return electrodes (Crossley, 2011).

Supraventricular Tachycardias

The most common arrhythmia seen in reproductive-aged women is paroxysmal SVT. The prevalence during pregnancy is 24 cases per 100,000 hospital admissions, and approximately 20 percent will experience symptomatic exacerbations during pregnancy (Enriquez, 2014). Interestingly, the mean heart rate of pregnant women with paroxysmal SVT is faster compared with nonpregnant women—184 versus 166 bpm, respectively (Yu, 2015). From Hungary, Bánhidy and associates (2015) found that approximately half of women with paroxysmal SVT had an initial onset during pregnancy. Notably, maternal paroxysmal SVT was associated with a twofold greater risk of septal cardiac defects, particularly secundum atrial septal defects, in their offspring.

In contrast, rarely do *atrial fibrillation* and *atrial flutter* present for the first time during pregnancy. Indeed, new-onset atrial fibrillation should prompt a search for underlying etiologies that include cardiac anomalies, hyperthyroidism, pulmonary embolism, drug toxicity, and electrolyte disturbances (DiCarlo-Meacham, 2011). Major complications include embolic stroke, and when associated with mitral stenosis, pulmonary edema may develop in later pregnancy if the ventricular rate is increased.

For acute treatment, vagal maneuvers, which include Valsalva maneuver, carotid sinus massage, bearing down, and immersion of the face in ice water, raise vagal tone and block the atrioventricular node (Link, 2012; Page, 2015). Intravenous adenosine is a short-acting endogenous nucleotide that also blocks atrioventricular nodal conduction. Our experiences are similar to those of others in that adenosine is safe and effective for cardioversion in hemodynamically stable gravidas (Page, 2015; Robins, 2004). Transient fetal bradycardia has been described with adenosine (Dunn, 2000).

If pharmacological therapy is ineffective or contraindicated, the American College of Cardiology and the American Heart Association recommend synchronized cardioversion in pregnant women with hemodynamically unstable SVT (Page, 2015). And although electrical cardioversion with standard energy settings is not contraindicated in pregnancy, vigilance is important. Barnes and colleagues (2002) described a case in which direct current cardioversion led directly to a sustained uterine contraction and fetal bradycardia. As an aside, pregnancy has no effect on the operation of implantable cardioverter-defibrillator devices (Boulé, 2014).

If cardioversion fails or is unsafe because of concurrent thrombus, then long-term anticoagulation and heart rate control with medication are necessary (DiCarlo-Meacham, 2011). Other treatment options recommended by the American College of Cardiology and the American Heart Association (Page, 2015) include:

Intravenous metoprolol or propranolol when adenosine is ineffective or contraindicated

Intravenous verapamil when adenosine and β-blocking agents are ineffective or contraindicated

Intravenous procainamide

Intravenous amiodarone with potentially life-threatening SVT and when other therapies are ineffective or contraindicated.

Pregnancy may predispose otherwise asymptomatic women with *Wolff-Parkinson-White (WPW) syndrome* to exhibit arrhythmias. In a study of 25 women who had SVT diagnosed before pregnancy, three of 12 women with WPW syndrome and six of 13 without the condition developed SVT during pregnancy (Pappone, 2003). In some patients, accessory pathway ablation may be indicated. Driver and coworkers (2015) have provided a review.

Ventricular Tachycardia

This form of arrhythmia is uncommon in healthy young women without underlying heart disease. Brodsky and associates (1992) described seven pregnant women with new-onset ventricular tachycardia and reviewed 23 reports. Most of these women were not found to have structural heart disease. In 14 cases, tachycardia was precipitated by physical exercise or psychological stress. Abnormalities found included two cases of myocardial infarction, two of prolonged QT interval, and one of anesthesia-provoked tachycardia. They concluded that pregnancy events precipitated the tachycardia and recommended β-blocking agents for control. As previously discussed (Heart Failure), arrhythmogenic right ventricular dysplasia will result occasionally in ventricular tachyarrhythmias (Lee, 2006). If unstable, emergency cardioversion is indicated, and standard adult energy settings are adequate (Jeejeebhoy, 2011; Lin, 2015).

Prolonged QT-Interval

This conduction anomaly may predispose individuals to a potentially fatal ventricular arrhythmia known as *torsades de pointes* (Roden, 2008). Two studies comprised of 502 pregnant women with *long QT syndrome* both reported a significant increase in cardiac events postpartum but not during pregnancy (Rashba, 1998; Seth, 2007). The normal rise in heart rate during pregnancy may be partially protective. Paradoxically, β-blocking agents—preferably propranolol—lower the risk of torsades de pointes in patients with long QT syndrome and should be continued throughout pregnancy and the puerperium (Enriquez, 2014; Seth, 2007). Importantly, many medications, including some used during pregnancy such as azithromycin, erythromycin, and clarithromycin, may predispose to QT prolongation (Ray, 2012; Roden, 2004).

DISEASES OF THE AORTA

Aortic Dissection

Marfan syndrome and coarctation are two aortic diseases that place the pregnant woman at increased risk for aortic dissection (Russo, 2017). Indeed, half of dissection cases in young women are related to pregnancy (O'Gara, 2004). Other risk factors are bicuspid aortic valve and Turner or Noonan syndrome. A high rate of aortic dissection or rupture is also reported in patients with Ehlers-Danlos syndrome (Murray, 2014; Pepin, 2000). Although the mechanism(s) involved are unclear, the initiating event is a tear in the intimal layer of the aorta, followed by hemorrhage into the media, and finally rupture.

In most cases, aortic dissection presents with severe chest pain described as ripping, tearing, or stabbing. Diminution or loss of peripheral pulses coupled with a recently acquired aortic insufficiency murmur is an important physical finding. The differential diagnosis of aortic dissection in pregnancy includes myocardial infarction, pulmonary embolism, pneumothorax, aortic valve rupture, and obstetrical catastrophes, especially placental abruption and uterine rupture.

More than 90 percent of patients with aortic dissection have an abnormal chest radiograph. Aortic angiography is the most definitive method for diagnosis confirmation. However, sonography, computed tomography, and MR imaging are used more frequently depending on the urgency of the clinical situation.

Initial medical treatment is given to lower blood pressure. Proximal dissections most often need to be resected, and the aortic valve replaced if necessary. Distal dissections are more complex, and many may be treated medically. Among *nonpregnant* patients, survival is not improved by immediate elective repair compared with surveillance and delayed repair of abdominal aortic aneurysms <5.5 cm. But, Karthikesalingam and colleagues (2016) suggest that the size threshold for aneurysm repair should be revisited.

Marfan Syndrome

This autosomal dominant connective tissue disorder has an incidence of 2 to 3 cases per 10,000 individuals and is without racial or ethnic predilection (Ammash, 2008). As discussed in Chapter 59 (Hereditary Connective Tissue Disorders), Marfan syndrome is characterized by generalized tissue weakness that can result in dangerous cardiovascular complications. Because all tissues are involved, other defects are frequent and include joint laxity and scoliosis. Progressive aortic dilation causes aortic valve insufficiency, and there may be infective endocarditis and mitral valve prolapse with insufficiency. Aortic dilation and dissecting aneurysm are the most serious abnormalities. Early death is due either to valvular insufficiency and heart failure or to a dissecting aneurysm.

Pregnancy

Of outcomes, a study using the Nationwide Inpatient Sample from 2003 to 2010 found 339 deliveries in women with Marfan syndrome. There was one maternal death and six (1.8 percent) aortic dissections (Hassan, 2015). Russo and associates (2017) used Texas obstetrical discharge data and found that eight of 47 women with aortic dissection had Marfan syndrome. A study from the United Kingdom reported similar results (Curry, 2014).

The aortic root usually measures approximately 2 cm, and during normal pregnancy, it expands slightly (Easterling, 1991). With Marfan syndrome, aortic root repair is recommended at diameters of 4.0 to 4.5 cm (Smok, 2014). The guidelines of the American College of Cardiology, the American Heart Association, and the American Association of Thoracic Surgeons advise prophylactic aortic repair in women considering pregnancy if the diameter of the ascending aorta exceeds 4 cm (Hiratzka, 2010). The guidelines of the European Society of Cardiology (2011) advise repair of the aorta at diameters ≥4.5 cm. Because shorter patients have dissection at a smaller diameter, surgical repair is also considered using a formula indexed to height (Bradley, 2014; Smok, 2014).

For pregnant women with known thoracic aortic root or ascending aortic dilation, monthly or bimonthly echocardiographic measurements of the ascending aortic dimensions are recommended to detect expansion (Hiratzka, 2010). Prophylactic β-blocking agents have become standard for pregnant women with Marfan syndrome because they reduce hemodynamic stress on the ascending aorta and slow the dilation rate (Simpson, 2012). Ideally, pregnant women with aortic aneurysms are delivered at facilities in which cardiothoracic surgery is available. Vaginal delivery with regional analgesia and an assisted second stage seem safe for women with an aortic root diameter <4 cm.

When the aortic root measures 4 to 5 cm or greater, elective cesarean delivery is recommended with consideration of postpartum replacement of the proximal aorta with a prosthetic graft (Simpson, 2012). Successful aortic root replacement during pregnancy has been described, but the surgery has also been associated with fetal hypoxic-ischemic encephalopathy (Mul, 1998; Seeburger, 2007). Several case reports describe emergency cesarean deliveries in women with acute type A dissections that were repaired successfully at the time of delivery (Guo, 2011; Haas, 2011; Papatsonis, 2009).

To evaluate obstetrical outcomes, investigators for one study of 63 women with Marfan syndrome analyzed their 142 pregnancies. Of 111 pregnancies progressing past 20 weeks' gestation, 15 percent delivered preterm, and 5 percent had preterm prematurely ruptured membranes (Meijboom, 2006). There were eight perinatal deaths, and half of the neonatal survivors were subsequently diagnosed with Marfan syndrome.

Aortic Coarctation

In this relatively rare lesion, the aorta is abnormally narrowed and is often accompanied by abnormalities of other large arteries. A fourth of affected patients have a bicuspid aortic valve, and another 10 percent have cerebral artery aneurysms. Other associated lesions are persistent ductus arteriosus, septal defects, and Turner syndrome. The collateral circulation arising above the coarctation remodels and expands, often strikingly, to cause localized erosion of rib margins by hypertrophied intercostal arteries. Typical findings include hypertension in the upper extremities but normal or reduced pressures in the lower extremities. Authors have described diagnosis during pregnancy using MR imaging (Sherer, 2002; Zwiers, 2006). Moreover, Jimenez-Juan and associates (2014) found that aortic diameter measured by MR and the risk of adverse events during pregnancy were inversely correlated. Of note, no adverse outcomes occurred if the minimum diameter at the coarctation exceeded 15 mm.

Major complications with aortic coarctation include congestive heart failure after long-standing severe hypertension, bacterial endocarditis of the bicuspid aortic valve, and aortic rupture. Because hypertension may worsen in pregnancy, antihypertensive therapy using β-blocking drugs is usually required. Aortic rupture is more likely late in pregnancy or early puerperium. Cerebral hemorrhage from *circle of Willis aneurysms* may also occur.

Of outcomes from 188 pregnancies, a third of women had hypertension that was related to significant coarctation gradients, and one woman died from dissection at 36 weeks' gestation (Beauchesne, 2001). Of nearly 700 deliveries in women with coarctation from the Nationwide Inpatient Sample, hypertensive complications of pregnancy were increased three- to fourfold (Krieger, 2011). Importantly, almost 5 percent of women with coarctation had an adverse cardiovascular outcome—maternal death, heart failure, arrhythmia, cerebrovascular or other embolic event—compared with only 0.3 percent of controls. Of women with coarctation, 41 percent underwent cesarean delivery compared with 26 percent of controls.

Congestive heart failure demands vigorous efforts to improve cardiac function and may warrant pregnancy interruption. Some authors recommend that resection of the coarctation be undertaken during pregnancy to protect against the possibility of a dissecting aneurysm and aortic rupture. This poses significant perfusion risk, especially for the fetus, because all the arterial collaterals must be clamped for variable periods.

ISCHEMIC HEART DISEASE

Pregnant women with coronary artery disease commonly have the classic risk factors of diabetes, smoking, hypertension, hyperlipidemia, and obesity (James, 2006). Although relatively rare, the risk of acute myocardial infarction is approximately threefold higher in pregnant women compared with nonpregnant women of similar age (Elkayam, 2014b). From more than 50 million hospitalizations in the United States between 1998 and 2009, rates of acute myocardial infarction approximated 2 per 100,000 delivery hospitalizations and 4 per 100,000 postpartum hospitalizations (Callaghan, 2012). Ladner and colleagues (2005) reported a similar rate of 2.7 per 100,000 deliveries.

Myocardial Infarction During Pregnancy

The mortality rate with myocardial infarction in pregnancy is higher compared with age-matched nonpregnant women. In a Nationwide Inpatient Sample study totaling 859 pregnancies complicated by acute infarction, the death rate was 5.1 percent (James, 2006). Women who sustain an infarction <2 weeks before delivery are at especially high risk of death due to the greater myocardial demand of labor and delivery (Esplin, 1999).

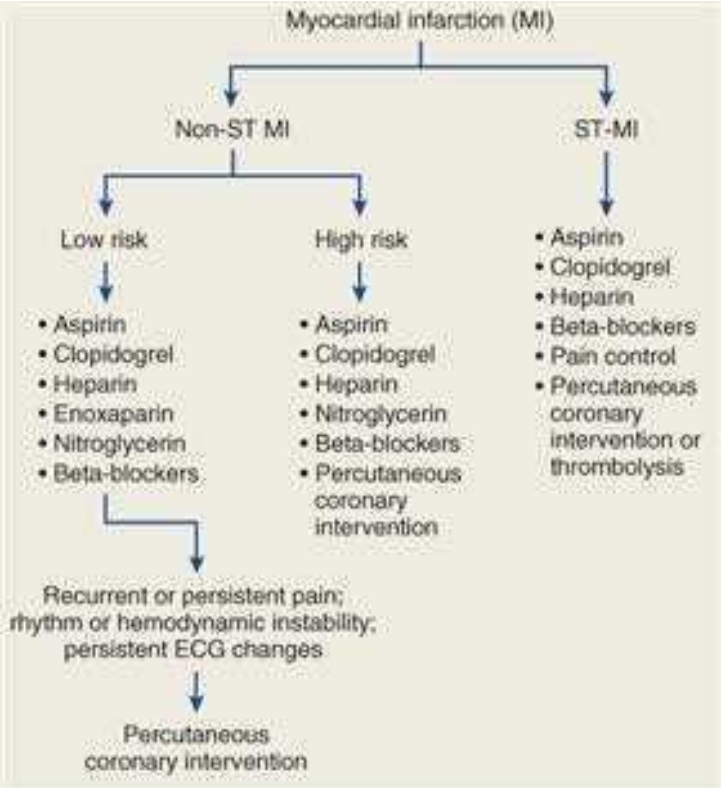
In a systematic review of 150 cases, most women developed an acute myocardial infarction (MI) during the third trimester or postpartum (Elkayam, 2014b). Approximately three fourths presented with ST segment-elevation MI (STEMI). The leading mechanisms of acute infarction included *spontaneous coronary dissection* (43 percent) and *atherosclerotic disease* (27 percent). Significant complications included heart failure/cardiogenic shock (38 percent), recurrent angina or infarction (19 percent), and ventricular arrhythmias (12 percent). The maternal and fetal mortality rates were 7 and 5 percent, respectively. Of other potential antecedents, coronary artery occlusion in two pregnant smokers with hypercholesterolemia has been described following ergometrine administration (Mousa, 2000; Ramzy, 2015; Sutaria, 2000). Schulte-Sasse (2000) reported myocardial ischemia associated with prostaglandin E_1 vaginal suppositories given for labor induction.

Diagnosis of acute myocardial infarction during pregnancy does not differ from that in nonpregnant patients and is based on clinical presentation, characteristic ECG changes, and evidence of myocardial necrosis reflected by elevated serum troponin levels (Pacheco, 2014). Of note, troponin I levels are undetectable near term in normal pregnancy and do not rise following either vaginal or cesarean delivery (Koscica, 2002; Shivvers, 1999). Importantly, however, troponin I levels are higher in preeclamptic women compared with normotensive controls (Atalay, 2005; Yang, 2006). With spontaneous coronary artery dissection, establishing the diagnosis requires a high index of suspicion in the gravida presenting with chest pain (Codsi, 2016). For this condition, coronary angiography is considered the diagnostic gold standard and should be expediently performed if acute coronary syndrome—defined as myocardial infarction or unstable angina—is present.

Treatment of acute myocardial infarction is similar to that for nonpregnant patients (Pacheco, 2014). An algorithm summarizing one approach to its management during pregnancy is shown in Figure 49-6. Several reports describe successful percutaneous transluminal coronary angioplasty and stent placement during pregnancy (Balmain, 2007; Duarte, 2011; Dwyer, 2005). Cardiopulmonary resuscitation may be required, as described in Chapter 47 (Cardiopulmonary Resuscitation). If the infarct has healed sufficiently, cesarean delivery is reserved for obstetrical indications, and epidural analgesia is ideal for labor (Esplin, 1999).

FIGURE 49-6

Initial management of acute myocardial infarction during pregnancy. Risk stratification refers to the risk of developing recurrent symptoms despite optimal medical management. (Adapted with permission from Pacheco LD, Saade GR, Hankins GD: Acute myocardial infarction during pregnancy, Clin Obstet Gynecol. 2014 Dec;57(4):835–843.)



Pregnancy with Prior Ischemic Heart Disease

The advisability of pregnancy after a myocardial infarction is unclear. Ischemic heart disease is characteristically progressive, and because it is usually associated with hypertension or diabetes, pregnancy in most of these women seems inadvisable. In a review of 30 pregnancies in women who had sustained an *infarction remote from pregnancy*, none of the women died, four had congestive heart failure, and four had worsening angina during pregnancy (Vinatier, 1994). Pombar and coworkers (1995) evaluated outcomes of women with diabetes-associated ischemic heart disease and infarction. Three had undergone coronary artery bypass grafting before pregnancy. Of 17 women, eight died during pregnancy. Certainly, pregnancy raises cardiac workload, and these investigators concluded that ventricular performance should be assessed using ventriculography, radionuclide studies, echocardiography, or coronary angiography before conception. Without significant ventricular dysfunction, pregnancy will likely be tolerated. For the woman who becomes pregnant before these studies are performed, echocardiography is done. Exercise tolerance testing may be indicated, and radionuclide ventriculography exposes the fetus to minimal radiation.

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CHAPTER 50: Chronic Hypertension

A small proportion of women suffering from chronic nephritis had eclampsia. For the most part, autopsy will reveal the presence of renal changes usually of acute nephritis, though occasionally it may be engrafted upon a chronic process.

—J. Whitridge Williams (1903)

INTRODUCTION

At the time of *Williams Obstetrics*' first edition, little attention was paid to blood pressure changes, even with "toxemia." At that time, chronic hypertension was designated "senile" and thought to develop only in older individuals (Lindheimer, 2015). Indeed, chronic hypertension is not mentioned, per se, in Williams' 1903 textbook, except for some deference given to chronic anatomical renal changes occasionally associated with eclampsia.

It is now apparent that chronic hypertension is one of the most common serious complications encountered during pregnancy. This is not surprising because, according to the National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention (2011), the prevalence of hypertension in women aged 18 to 39 years approximates 7 percent.

The incidence of chronic hypertension complicating pregnancy varies depending on population vicissitudes. In a study of more than 56 million births from the Nationwide Patient Sample, the incidence was 1.8 percent (Bateman, 2012). And, in more than 878,000 pregnancies from the Medicaid Analytic Extract, 2.3 percent were complicated by chronic hypertension (Bateman, 2015). Despite this substantive prevalence, optimal management has not been well studied. It is known that chronic hypertension usually improves during early pregnancy. This is followed by variable behavior later in pregnancy and, importantly, by the unpredictable development of superimposed preeclampsia. The latter carries increased risks for maternal and perinatal morbidity and mortality.

GENERAL CONSIDERATIONS

To define chronic hypertension, the range of normal blood pressure must first be established. This is not a simple task because, like all polygenically determined biological variants, blood pressure norms differ between populations. And, within these norms, wide variations are found between individuals. Moreover, numerous epigenetic factors influence presentation. For example, not only do blood pressures vary between races and genders, but pressures—especially systolic—rise directly with increasing age and weight. Thus, pragmatically, normal adults have a broad range of blood pressures, but so do those with chronic hypertension. And finally, resting blood pressure measurements do not reflect daily activities.

After these variables are acknowledged, important considerations for any population are the attendant risks of chronic hypertension. It is a leading cause of death and accounts for nearly 15 percent of mortality worldwide. Approximately 65 million Americans have hypertension, and this number is growing concurrently with epidemic obesity (Kotchen, 2015). Hypertension increases substantively the risk of cardiovascular disease, coronary heart disease, congestive heart failure, stroke, renal failure, and peripheral arterial disease (Forouzanfar, 2017).

Definition and Classification

For the foregoing reasons, chronic hypertension would logically be defined as some level of sustained resting blood pressure that is associated with acute or long-term adverse effects. In this regard, most consider 140/90 mm Hg as the upper limit of normal for blood pressure values. But, in the United States, these values are based primarily on actuarial tables constructed using data derived from white adult males and compiled by life insurance companies. These "norms" disregard interrelated factors such as ethnicity, gender, and other important covariants. The importance of race, for example, was emphasized by Kotchen (2015), who cites the incidence of hypertension—defined as blood pressure >140/90 mm Hg—to be 34 percent in blacks, 29 percent in whites, and 21 percent in Mexican Americans.

For many years, the Joint National Committee has promulgated guidelines for diagnosis, classification, and management of chronic hypertension. In 2008, the National Heart, Lung, and Blood Institute discontinued these guidelines, and the Joint National Committee 8 (JNC 8) was instead asked to provide an evidence-based review (James, 2014). Findings pertinent to caring for young women with chronic hypertension are summarized in Table 50-1.

TABLE 50-1

Eighth Joint National Committee (JNC 8)—2014 Chronic Hypertension Guidelines and Recommendations

Evidence-based recommendations from randomized controlled trials
Definitions for hypertension and prehypertension not addressed
Lifestyle modifications endorsed from the Lifestyle Work Group (Eckel, 2013)
Recommend selection among four specific medication classes: angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-receptor blockers (ARB), calcium-channel blockers, or diuretics:
General population: <60 years old—initiate pharmacological therapy to lower diastolic pressure ≤90 mm Hg and systolic pressure ≤140 mm Hg
Diabetics: lower pressure to <140/90 mm Hg
Chronic kidney disease: lower pressure to <140/90 mm Hg. Also add ACE-I or ARB to improve outcomes
General nonblack population: initial therapy should include thiazide-type diuretic, calcium-channel blocker, ACE-I, or ARB
General black population: primary antihypertensive therapy should include thiazide-type diuretic or calcium-channel blocker
Assess monthly, and after 1 month, if goals not met, then increase primary drug dose or add second drug. If no response, increase either or add third drug; then if no response, refer to hypertension specialist

Summarized from James, 2014.

Treatment and Benefits for Nonpregnant Adults

Proven benefits accrue with treatment of otherwise normal adults who have sustained hypertension. Numerous studies evaluating many combinations of antihypertensive therapy have been conducted. Importantly, these trials evaluated monotherapy versus combination therapeutic regimens and their ethnospecific benefits. Most evaluated cardiovascular outcomes, but many also confirmed risk reductions in rates of cerebrovascular accident, renal insufficiency, and mortality. Because of these incontrovertible benefits, the JNC 8 recommends the management outlined in Table 50-1.

Thus, even for mildly elevated blood pressure, interventions to reduce these sequelae are beneficial (SPRINT Research Group, 2015). Moreover, antihypertensive therapy in nonpregnant reproductive-aged women with sustained diastolic pressures ≥90 mm Hg is considered standard. Not clear from these observations, however, is what constitutes the best management for women being treated who contemplate pregnancy, for those undergoing treatment who become pregnant, or for those first identified to have chronic hypertension during pregnancy (August, 2015). In these women, the benefits and safety of instituting antihypertensive therapy are less clear, as subsequently discussed in Antihypertensive Treatment in Pregnancy.

Preconceptional Counseling

Women with chronic hypertension are ideally counseled before pregnancy. The duration of hypertension, degree of blood pressure control, and current therapy are ascertained. Those women who require multiple medications for control or those who are poorly controlled carry greater risk for adverse pregnancy outcomes. Home measurement devices are checked for accuracy. General health, daily activities, and dietary habits are also assessed (Table 50-2).

TABLE 50-2

Lifestyle Modifications for Hypertensive Patients

Weight reduction
Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; limits sweets and red meats. Examples are DASH, USDA Food Pattern, or the AHA Diet
Lower sodium intake—consume no more than 2400 mg sodium/d; 1500 mg/d desirable
Engage in aerobic physical activity three to four sessions per week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity
Moderation of alcohol consumption

AHA = American Heart Association; DASH = Dietary Approaches to Stop Hypertension; USDA = United States Department of Agriculture.

Summarized from Eckel, 2013; Kotchen, 2015.

For hypertensive women with disease lasting longer than 5 years or with comorbid diabetes, cardiovascular and renal function is assessed (August, 2015; Gainer, 2005). Women with evidence for organ dysfunction or those with prior adverse events such as a stroke, myocardial infarction (MI), arrhythmias, or ventricular failure are at markedly higher risk for a recurrence or worsening dysfunction during pregnancy. Renal function is evaluated by serum creatinine measurement. Also, if a urine spot protein/creatinine ratio is abnormally high (>0.3), proteinuria is further quantified with a 24-hour urine collection (Hladunewich, 2011; Kuper, 2016; Morgan, 2016a). The Working Group Report on High Blood Pressure in Pregnancy (2000) of the National Heart, Lung, and Blood Institute concluded that the risks of fetal loss and accelerated renal disease deterioration are increased if the serum creatinine level is above 1.4 mg/dL (Chap. 53, Chronic Kidney Disease).

Although pregnancy is considered by many to be contraindicated in women with severe, poorly controlled hypertension, there is no consensus. Certainly, women who maintain persistent diastolic pressures ≥110 mm Hg despite therapy; require multiple antihypertensives; have a serum creatinine level >2 mg/dL; or have a history of prior stroke, MI, or cardiac failure must be counseled as to the marked risks to themselves and to their pregnancy outcome.

DIAGNOSIS AND EVALUATION IN PREGNANCY

The hypertensive disorders that uniquely complicate pregnancy are discussed in Chapter 40 (Terminology and Diagnosis). Women are diagnosed with chronic hypertension if it is documented to precede pregnancy or if hypertension is identified before 20 weeks' gestation. Evidence also supports that *prehypertension* may herald adverse outcomes similar to those in women with chronic hypertension (Rosner, 2017). In some women without overt chronic hypertension, a history of repeated pregnancies complicated by gestational hypertension, with or without the preeclampsia syndrome, may be elicited. Each is a risk marker for latent chronic hypertension, and this is especially so for preeclampsia, and in particular early-onset preeclampsia. In many ways, gestational hypertension is analogous to gestational diabetes in that such women have a *chronic hypertensive diathesis*, in which heredity and environment play a major role.

Although uncommon, secondary causes of hypertension are always a possibility in affected women. Thus, consideration is given to underlying chronic renal disease, connective-tissue disease, primary aldosteronism, Cushing syndrome, pheochromocytoma, and myriad other causes. That said, most pregnant women with antecedent hypertension will have otherwise uncomplicated disease.

Associated Risk Factors

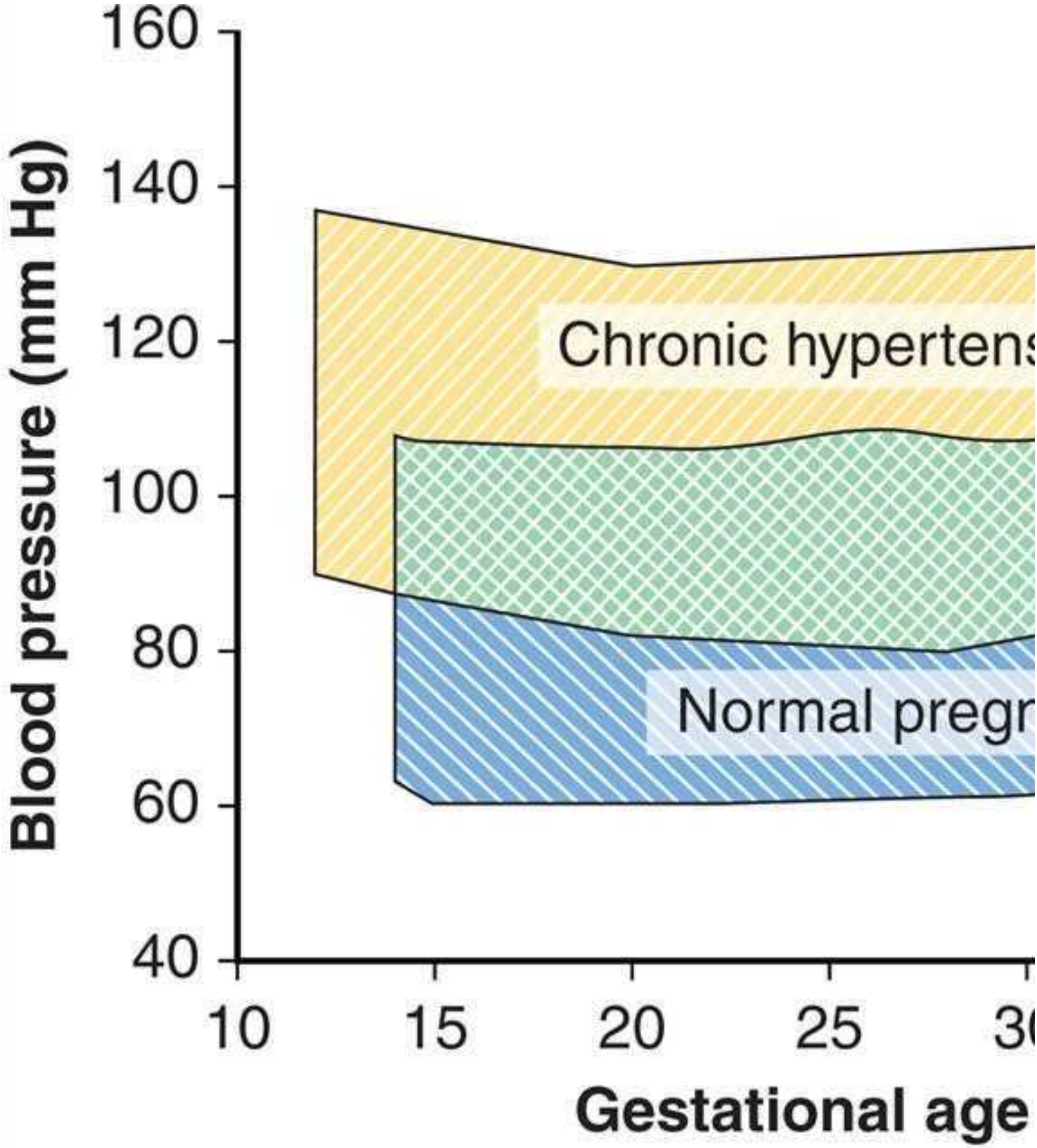
Several factors increase the likelihood that pregnant women will have chronic hypertension. Three of those most frequently cited are ethnicity, obesity, and diabetes. As previously discussed, chronic hypertension has a population incidence that is highest in black women and lowest in Mexican-American women (Kotchen, 2015). Related to this, hundreds of blood pressure-related phenotypes and genomic regions have been identified, including candidate genes for preeclampsia and chronic hypertension (Cowley, 2006; Ward, 2015).

The *metabolic syndrome* is a clinical cluster that includes hypertension, high blood sugar, excess fat at the waist, and abnormal cholesterol or triglyceride levels. This constellation is a risk marker for superimposed preeclampsia and for persistent postpartum hypertension (Jeyabalan, 2015; Spaan, 2012). This is not surprising because obesity may increase the prevalence of chronic hypertension tenfold (Chap. 48, Pregnancy and Obesity). In addition, obese women are more likely to develop superimposed preeclampsia. Diabetes is also prevalent in chronically hypertensive women, and its interplay with obesity and preeclampsia is overwhelming (Leon, 2016). In aforementioned study from the Nationwide Patient Sample, the most frequent comorbidities associated with chronic hypertension were pregestational diabetes—6.6 percent, thyroid disorders—4.1 percent, and collagen-vascular disease—0.6 percent (Bateman, 2012). Similar comorbidities were described by Cruz and associates (2011).

Effects of Pregnancy on Chronic Hypertension

Blood pressure drops in early pregnancy in most women with chronic hypertension, and it rises again during the third trimester (Fig. 50-1). According to studies by Tihtonen and coworkers (2007), women with chronic hypertension have persistently elevated vascular resistance and possibly reduced intravascular volume expansion. Adverse outcomes in these women are dependent largely on whether superimposed preeclampsia develops. This may be related to observations reported by Hibbard and colleagues (2005, 2015) that arterial mechanical properties are most marked in women with superimposed preeclampsia.

FIGURE 50-1
Mean systolic and diastolic blood pressures across pregnancy in 107 untreated chronically hypertensive women (*yellow*) compared with blood pressures across pregnancy in 4589 healthy nulliparas (*blue*). (Data from August, 2015; Levine, 1997; Sibai, 1990a.)



ADVERSE PREGNANCY EFFECTS

Chronic hypertension is associated with several adverse maternal and perinatal outcomes listed in Table 50-3. In sum, these adversities are directly related to severity and duration of hypertension before pregnancy and whether superimposed preeclampsia develops, especially early in gestation. Importantly, in women with mild chronic hypertension, outcomes are also related to blood pressure levels during pregnancy. At this time, however, there are no proven benefits of "tight" versus "less-tight" control of chronic hypertension during pregnancy, as discussed later ("Tight Control") (Magee, 2015).

TABLE 50-3

Some Adverse Effects of Chronic Hypertension on Maternal and Perinatal Outcomes

Maternal	Perinatal
Superimposed preeclampsia	Stillbirth
HELLP syndrome	Growth restriction
Placental abruption	Preterm delivery
Stroke	Neonatal death
Acute kidney injury	Neonatal morbidity
Heart failure	
Hypertensive cardiomyopathy	
Myocardial infarction	
Maternal death	

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Maternal Morbidity and Mortality

Most women whose chronic hypertension is well controlled with therapy before pregnancy will do well. Even these women, however, are at increased risk for adverse outcomes. Complications are more likely with severe baseline hypertension and especially with documented end-organ damage (Czeizel, 2011; Odibo, 2013). In a study of pregnancy outcomes in nearly 30,000 chronically hypertensive women, Gilbert and associates (2007) reported markedly increased rates of maternal morbidity that included stroke, pulmonary edema, and renal failure. These observations were verified in the report from the Nationwide Patient Sample by Bateman and colleagues (2012). In this latter study, hypertension complications included stroke—2.7 per 1000, acute renal failure—5.9 per 1000, pulmonary edema—1.5 per 1000, mechanical ventilation—3.8 per 1000, and in-house maternal mortality—0.4 per 1000. The contribution of hypertension to pregnancy-related strokes is discussed in Chapter 60 (Cerebrovascular Diseases) and to hypertensive and idiopathic peripartum cardiomyopathy in Chapter 49 (Dilated Cardiomyopathy).

Pregnancy-aggravated hypertension may be due to gestational hypertension or to superimposed preeclampsia. In either instance, blood pressures can be dangerously elevated. As emphasized by Clark and Hankins (2012), systolic pressure ≥160 mm Hg or diastolic pressure ≥110 mm Hg will rapidly cause renal or cardiopulmonary dysfunction or cerebral hemorrhage. With superimposed severe preeclampsia or eclampsia, the maternal prognosis is poor unless the pregnancy is ended. Placental abruption is a common and serious complication (Chap. 41, Placental Abruption). In addition to hypertensive heart failure mentioned above, aortic dissection was described by Weissman-Brenner and coworkers (2004) and is discussed in Chapter 49 (Diseases of the Aorta).

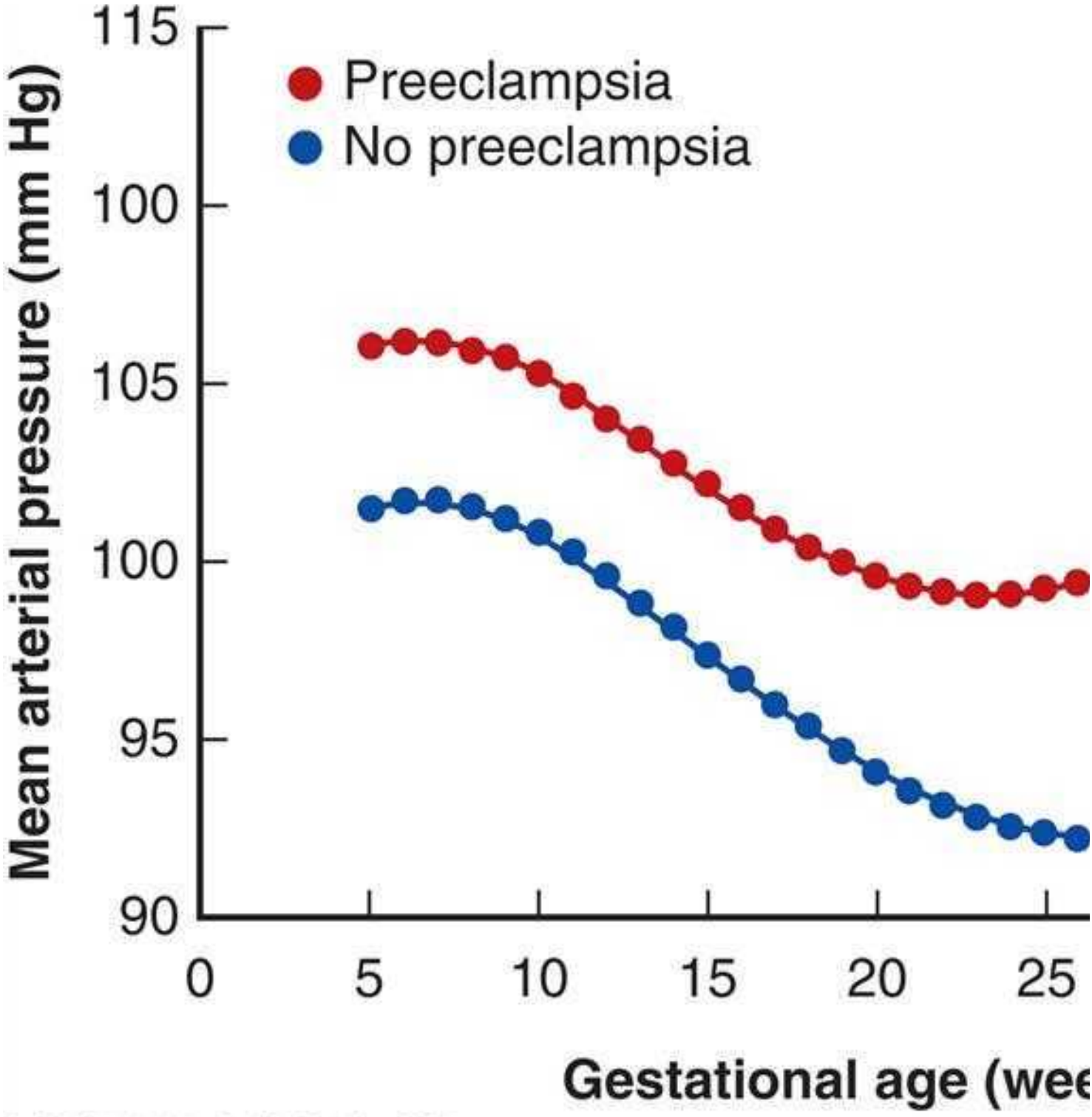
In aggregate, chronic hypertension is associated with a fivefold risk for maternal death (Gilbert, 2007). This is emphasized by the report by Creanga and colleagues (2015) describing 3358 pregnancy-related deaths in the United States from 2006 through 2010. Hypertensive disorders, including chronic hypertension and preeclampsia syndrome, accounted for 9.4 percent of these deaths. Undoubtedly related were other causes of death such as cardiovascular conditions—14.6 percent, cerebrovascular conditions—6.2 percent, and cardiomyopathy—11.8 percent. Moodley (2007) reported similar findings with 3406 maternal deaths from South Africa.

Superimposed Preeclampsia

Because superimposed preeclampsia is not precisely defined in women with chronic hypertension, the reported incidence varies from 13 to 40 percent (American College of Obstetricians and Gynecologists, 2013; Bramham, 2016; Kim, 2016b; Moussa, 2017). August and colleagues (2015) posit that this predilection may stem from similar genetic, biochemical, and metabolic abnormalities. For example, the risk for superimposed preeclampsia is directly related to the severity of baseline hypertension (Ankumah, 2014; Morgan, 2016b). In a Maternal-Fetal Medicine Units (MFMU) Network trial, Caritis and coworkers (1998) identified superimposed preeclampsia in 25 percent of hypertensive gravidas. The rate was 29 percent in a California database study (Yanit, 2012). And, women whose hypertension becomes severe enough to warrant chronic antihypertensive therapy during pregnancy are at inordinately high risk for superimposed preeclampsia (Morgan, 2016a). And, this risk is even higher if there is baseline proteinuria. Finally, and shown in Figure 50-2, chronically hypertensive women destined to develop severe superimposed preeclampsia have higher initial blood pressures that nadir earlier than those of women who do not develop severe disease.

FIGURE 50-2

Blood pressure trends in treated, chronically hypertensive women with and without superimposed preeclampsia. Mean maternal pressures (MAPs) at entry (p = 0.002) and throughout gestation (p <0.001) are significantly different for each group. MAP nadir at 23.3 weeks (95% CI, 22.5–24.1) for superimposed preeclampsia versus 26.4 weeks (95% CI, 22.5–27.6) for those without preeclampsia is significant (3.1 weeks, 95% CI, 2.3–4.3). (Data from Morgan, 2016a.)



Thus far, clinical prognostic and predictive tests for superimposed preeclampsia have been disappointing (Conde-Agudelo, 2015). Di Lorenzo and colleagues (2012) studied serum markers for Down syndrome to predict preeclampsia and calculated a sensitivity of 60 percent, with a 20-percent false-positive rate. Similar results were found using antiangiogenic factors to discriminate among chronic hypertension, gestational hypertension, and preeclampsia (Costa, 2016; Sibai, 2008). According to Anton and coworkers (2013), microRNA assays may prove valuable as predictors of pregnancy-associated hypertension.

Prevention

Trials of various medications to prevent preeclampsia in women with chronic hypertension have generally been disappointing and show little or no benefit. Low-dose aspirin has been evaluated most frequently (Mol, 2016; Staff, 2015). In the MFMU Network study by Caritis (1998) cited above, the incidence of superimposed preeclampsia, fetal-growth restriction, or both is similar in women given low-dose aspirin or placebo. Using the same database, Moore and associates (2015) found that early administration of low-dose aspirin (<17 weeks' gestation) resulted in a significant 41-percent lower frequency of superimposed preeclampsia in chronically hypertensive women—18 versus 31 percent. Duley (2007) and Meads (2008) and their colleagues performed systematic reviews and noted that low-dose aspirin was

beneficial in some high-risk women. Moderate benefits were also found from a metaanalysis by Askie and coworkers (2007). In a secondary analysis, Poon and associates (2017) noted that aspirin was ineffective to reduce the incidence of preterm preeclampsia.

The U.S. Preventive Services Task Force recommends treatment with low-dose aspirin for chronically hypertensive women at high risk for preeclampsia (Henderson, 2014). The recommendation to initiate 81 mg between 12 and 28 weeks' gestation and continue therapy until delivery was adopted by the American College of Obstetricians and Gynecologists (2016b). In addition to chronic hypertension, indications for aspirin prophylaxis for those at high-risk of preeclampsia include a history of preeclampsia, multifetal gestation, diabetes, renal disease, and autoimmune disease.

Antioxidants to prevent preeclampsia have been studied. Spinnato and coworkers (2007) randomly assigned 311 women with chronic hypertension to treatment with vitamins C and E or with a placebo. A similar number in both groups developed preeclampsia—17 versus 20 percent, respectively.

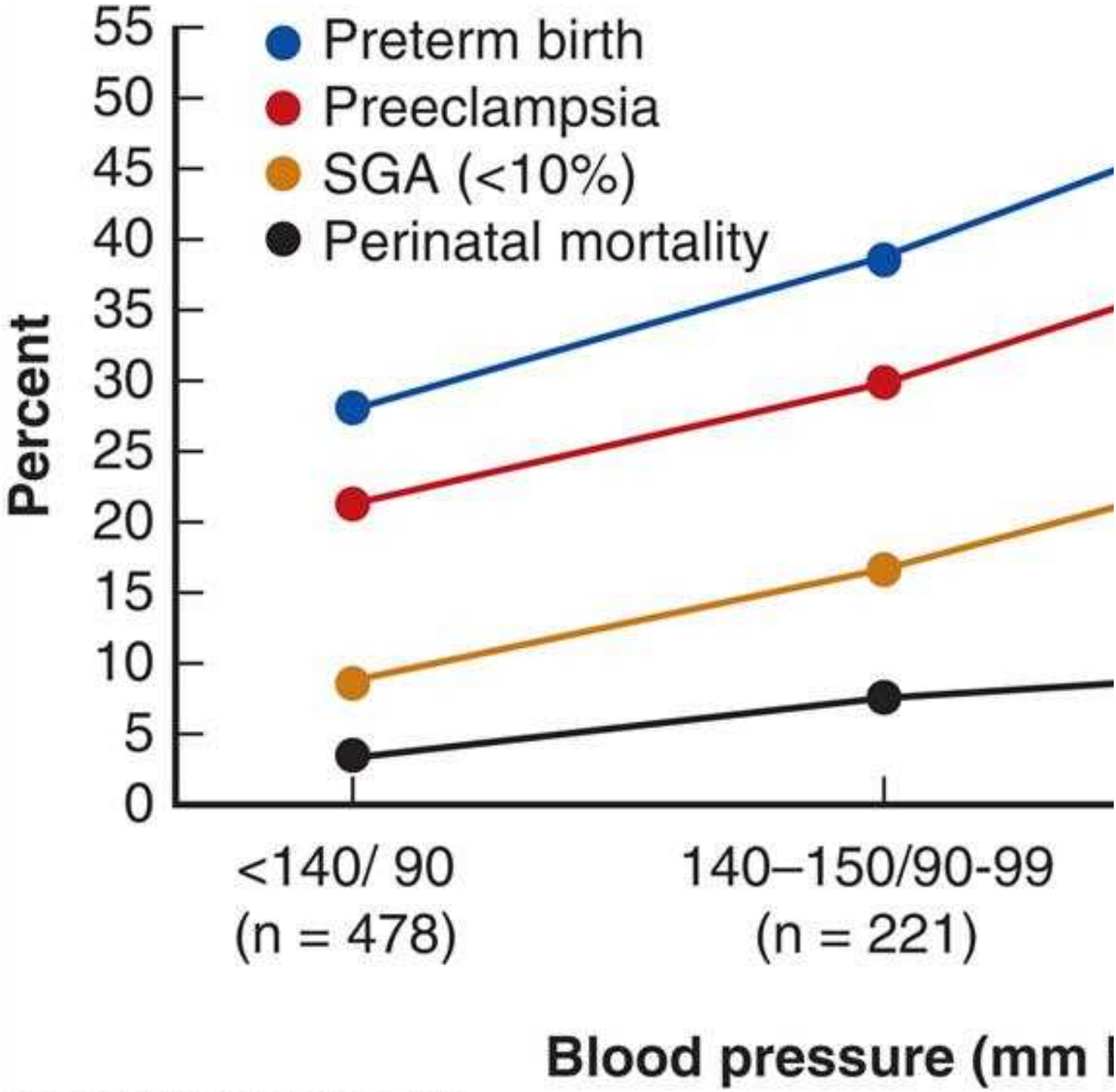
Placental Abruption

Chronic hypertension augments the risk two- to threefold for premature placental separation. The general obstetrical population risk is 1 in 200 to 300 pregnancies, and this rises to 1 in 60 to 120 pregnancies in women with chronic hypertension (Ankumah, 2014; Cruz, 2011; Magee, 2015). The abruption risk is elevated further if the woman smokes. Most abruptions are in women with worsening gestational hypertension or superimposed preeclampsia. The abruption risk is highest with severe hypertension, and Vigil-De Gracia and colleagues (2004) reported it to be 8.4 percent. From medical record data from the Norwegian Birth Registry, folic acid and/or multivitamin supplements slightly lowered the abruption incidence in women with chronic hypertension (Nilsen, 2008).

Perinatal Morbidity and Mortality

Rates of almost all adverse perinatal outcomes are greater in women with chronic hypertension than in nonaffected controls. As expected, for the entire group of hypertensive women, those who developed preeclampsia have substantially higher adverse outcome rates compared with those without preeclampsia. As shown in Figure 50-3, adverse outcome rates rise incrementally with rising blood pressures. Evidence also supports that chronic hypertension—treated or untreated—is associated with congenital anomalies. Bateman and coworkers (2015) from the Medicaid Analytic Extract cited earlier found an elevated risk for severe congenital malformations—especially cardiac defects. Moreover, severe hypertension and fetal esophageal atresia or stenosis have been associated (Bánhidy, 2011; Van Gelder, 2015).

FIGURE 50-3
Frequency of selected adverse maternal and perinatal outcomes by blood pressure stratification in women with mild chronic hypertension. SGA = small for gestational age. (Data from Ankumah, 2014.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics: 25th Edition

The stillbirth frequency with chronic hypertension is substantively greater in most reports (Chap. 35, Risk Factors). In the Nationwide Patient Sample study, the stillbirth rate was 15.1 per 1000 births (Bateman, 2012). This is similar to that of 18 per 1000 from a Norwegian study by Ahmad and coworkers (2012) and of 24 per 1000 births from a Network study reported by Ankumah and colleagues (2014) and described in "Tight Control". Low-birthweight neonates are also common. They are due to fetal-growth restriction, preterm delivery that is largely clinically indicated, or both (see Fig. 50-3). In the California database study noted earlier, a fourth of fetuses were delivered preterm (Yanit, 2012).

These and other studies attest to the elevated risk for fetal-growth restriction, and the incidence averages 20 percent. Zetterström and coworkers (2006) reported a 2.4-fold risk for fetal-growth restriction in 2754 chronically hypertensive Swedish women compared with the risk in normotensive women. Broekhuijsen and associates (2012) found a 1.3-fold increased risk for 1609 Dutch nulliparas with chronic hypertension compared with that in normotensive controls. As with other complications, fetal-growth dysfunction is more likely in chronically hypertensive women who develop superimposed preeclampsia. In one study, the incidence of growth-restricted fetuses born to women with superimposed preeclampsia was almost 50 percent compared with only 21 percent in chronically hypertensive women without preeclampsia (Chappell, 2008). Finally, women with chronic hypertension severe enough to warrant treatment had an 11-percent incidence of fetal-growth restriction to a degree yielding birthweights ≤3rd percentile (Morgan, 2016a). For all of these reasons, neonates born to these women have a correspondingly high rate of intensive-care nursery admission.

All of these adverse perinatal effects of chronic hypertension contribute to the greater perinatal mortality rate, which is three- to fourfold higher than the rate in nonaffected gravidas (American College of Obstetricians and Gynecologists, 2013). In the Network study by Ankumah (2014) referenced in Figure 50-3, the perinatal death rate was 31 per 1000 births with mild hypertension, 72 per 1000 births with moderate disease, and 100 per 1000 births in women with severe chronic hypertension. And, in the study from Parkland Hospital by Morgan (2016a), the perinatal mortality rate was 32 per 1000 births in women who were treated for their chronic hypertension. Again, as expected, the highest rates are in women who develop superimposed preeclampsia, for whom the risk doubled from 4 to 8 percent. Finally, if diabetes coexists with chronic hypertension, then preterm delivery, fetal-growth restriction, and perinatal mortality rates are increased even more (Gonzalez-Gonzalez, 2008; Yanit, 2012).

MANAGEMENT DURING PREGNANCY

The diagnosis of chronic hypertension in pregnancy should be confirmed. The American College of Obstetricians and Gynecologists (2013) recommends use of ambulatory monitoring to exclude suspected white-coat hypertension before initiating antihypertensive therapy. Goals for chronic hypertension management include rate reductions of adverse maternal or perinatal outcomes just discussed. Treatment is targeted to prevent moderate or severe hypertension and to delay or dampen the severity of pregnancy-aggravated hypertension. To some extent, these goals can be achieved pharmacologically. Blood pressure self-monitoring is encouraged, but for accuracy, automated devices must be properly calibrated (Brown, 2004; Staessen, 2004). Personal health modification includes dietary counseling and reduction of behaviors such as tobacco, alcohol, cocaine, or other substance use (see Table 50-2). A low-sodium diet is not required (American College of Obstetricians and Gynecologists, 2013).

Some women—especially those with long-term or untreated hypertension—have complications that increase the risk of adverse pregnancy events. For example, in one study, a fourth of gravidas with chronic hypertension also had concentric ventricular hypertrophy (Ambia, 2017; Kim, 2016a). Thus, if not already accomplished, assessment during pregnancy is done for the cardiovascular and renal systems (Morgan, 2016a,b).

Antihypertensive Drugs

As concluded by the American College of Obstetricians and Gynecologists (2013, 2016a), treatment of hypertension during pregnancy has included every drug class, but information is still limited regarding safety and efficacy (Czeizel, 2011; Podymow, 2011). Although many studies indicate greater perinatal adverse effects in gravidas requiring treatment, it is still not known whether this is due to cause or effect (Orbach, 2013). The following summary of antihypertensive drugs is abstracted from several sources, including the *2016 Physicians' Desk Reference*. Many of these drugs are also discussed throughout Chapter 12 (Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs) and have been reviewed by Umans and associates (2015).

Adrenergic-Receptor Blocking Agents

Peripherally acting β-adrenergic-receptor blockers cause a generalized decline in sympathetic tone and decreased cardiac output. Examples are propranolol, metoprolol, and atenolol. Labetalol is a popular and commonly used α/β-adrenergic blocker that is considered safe.

Some adrenergic-blocking drugs act *centrally* by reducing sympathetic outflow to effect a generalized decreased vascular tone. These include clonidine and α-methyldopa. Drugs in this class most frequently used in pregnancy to treat hypertension are methyldopa or an α- or β-receptor blocking agent such as labetalol.

Calcium-Channel Blocking Agents

These drugs are divided into three subclasses based on their modification of calcium entry into cells and interference with binding sites on voltage-dependent calcium channels. Common agents include nifedipine—a dihydropyridine, and verapamil—a phenylalkyl amine derivative. These agents have negative inotropic effects and thus can worsen ventricular dysfunction and congestive heart failure. Theoretically, they may potentiate the vasoactive actions of magnesium sulfate that is given for eclampsia neuroprophylaxis. Although data are limited regarding their use during pregnancy, they appear to be safe therapy for chronic hypertension (Briggs, 2015; Umans, 2015).

Diuretics

Thiazide diuretics are sulfonamides, and these were the first drug group used to successfully treat chronic hypertension (Beyer, 1982). These agents and loop-acting diuretics such as furosemide are commonly used in nonpregnant hypertensive patients. In the short term, they provide sodium and water diuresis with volume depletion. But with time, there is *sodium escape,* and volume depletion is partially corrected. Some aspect of lowered peripheral vascular resistance likely contributes to their effectiveness in reducing long-term morbidity (Umans, 2015).

Thiazide drugs may be mildly diabetogenic, and expected volume expansion may be curtailed in pregnant women. Sibai and colleagues (1984) showed that plasma volume expanded only about 20 percent over time in hypertensive pregnant women who continued diuretic therapy compared with a 50-percent expansion in women who discontinued treatment. Although perinatal outcomes were similar in these women, such concerns have led to practices of withholding diuretics as first-line therapy for chronic hypertension, particularly after 20 weeks' gestation (Working Group Report, 2000). Even so, in a Cochrane review, Churchill and associates (2007) reported no differences in perinatal outcomes in 1836 nonhypertensive women randomly assigned to a thiazide diuretic or placebo for primary preeclampsia prevention. Overall, thiazide diuretics are considered safe in pregnancy (Briggs, 2015). But for preeclampsia treatment, they are considered to be ineffective (Umans, 2015).

Vasodilators

Hydralazine relaxes arterial smooth muscle and has been used parenterally for decades to safely treat severe peripartum hypertension (Chap. 40, Hydralazine). Oral hydralazine monotherapy for chronic hypertension is not generally used because of its weak antihypertensive effects and resultant tachycardia. It may be an effective adjunct for long-term use with other antihypertensives, especially if there is chronic renal insufficiency. In one study, vasodilator treatment of chronically hypertensive women was associated with a twofold rise in rates of low-birthweight and growth-restricted neonates (Su, 2013).

Angiotensin-Converting Enzyme Inhibitors

These drugs inhibit the conversion of angiotensin-I to the potent vasoconstrictor angiotensin-II. They can cause severe fetal malformations when given in the second and third trimesters. These include oligohydramnios, hypocalvaria, and renal dysfunction (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Some preliminary studies also suggest teratogenic effects, and because of this, they are not recommended at any time during pregnancy (Briggs, 2015; Podymow, 2011).

Angiotensin-receptor blockers act in a similar manner. But, instead of blocking the production of angiotensin-II, they inhibit binding to its receptor. They are presumed to have the same fetal effects as angiotensin-converting enzyme inhibitors and thus are also contraindicated.

Antihypertensive Treatment in Pregnancy

Severe Chronic Hypertension

The prognosis for pregnancy outcome with chronic hypertension is somewhat dependent on the severity of disease antedating pregnancy. This may be related to findings that many women with severe hypertension have renal disease—as either cause or effect (Cunningham, 1990; Morgan, 2016a). It follows that women whose hypertension is severe enough to require antihypertensive therapy are at inordinately high risk for superimposed preeclampsia.

Sibai and coworkers (1986) described outcomes from 44 pregnancies in women whose blood pressure at 6 to 11 weeks' gestation was ≥170/110 mm Hg. All were given oral treatment with α-methyldopa and hydralazine to maintain pressures <160/110 mm Hg. Of the 44 pregnancies, superimposed preeclampsia developed in half, and all adverse perinatal outcomes were in this group. Moreover, all neonates of women in the superimposed group were delivered preterm, nearly 80 percent were also growth restricted, and 48 percent suffered perinatal death. Conversely, those women with severe chronic hypertension who did not develop superimposed preeclampsia had reasonably good outcomes. There were no perinatal deaths, and only 5 percent of fetuses were growth restricted. Webster and colleagues (2017) found labetalol and nifedipine to be equally effective for chronic hypertension in pregnant women.

Morgan and coworkers (2016a) reported 447 women whose chronic hypertension required treatment beginning prior to 20 weeks. More than half of these women developed superimposed severe preeclampsia. The rate of preeclampsia was 53 percent for those whose 24-hour protein excretion was <300 mg. But for those with antecedent baseline proteinuria >300 mg/day, 79 percent developed severe preeclampsia.

Mild or Moderate Hypertension

Continuing prepregnancy antihypertensive treatment during pregnancy is debatable for those with mild or moderate hypertension. Although blood pressure reduction certainly benefits the mother long term, it at least theoretically can reduce uteroplacental perfusion. In older observational reports, most pregnancy outcomes in women with mild to moderate hypertension generally were good without treatment and unless superimposed preeclampsia developed (Chesley, 1978; Umans, 2015).

Newer data are accruing that address potential salutary effects on pregnancy outcomes by simply lowering blood pressure. Earlier studies were relatively small and had widely varying inclusion and outcome criteria. In a Cochrane review of 49 of these studies that included a total of 4723 women with mild to moderate hypertension, Abalos and coworkers (2014) confirmed that the risk for subsequent severe hypertension was lowered with therapy. Compared with untreated women, the frequencies of superimposed preeclampsia, eclampsia, abruption, preterm birth, fetal-growth restriction, and perinatal or maternal mortality did not differ. This latter Cochrane review raised concerns for fetal-growth restriction with **β**-blocking drugs, notably atenolol. It is not resolved, however, because diminished placental perfusion secondary to lowered maternal blood pressure is confounded by the fact that worsening blood pressure itself is associated with abnormal fetal growth. Some also posit that the drugs have a direct fetal action (Umans, 2015). In two of the larger randomized trials, however, the incidence of growth restriction was not altered in women randomly assigned to treatment (Gruppo di Studio Ipertensione in Gravidanza, 1998; Sibai, 1990a).

The observations of Morgan and colleagues (2016a) support the findings of the Cochrane review by Abalos. Specifically, they reported that despite therapy for chronic hypertension, there was frequent superimposed preeclampsia, fetal-growth restriction, preterm delivery, and perinatal mortality. Moreover, and as shown in Table 50-4, women with baseline proteinuria >300 mg/d had even worse obstetrical outcomes.

TABLE 50-4

Selected Pregnancy Outcomes in Women with Chronic Hypertension Treated During Pregnancy with and without Baseline Proteinuria[a]

Outcome	Baseline Proteinuria[a]	No Proteinuria	*P*-value
Superimposed preeclampsia	79%	49%	<0.001
Abruption	0	1%	0.45
EGA at delivery (mean)[b]	35.1 ± 4.3 wks	37.2 ± 3.3 wks	<0.001
≤30 weeks	18%	6%	0.001
≤34 weeks	34%	17%	0.005
≤37 weeks	48%	26%	0.002
Birthweight (mean)[b]	2379 ± 1028 g	2814 ± 807 g	<0.001
≤3rd percentile	20%	9%	0.01
≤10th percentile	41%	22%	<0.001
Perinatal mortality	36/1000	31/1000	0.47

[a]Defined as ≥300 mg/d protein excretion before 20 weeks' gestation.

[b]Mean ± standard deviations.

EGA = estimated gestational age.

Data from Morgan, 2016b.

"Tight Control"

During the past decade, the concept of *tight control* of blood pressure has been espoused as a means of optimizing maternal and perinatal outcomes. Such control is analogous to that of glycemic control for management of the pregnant diabetic patient. The observational study by Ankumah (2014) noted earlier lends credence to tighter control of blood pressure. These investigators showed that the risk of adverse pregnancy outcomes in 759 women with chronic hypertension was lower when blood pressures before 20 weeks were <140 mm Hg compared with higher pressure categories and increasing blood pressures. Unfortunately, this did not hold up when less-tight was compared with tight control. Specifically, Magee and coworkers (2015) randomized 987 women with chronic hypertension or gestational hypertension to either one of these two management schemes. Except for a lower rate of severe hypertension in the tightly controlled group, they found no significant differences between these two groups' other adverse pregnancy outcomes (Table 50-5). Tight control was also not more costly (Ahmed, 2016). These and similar findings prompted an ongoing randomized controlled trial—Project CHAP (ClinicalTrials.gov, 2016)—to answer this question.

TABLE 50-5

Selected Maternal and Perinatal Outcomes in Pregnant Women with Chronic Hypertension According to Less-Tight versus Tight Control

Outcome	Less-Tight Control (n = 493)	Tight Control (n = 488)
Maternal		
Placental abruption	2.2%	2.3%
Severe hypertension[a]Preeclampsia	41%	28%
Preeclampsia	49%	46%
HELLP syndrome	1.8%	0.4%
Perinatal		
Deaths	28/1000	23/1000
<10th percentile	16%	20%
<3rd percentile	4.7%	5.3%
Respiratory problem	17%	14%

[a] $p < 0.001$, all other comparisons $p > 0.05$.

HELLP = hemolysis, elevated liver enzyme levels, low platelet count.

Data from Magee, 2015.

Recommendations for Therapy

Until there are data to confirm any salutary effects of treatment of uncomplicated mild to moderate chronic hypertension in pregnancy, it seems reasonable to follow the guidelines of the American College of Obstetricians and Gynecologists (2013) and the Society for Maternal-Fetal Medicine (2015). Pregnant women with *severe hypertension* must be treated for maternal neuro-, cardio-, and renoprotection. Treatment is also mandatory for women with prior adverse outcomes such as strokes, MIs, and evidence for cardiac or renal dysfunction. With end-organ dysfunction, treatment to diastolic pressure level ≤90 mm Hg is reasonable to mitigate further organ damage.

For most women with mild to moderate hypertension, the College recommends that treatment be withheld as long as systolic blood pressure is <160 mm Hg and diastolic blood pressure is <105 mm Hg. Some find it reasonable to begin antihypertensive treatment in otherwise healthy pregnant women with persistent systolic pressures >150 mm Hg or diastolic pressures of 95 to 100 mm Hg or greater (August, 2015; Working Group Report, 2000). At Parkland Hospital we initiate treatment with antihypertensive agents for blood pressures of 150/100 mm Hg or higher. Our preferred regimens include monotherapy with a β-blocking drug such as labetalol or a calcium-channel blocking agent such as amlodipine. For women in the first half of pregnancy, therapy with a thiazide diuretic seems reasonable. This is especially true in black women, in whom there is a high prevalence of salt-sensitive chronic hypertension.

It is controversial whether or not women who present early in pregnancy and who are already taking antihypertensive drugs should continue to take these (Rezk, 2016). According to the American College of Obstetricians and Gynecologists (2013) and the Society for Maternal-Fetal Medicine (2015), for women with mild to moderate hypertension, it is *reasonable* to discontinue medications during the first trimester and to restart them if blood pressures approach the severe range. Our practice at Parkland Hospital is to continue treatment if the woman is already taking drugs when she presents for prenatal care. Exceptions are discontinuation of angiotensin-converting enzyme inhibitors and receptor blockers.

Some women will have persistently worrisome hypertension despite usual therapy (Samuel, 2011; Sibai, 1990a). In these women, primary attention is given to the likelihood of pregnancy-aggravated hypertension, with or without superimposed preeclampsia. Other possibilities include inaccurate blood-pressure measurements, suboptimal treatment, and antagonizing substances such as chronic ingestion of nonsteroidal antiinflammatory drugs (NSAIDs) (Moser, 2006; Sowers, 2005).

Pregnancy-Aggravated Hypertension or Superimposed Preeclampsia

As discussed, the frequency of superimposed preeclampsia for women with chronic hypertension varies depending on the study population and hypertension severity (Ankumah, 2014). Importantly, in 40 to 50 percent of chronically hypertensive women, superimposed preeclampsia develops before 37 weeks (Chappell, 2008; Harper, 2016). This proportion is even higher in women who required hypertension treatment during pregnancy (Morgan, 2016a).

The diagnosis may be difficult to make, especially in women with hypertension who have underlying renal disease with chronic proteinuria (Cunningham, 1990; Morgan, 2016b). As discussed in Chapter 40 (Preeclampsia Superimposed on Chronic Hypertension), conditions that support the diagnosis of superimposed preeclampsia include worsening hypertension, new-onset proteinuria, neurological symptoms such as severe headaches and visual disturbances, generalized edema, oliguria, and certainly, convulsions or pulmonary edema. Making the diagnosis based on worsening proteinuria in women with baseline proteinuria is problematic. Supporting laboratory abnormalities are rising serum creatinine or hepatic transaminase levels, thrombocytopenia, or any of the facets of HELLP (hemolysis, elevated liver enzyme levels, low platelet count) syndrome. For women with chronic hypertension and superimposed preeclampsia with severe features, magnesium sulfate for maternal neuroprophylaxis is recommended (American College of Obstetricians and Gynecologists, 2013). Severe hypertension is treated as described in Chapter 40 (Management Considerations).

Some pregnant women with chronic hypertension have worsening hypertension with no other findings of superimposed preeclampsia. This is most commonly encountered near the end of the second trimester. In the absence of other supporting criteria for superimposed preeclampsia, this likely represents the higher end of the normal blood-pressure curve shown in Figure 50-1. In such women, if preeclampsia can be confidently excluded, it is reasonable to begin or to increase the dose of antihypertensive therapy.

Fetal Assessment

Women with well-controlled chronic hypertension who have no complicating factors can generally be expected to have a good pregnancy outcome. Because even those with mild hypertension have a greater risk of superimposed preeclampsia and fetal-growth restriction, serial antepartum assessment of fetal well-being is recommended by many. That said, according to the American College of Obstetricians and Gynecologists (2013), with the exception of sonographic fetal-growth monitoring, described in Chapter 44 (Fetal-Growth Restriction Recognition), no conclusive data address either benefit or harm associated with various antepartum surveillance strategies.

Expectant Management of Early-Onset Preeclampsia

Given that many women with chronic hypertension develop superimposed preeclampsia before term, considerations for expectant management may be reasonable in some cases. In a study from Magee-Women's Hospital, 41 carefully selected women with a median gestational age of 31.6 weeks were expectantly managed (Samuel, 2011). Despite liberal criteria to mandate delivery, 17 percent developed either placental abruption or pulmonary edema. The latency period was extended by a mean of 9.7 days. There were no perinatal deaths, however, salutary outcomes were similar. These investigators recommend randomized trials to study expectant management before this becomes usual care.

Delivery

For chronically hypertensive women who have complications such as fetal-growth restriction or superimposed preeclampsia, the decision to deliver is made by clinical judgment. The route of delivery is dictated by obstetrical factors. Certainly, most women with superimposed severe preeclampsia are better delivered even when the fetus is markedly preterm. Increased risk for placental abruption, cerebral hemorrhage, and peripartum heart failure attend delivery delays (Cunningham, 1986, 2005; Martin, 2005).

For women with chronic hypertension without preeclampsia, expectant management at later gestational ages was reported recently by Harper and colleagues (2016). They concluded that expectant management beyond 39 weeks' gestation was associated with an increasing incidence of severe preeclampsia and that planned delivery before 37 weeks was associated with a rise in rates of adverse neonatal outcomes.

For women with mild to moderate chronic hypertension who continue to have an uncomplicated pregnancy, the American College of Obstetricians and Gynecologists (2013) recommends delivery not be pursued until $38^{0/7}$ weeks. The consensus committee findings by Spong and associates (2011) recommend consideration for delivery at 38 to 39 weeks, that is, ≥37 completed weeks. A trial of labor induction is preferable, and many of these women respond favorably and will be delivered vaginally (Alexander, 1999; Atkinson, 1995).

Intrapartum Considerations

For women with severe preeclampsia, peripartum management is the same as described in Chapter 40 (Consideration for Delivery). Epidural analgesia for labor and delivery is optimal with the caveat that it is not given to treat hypertension (Lucas, 2001). That said, women with severe superimposed preeclampsia are more sensitive to the acute hypotensive effects of epidural analgesia (Vricella, 2012). Also in this group, magnesium sulfate neuroprophylaxis is initiated for prevention of eclampsia. Severe hypertension—diastolic blood pressure ≥110 mm Hg or systolic pressure ≥160 mm Hg—is treated with either intravenous hydralazine or labetalol. Some prefer to treat women when the diastolic pressure reaches 100 to 105 mm Hg. Vigil-De Gracia and colleagues (2006) randomly assigned 200 women to intravenous hydralazine or labetalol to acutely lower severe high blood pressure in pregnancy. Outcomes were similar except for significantly more maternal palpitations and tachycardia with hydralazine and significantly more neonatal hypotension and bradycardia with labetalol.

Postpartum Care

In most respects, postpartum observation, prevention, and management of adverse complications are similar in women with severe chronic hypertension and in those with severe preeclampsia–eclampsia. For persistent severe hypertension, consideration is given for a cause such as pheochromocytoma or Cushing disease (Sibai, 2012). And, in women with chronic end-organ damage, certain complications are more common. These include cerebral or pulmonary edema, heart failure, renal dysfunction, or cerebral hemorrhage, especially within the first 48 hours after delivery (Martin, 2005; Sibai, 1990b, 2012). These frequently are preceded by sudden elevations—"spikes"—of mean arterial blood pressure and of the systolic component (Cunningham, 2000, 2005).

Following delivery, as maternal peripheral resistance rises, left ventricular workload also grows. This elevation is further aggravated by appreciable and pathological amounts of interstitial fluid that are mobilized to be excreted as endothelial disruption from preeclampsia resolves. In these women, sudden hypertension—either moderate or severe—may exacerbate diastolic dysfunction, cause systolic dysfunction, and lead to pulmonary edema (Cunningham, 1986; Gandhi, 2001). Prompt hypertension control, along with furosemide-evoked diuresis, usually quickly resolves pulmonary edema.

The antihypertensive regimen given antepartum can be restarted in the puerperium. It is also possible in many women to forestall postpartum hypertension by administering intravenous or oral furosemide to augment the normal postpartum diuresis. In one study, 20-mg oral furosemide given daily for 5 days to postpartum women with severe preeclampsia aided blood pressure control (Ascarelli, 2005). Daily weights are helpful in this regard. On average, a woman should weigh 15 pounds less immediately after delivery. Excessive extracellular fluid can then be estimated. Other studies are in progress to determine aspects of postpartum blood pressure management (Cursino, 2015).

Some evidence supports that *chronic* ingestion of NSAIDs in the puerperium elevates blood pressure in women with severe preeclampsia (Vigil-De Gracia, 2017). This may not be problematic if these drugs are given only as needed (Wasden, 2014).

Women with chronic hypertension have special considerations for contraceptive and sterilization choices. These are discussed in detail throughout Chapters 38 and 39.

Long-Term Prognosis

Ultimately, women with chronic hypertension are at high risk for lifetime cardiovascular complications, especially when accompanied by diabetes, obesity, and the metabolic syndrome. Recent evidence also suggests that these women are at greater risk to develop cardiomyopathy remote from pregnancy (Behrens, 2016).

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CHAPTER 51: Pulmonary Disorders

A lung which is partially destroyed or thrown out of function may suffice for the respiration of a normal individual, but be unable to respond to the added demands of pregnancy, particularly in the latter months, when the enlarged uterus restricts the mobility of the diaphragm.

—J. Whitridge Williams (1903)

INTRODUCTION

As indicated by the above, it has long been appreciated that women in advanced pregnancy tolerate lung disease poorly. Nevertheless, pulmonary disorders are frequently encountered during pregnancy. Chronic asthma or an acute exacerbation is the most common and affects up to 8 percent of pregnant women. Moreover, asthma along with community-acquired pneumonia accounted for almost 10 percent of nonobstetrical antepartum hospitalizations in one managed care plan (Gazmararian, 2002). Pneumonia is also a frequent postpartum complication requiring readmission (Belfort, 2010). These and other pulmonary disorders are superimposed on several important pregnancy-induced changes of ventilatory physiology. For example, pregnant women, especially those in the last trimester, are susceptible to complications of severe acute pneumonitis as evidenced by the disparate number of maternal deaths during influenza pandemics.

The important and sometimes marked changes in the respiratory system induced by pregnancy are reviewed in Chapter 4 (Respiratory Tract), and values for associated tests can be found in the Appendix (Serum and Blood Constituents). Lung volumes and capacities that are measured directly to assess pulmonary pathophysiology may be significantly altered. In turn, these change gas concentrations and acid-base values in blood. Some of the physiological alterations induced by pregnancy were summarized by Wise and associates (2006):

1. *Vital capacity* and *inspiratory capacity* increase by approximately 20 percent by late pregnancy.
2. *Expiratory reserve volume* decreases from 1300 mL to approximately 1100 mL.
3. *Tidal volume* increases approximately 40 percent as a result of respiratory stimulation by progesterone.
4. *Minute ventilation* increases 30 to 40 percent due to increased tidal volume. As a result, arterial P_{O_2} increases from 100 to 105 mm Hg.
5. Increasing metabolic demands cause a 30-percent rise in *carbon dioxide (CO2) production*. But, because of its concomitantly increased diffusion capacity and hyperventilation, the arterial P_{CO_2} decreases from 40 to 32 mm Hg.
6. *Residual volume* decreases approximately 20 percent from 1500 mL to approximately 1200 mL.
7. *Chest wall compliance* is reduced by a third by the expanding uterus and increased intraabdominal pressure. This causes a 10- to 25-percent decrease in *functional residual capacity*—the sum of expiratory reserve and residual volumes.

In a longitudinal cohort study, Grindheim and colleagues (2012) also showed that forced vital capacity and peak expiratory flow rose progressively across pregnancy after 14 to 16 weeks' gestation. The end result of these pregnancy-induced changes is substantively increased ventilation due to deeper but not more frequent breathing. These are thought to be stimulated by basal oxygen consumption as it rises incrementally from 20 to 40 mL/min in the second half of pregnancy.

ASTHMA

Reactive airway disease is seen frequently in young women and therefore often complicates pregnancy. Asthma prevalence grew steadily in many countries beginning in the mid-1970s but may have plateaued in the United States with a prevalence in adults of approximately 10 percent (Barnes, 2015; Centers for Disease Control and Prevention, 2010c, 2013). The estimated asthma prevalence during pregnancy ranges between 4 and 8 percent, and this appears to be rising (Kelly, 2015; Racusin, 2013). Finally, evidence is accruing that fetal and neonatal environmental exposures may contribute to the origins or mitigation of asthma (Grant, 2016; Litonjua, 2016; Spiegel, 2016).

Pathophysiology

Asthma is a chronic inflammatory airway syndrome with a major hereditary component. Increased airway responsiveness and persistent subacute inflammation are associated with polymorphism genes on chromosomes 5q that include cytokine gene clusters, β-adrenergic and glucocorticoid receptor

genes, and the T-cell antigen receptor gene (Barnes, 2015). Asthma is etiologically and clinically heterogeneous, and an *environmental allergic stimulant* such as influenza or cigarette smoke serves as a promoter for susceptible individuals (Bel, 2013).

The hallmarks of asthma are reversible airway obstruction from bronchial smooth muscle contraction, vascular congestion, tenacious mucus, and mucosal edema. Mucosal inflammation is characterized by infiltration with eosinophils, mast cells, and T lymphocytes. These causes airway inflammation and increased responsiveness to numerous stimuli that include irritants, viral infections, aspirin, cold air, and exercise. Several inflammatory mediators produced by these and other cells include histamine, leukotrienes, prostaglandins, cytokines, IgE, and many others. Importantly, because F-series prostaglandins and ergonovine exacerbate asthma, these commonly used obstetrical drugs should be avoided if possible.

Clinical Course

Pulmonary function changes are more pronounced in asthmatics compared with healthy women (Zairina, 2015). Asthma manifestations range from mild wheezing to severe bronchoconstriction, which obstructs airways and decreases airflow. This lowers the forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio and the peak expiratory flow (PEF). The work of breathing progressively increases, and patients note chest tightness, wheezing, or breathlessness. Subsequent alterations in oxygenation primarily reflect ventilation–perfusion mismatching because the distribution of airway narrowing is uneven.

Varied manifestations of asthma have led to a simple classification that considers severity, onset, and duration of symptoms (Table 51-1). With persistent or worsening bronchial obstruction, clinical stages progress as shown in Figure 51-1. Hypoxia initially is mitigated by hyperventilation, which maintains arterial P_{O_2} within a normal range but lowers P_{CO_2}, creating respiratory alkalosis. As airway narrowing worsens, ventilation–perfusion defects increase, and arterial hypoxemia ensues. With severe obstruction, ventilation becomes impaired as fatigue causes early CO_2 retention. Because of hyperventilation, this may only be seen initially as an arterial P_{CO_2} returning to the normal range. With continuing obstruction, respiratory failure follows from fatigue.

TABLE 51-1

Classification of Asthma Severity

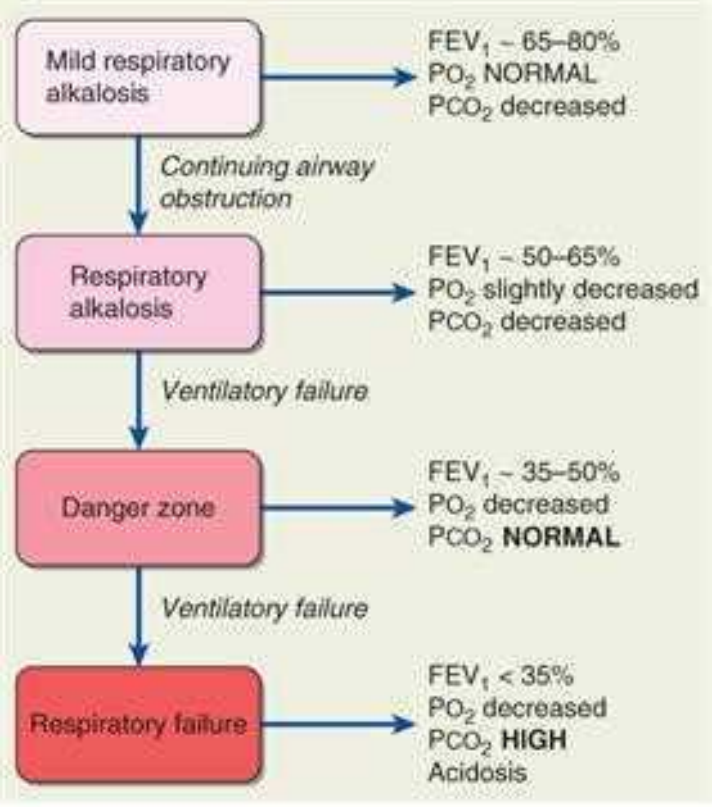
	Severity			
		Persistent		
Component	**Intermittent**	**Mild**	**Moderate**	**Severe**
Symptoms	≤2 day/wk	>2 day/wk, not daily	Daily	Throughout day
Nocturnal awakenings	≤2×/mo	3–4×/mo	>1×/wk, not nightly	Often 7×/wk
Short-acting β-agonist for symptoms	≤2 day/wk	≥2 day/wk, but not >1×/day	Daily	Several times daily
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung function	Normal between exacerbations			
• FEV_1	>80% predicted	≥80% predicted	60–80% predicted	<60% predicted
• FEV_1/FVC	Normal	Normal	Reduced 5%	Reduced >5%

FEV = forced expiratory volume; FVC = forced vital capacity.

From National Heart, Lung, and Blood Institute, 2007.

FIGURE 51-1

Clinical stages of asthma. FEV_1 = forced expiratory volume in 1 second.



Although these changes are generally reversible and well tolerated by the healthy nonpregnant individual, even early asthma stages may be dangerous for the pregnant woman and her fetus. This is because smaller functional residual capacity and increased pulmonary shunting render the woman more susceptible to hypoxia and hypoxemia.

Effects of Pregnancy on Asthma

Pregnancy has an unpredictable effect on underlying asthma. In their review of six prospective studies of more than 2000 gravidas, Gluck and Gluck (2006) reported that approximately a third each improved, remained unchanged, or clearly worsened. Exacerbations are more common with severe disease (Ali, 2013). In a study by Schatz and associates (2003), baseline severity correlated with asthma morbidity during pregnancy. With mild disease, 13 percent of women had an exacerbation and 2.3 percent required admission; with moderate disease, these numbers were 26 and 7 percent; and for severe asthma, 52 and 27 percent. Others have reported similar observations (Charlton, 2013; Hendler, 2006). Finally, morbidity rates are disproportionately increased in black compared with white women.

Up to 20 percent of women with mild or moderate asthma have been reported to have an intrapartum exacerbation (Schatz, 2003). Conversely, Wendel and associates (1996) reported exacerbations at the time of delivery in only 1 percent of women. Mabie and coworkers (1992) reported an 18-fold increased exacerbation risk following cesarean versus vaginal delivery.

Pregnancy Outcome

Women with asthma have had improved pregnancy outcomes during the past 20 years. The incidence of spontaneous abortion in women with asthma may be slightly increased (Blais, 2013). Maternal and perinatal outcomes for nearly 30,000 pregnancies in asthmatic women are shown in Table 51-2. Findings are not consistent among these studies. For example, in some, but not all, the incidences of preeclampsia, preterm labor, growth-restricted infants, and perinatal mortality are slightly increased (Murphy, 2011). Other reports cited a small rise in the incidence of placental abruption and previa, preterm rupture of membranes, and gestational diabetes (Getahun, 2006; Wang, 2014). But, in a European report of 37,585 pregnancies of women with asthma, the risks for most obstetrical complications were not increased (Tata, 2007). Finally, Cossette and coworkers (2013) reported a nonsignificant trend between perinatal complications and increasing inhaled-corticosteroid dosage.

TABLE 51-2

Maternal and Perinatal Outcomes in Pregnancies Complicated by Asthma

	Perinatal Outcomes (%)			
Study	**No.**	**Gestational Hypertension[a]**	**Growth Restriction**	**Preterm Delivery**
Liu (2001)	2193	13	12	10
Dombrowski (2004a)	1739	12.2[b]	7.1[b]	16[b]
Mendola (2013)	17,044	10.2[c]	NS	14.8[c]
Cossette (2013)	7376	NS	13.5[c]	9.5[c]
Approximate average	28,352	~11	~11	~13

[a]Includes preeclampsia syndromes.

[b]Incidence not significantly different compared with control group or general obstetrical population.

[c]Incidence significantly greater than control group or general obstetrical population.

NS = not stated.

Increased morbidity appears to be significantly linked to severe disease, poor control, or both. In the study by the Maternal-Fetal Medicine Units (MFMU) Network, delivery before 37 weeks' gestation was not increased among the 1687 pregnancies of asthmatic women compared with those of 881 controls (Dombrowski, 2004a). But for women with severe asthma, the rate was increased approximately twofold. In a prospective evaluation of 656 asthmatic pregnant women and 1052 pregnant controls, Triche and coworkers (2004) found that women with moderate to severe asthma, regardless of treatment, are at increased risk of preeclampsia. Finally, the MFMU Network study suggests a direct relationship of baseline pregnancy FEV_1 with birthweight and an inverse relationship with rates of gestational hypertension and preterm delivery (Schatz, 2006).

Maternal morbidity includes life-threatening complications from status asthmaticus. This causes muscle fatigue with respiratory arrest, pneumothorax, pneumomediastinum, acute cor pulmonale, and cardiac arrhythmias. Not surprisingly, maternal and perinatal mortality rates rise substantively when mechanical ventilation is required.

Fetal Effects

As discussed, with reasonable asthma control, perinatal outcomes are generally good. In the Network study cited above, rates of adverse neonatal sequelae caused by asthma were not significantly increased (Dombrowski, 2004a). The caveat is that severe asthma was uncommon in this closely monitored group. When respiratory alkalosis develops, earlier animal and human studies suggest that fetal hypoxemia develops well before the alkalosis compromises maternal oxygenation (Rolston, 1974). It is hypothesized that the fetus is jeopardized by decreased uterine blood flow, decreased maternal venous return, and an alkaline-induced leftward shift of the oxyhemoglobin dissociation curve (Chap. 47, Positive End-Expiratory Pressure).

The fetal response to maternal hypoxemia is decreased umbilical blood flow, increased systemic and pulmonary vascular resistance, and decreased cardiac output. Observations by Bracken and colleagues (2003) confirm that the incidence of fetal-growth restriction increases with asthma severity. Because the fetus may be seriously compromised as asthma severity increases, the need for aggressive management is underscored. Monitoring the fetal response is, in effect, an indicator of maternal status.

Possible teratogenic or adverse fetal effects of drugs given to control asthma have been a concern. Several reports show a slightly greater risk for varied abnormalities such as cleft lip and palate and autism spectrum disorders. However, not all studies have verified this (Eltonsy, 2016; Gidaya, 2016; Murphy, 2013b; Wang, 2014). It is worrisome that up to half of these women discontinue essential treatment between 5 and 13 weeks' gestation (Enriquez, 2006).

Clinical Evaluation

The subjective severity of asthma frequently does not correlate with objective measures of airway function or ventilation. Although clinical examination can also be an inaccurate predictor, useful signs include labored breathing, tachycardia, pulsus paradoxus, prolonged expiration, and use of accessory muscles. Signs of a potentially fatal attack include central cyanosis and altered consciousness.

Arterial blood gas analysis provides objective assessment of maternal oxygenation, ventilation, and acid-base status. With this information, the severity of an acute attack can be assessed (see Fig. 51-1). That said, in a prospective evaluation, Wendel and associates (1996) found that *routine* arterial blood gas analysis did not help to manage most pregnant women who required admission for asthma control. If used, the results must be interpreted in relation to normal values for pregnancy. For example, a P_{CO_2}>35 mm Hg with a pH <7.35 is consistent with hyperventilation and CO_2 retention in a pregnant woman.

Pulmonary function testing should be routine in the management of chronic and acute asthma. Sequential measurement of the FEV_1 or of the *peak expiratory flow rate—PEFR*—is the best measure of severity. An FEV_1 less than 1 L, or less than 20 percent of predicted value, correlates with severe disease defined by hypoxia, poor response to therapy, and a high relapse rate. The PEFR correlates well with the FEV_1, and it can be measured reliably with inexpensive portable meters. It is advantageous for each woman to determine her own baseline when asymptomatic to compare with values when symptomatic.

Management of Chronic Asthma

Asthma management by an experienced team produces the most salutary outcomes (Bonham, 2017; Lim, 2014; Wendel, 1996). Management guidelines include:

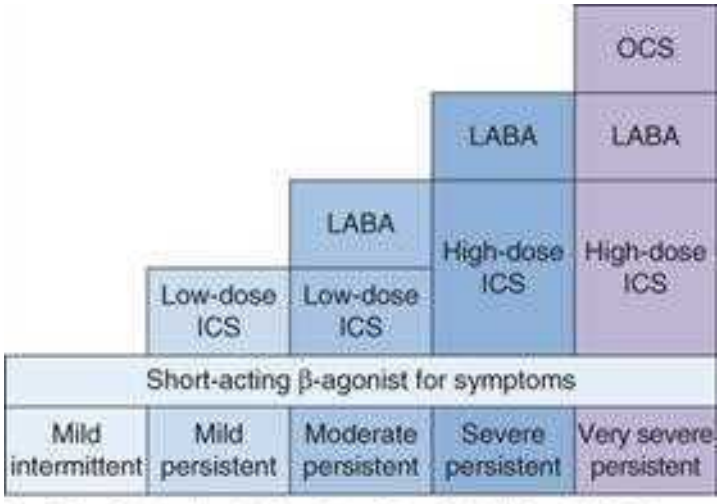
1. Patient education—general asthma management and its effect on pregnancy.
2. Environmental precipitating factors—avoidance or control. Viral infections that include the common cold are frequent triggering events (Ali, 2013; Murphy, 2013a).
3. Objective assessment of pulmonary function and fetal status—monitor with PEFR or FEV_1.
4. Pharmacological therapy—in appropriate combinations and doses to provide baseline control and treat exacerbations. Compliance may be a problem, and periodic medication reviews are helpful (Sawicki, 2012).

In general, women with moderate to severe asthma ideally measure and record either their FEV_1 or PEFR twice daily. The FEV_1 ideally is >80 percent of predicted. For PEFR, predicted values range from 380 to 550 L/min. Each woman has her own baseline value, and therapeutic adjustments can be made using this (American College of Obstetricians and Gynecologists, 2016a; Rey, 2007).

Treatment depends on disease severity. No therapeutic regimen for management of pregnant asthmatics is universally accepted (Bain, 2014). β-Agonists help abate bronchospasm, and corticosteroids treat inflammation. Regimens recommended for outpatient management are listed in Figure 51-2. For mild asthma, inhaled β-*agonists* as needed are usually sufficient. For persistent asthma, *inhaled corticosteroids* are administered every 3 to 4 hours. The goal is to reduce the use of β-agonists for symptomatic relief. A case-control study from Canada with a cohort of more than 15,600 nonpregnant women with asthma showed that inhaled corticosteroids reduced hospitalizations by 80 percent (Blais, 1998). At Parkland Hospital, Wendel and colleagues (1996) achieved a 55-percent reduction in readmissions for severe exacerbations with inhaled steroids.

FIGURE 51-2

Stepwise approach to asthma treatment. ICS = inhaled corticosteroids; LABA = long-acting β-agonists; OCS = oral corticosteroids. (Modified from Barnes PJ: Asthma. In Kasper D, Fauci A, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015, p 1669.)



Theophylline has been used less frequently since inhaled corticosteroids became available. Minimal benefit is gained with use of these compounds and they have a high rate of side effects. However, some theophylline derivatives are considered useful for oral maintenance therapy if the initial response to

inhaled corticosteroids and β-agonists is not optimal (Dombrowski, 2004b).

Antileukotrienes inhibit leukotriene synthesis and include *zileuton, zafirlukast*, and *montelukast*. These drugs are given orally or by inhalation for prevention, but they are not effective for acute disease (Barnes, 2015). For maintenance, they are used in conjunction with inhaled corticosteroids to allow minimal dosing. Approximately half of asthmatics will improve with these drugs. These agents are not as effective as inhaled corticosteroids, and there is little experience with their use in pregnancy (Fanta, 2009).

Cromones include *cromolyn* and *nedocromil,* which inhibit mast cell degranulation. They are ineffective for acute asthma and are used primarily to treat childhood asthma.

Management of Acute Asthma

Treatment of acute asthma during pregnancy is similar to that for the nonpregnant asthmatic. Importantly, the threshold for hospitalization is significantly lower. Intravenous (IV) hydration may help clear pulmonary secretions, and supplemental oxygen is given by mask. The therapeutic aim is to maintain the Po_2 >60 mm Hg, and preferably normal, along with 90- to 95-percent oxygen saturation. Baseline pulmonary function testing includes FEV_1 or PEFR. Continuous pulse oximetry and electronic fetal monitoring, depending on gestational age, may provide useful information. Antibiotics are not given unless there is concomitant pneumonitis, which is caused by the same organisms discussed in Pneumonia (Terraneo, 2014).

First-line therapy for acute asthma includes a short-acting β-adrenergic agonist, such as terbutaline, albuterol, isoetharine, epinephrine, isoproterenol, or metaproterenol, which is given subcutaneously, taken orally, or inhaled. In severely ill women, these drugs can be given IV (Barnes, 2015). They bind to specific cell-surface receptors and activate adenylyl cyclase to increase intracellular cyclic AMP and modulate bronchial smooth muscle relaxation. Long-acting preparations are used for outpatient therapy.

If not previously given for maintenance, inhaled corticosteroids are commenced. A nebulized anticholinergic drug may be added if the response at this point is unsatisfactory (Barnes, 2015). Also, for severe exacerbations, IV magnesium sulfate or theophylline may prove efficacious. Corticosteroids are given early to all patients with severe acute asthma. Unless the response to bronchodilator and inhaled corticosteroid therapy is prompt, oral or parenteral corticosteroids are given (Lazarus, 2010). One regimen is oral prednisone or prednisolone or IV methylprednisolone in a dose of 30 to 45 mg daily for 5 to 10 days without tapering (Barnes, 2015). Because their onset of action is several hours, corticosteroids are given initially along with β-agonists for severe acute asthma.

At this juncture, further management depends on the severity and response to therapy. If initial therapy with β-agonists is associated with improvement of FEV_1 or PEFR to above 70 percent of baseline, then discharge can be considered. Some women may benefit from longer observation. Alternatively, for the woman with obvious respiratory distress, or if the FEV_1 or PEFR is <70 percent of predicted after three doses of β-agonist, admission is usually advisable (Lazarus, 2010). Intensive therapy is continued with inhaled β-agonists, IV corticosteroids, and close observation for worsening respiratory distress or fatigue in breathing (Racusin, 2013). The woman is cared for in the delivery unit or an intermediate or intensive care unit (ICU) (Dombrowski, 2006; Zeeman, 2003).

Status Asthmaticus and Respiratory Failure

Severe asthma of any type not responding after 30 to 60 minutes of intensive therapy is termed status asthmaticus. This has been termed by some as critical asthma symptoms (Kenyon, 2015). Generally, management of nonpregnant patients with status asthmaticus in an intensive care setting results in a good outcome. Consideration should be given to early intubation when maternal respiratory status worsens despite aggressive treatment (see Fig. 51-1). Fatigue, CO_2 retention, and hypoxemia are indications for mechanical ventilation (Chan, 2015). Although Lo and colleagues (2013) described a woman with status asthmaticus in whom cesarean delivery was necessary to effect ventilation, Andrews (2013) cautioned that such clinical situations are uncommon.

Labor and Delivery

For the laboring asthmatic, maintenance medications are continued through delivery. Stress-dose corticosteroids are administered to any woman given systemic corticosteroid therapy within the preceding 4 weeks. The usual dose is 100 mg of hydrocortisone given IV every 8 hours during labor and for 24 hours after delivery. The PEFR or FEV_1 is determined on admission, and serial measurements are taken if symptoms develop.

Oxytocin or prostaglandins E_1 or E_2 are used for cervical ripening and induction. A nonhistamine-releasing narcotic such as fentanyl may be preferable to meperidine for labor, and epidural analgesia is ideal. For surgical delivery, conduction analgesia is preferred because tracheal intubation can trigger severe bronchospasm. Postpartum hemorrhage is treated with oxytocin or prostaglandin E_1 or E_2. Prostaglandin $F_{2\alpha}$ or ergotamine derivatives are contraindicated because they may cause significant bronchospasm.

ACUTE BRONCHITIS

Infection of the large airways is manifest by cough without pneumonitis. It is common in adults, especially in winter months. Infections are usually caused by viruses, and of these, influenza A and B, parainfluenza, respiratory syncytial, coronavirus, adenovirus, and rhinovirus are frequent isolates (Wenzel, 2006). Bacterial agents causing community-acquired pneumonia are rarely implicated. The cough of acute bronchitis persists for 10 to 20 days (mean 18 days) and occasionally lasts for a month or longer. According to the 2006 guidelines of the American College of Chest Physicians, routine antibiotic treatment is not indicated (Smith, 2014).

PNEUMONIA

This is a leading cause of death in the United States (Heron, 2016). Current classification includes *community-acquired pneumonia (CAP),* which is typically encountered in otherwise healthy young women, including during pregnancy. *Health-care-associated pneumonia (HCAP)* develops in patients in outpatient care facilities and more closely resembles *hospital-acquired pneumonia (HAP).*

In most cases of community-acquired pneumonia, the offending pathogen is not identified. In a recent study from the Centers for Disease Control and Prevention (CDC), pathogens were identified in only 38 percent of nearly 2500 adults with pneumonia (Jain, 2015). These included viruses in 23 percent, bacteria in 11 percent, both in 3 percent, and fungi or protozoa in 1 percent. Half of bacterial isolates were *Streptococcus pneumoniae*.

Pneumonia in pregnant women is relatively common (Brito, 2011; Sheffield, 2009). Gazmararian and coworkers (2002) reported that pneumonia accounts for 4.2 percent of antepartum admissions for nonobstetrical complications. Pneumonia is also a frequent indication for postpartum readmission (Belfort, 2010). During influenza season, admission rates for respiratory illnesses double compared with rates in the remaining months (Cox, 2006). Regardless of etiology, mortality from pneumonia is infrequent in young women, but during pregnancy severe pneumonitis with appreciable loss of ventilatory capacity is not as well tolerated (Callaghan, 2015; Rogers, 2010). Hypoxemia and acidosis are also poorly accommodated by the fetus and frequently stimulate preterm labor after midpregnancy. Because many cases of pneumonia follow viral upper respiratory illnesses, worsening or persistence of symptoms may represent developing pneumonia. Any gravida suspected of having pneumonia should undergo chest radiography.

Bacterial Pneumonia

Many bacteria that cause community-acquired pneumonia, such as *Streptococcus pneumoniae*, are part of the normal resident flora. Some factors that perturb the symbiotic relationship between colonizing bacteria and mucosal phagocytic defenses include acquisition of a virulent strain or bacterial infections following a viral infection. Cigarette smoking and chronic bronchitis favor colonization with *S pneumoniae*, *Haemophilus influenzae*, and *Legionella* species. Other risk factors include asthma, binge drinking, and human immunodeficiency virus (HIV) infection (Sheffield, 2009).

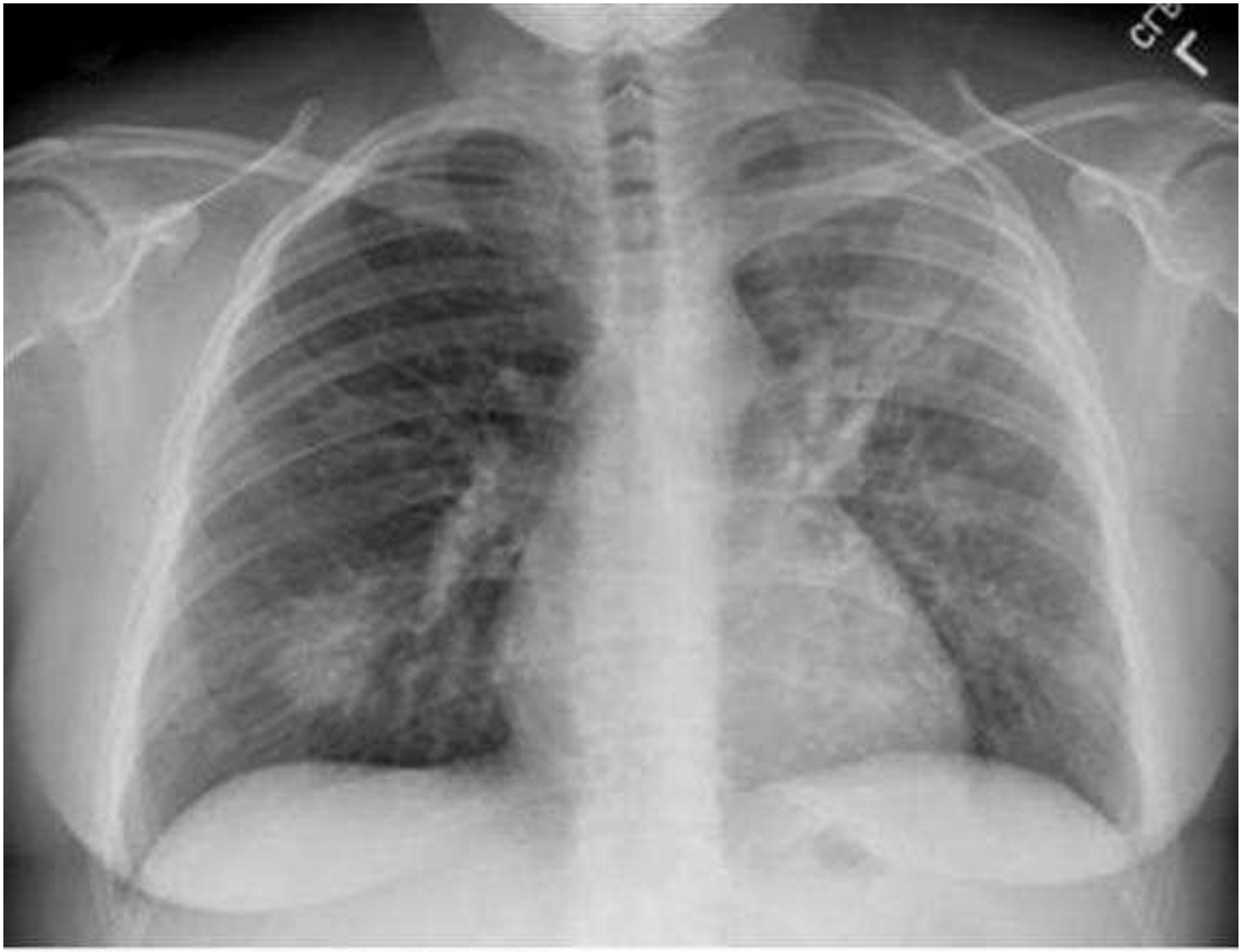
Incidence and Causes

Pregnancy itself does not appear to predispose to pneumonia. Jin and colleagues (2003) reported the antepartum hospitalization rate for pneumonia in Alberta, Canada, to be 1.5 per 1000 deliveries—almost identical to the rate of 1.47 per 1000 for nonpregnant women. Likewise, Yost and associates (2000) reported an incidence of 1.5 per 1000 for pneumonia complicating 75,000 pregnancies cared for at Parkland Hospital. As discussed, at least half are caused by viruses. A fourth are bacterial, and *S pneumoniae* causes half of the latter. Over the past few years community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a common pathogen that may cause necrotizing pneumonia (Mandell, 2015; Moran, 2013). Occasionally, Legionnaires disease is encountered (Close, 2016).

Diagnosis

Typical symptoms of pneumonia include cough, dyspnea, sputum production, and pleuritic chest pain. Mild upper respiratory symptoms and malaise usually precede these symptoms, and mild leukocytosis is usually present. Chest radiography is essential for diagnosis (Fig. 51-3). Radiographical findings do not accurately predict the etiology, and as discussed, the responsible pathogen is identified in fewer than half of cases. According to the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS), tests to identify a specific agent are optional (Mandell, 2007). Thus, sputum cultures, serological testing, cold agglutinin identification, and tests for bacterial antigens are not routinely recommended. The one exception to this may be rapid serological testing for influenza A and B (Sheffield, 2009).

FIGURE 51-3
Chest radiograph in a pregnant woman with right lower lobe and left upper lobe pneumonia. Rounded right basilar and left apical infiltrates are consistent with the diagnosis.



Management

Although many otherwise healthy young adults can be safely treated as outpatients, at Parkland Hospital we hospitalize all pregnant women with radiographically proven pneumonia. Another option is outpatient therapy or 23-hour observation, which is reasonable with optimal follow-up. At least for nonpregnant patients, the pneumonia severity index (PSI) and the CURB-65 scoring system are used as a guide to admission (Mandell, 2015). Neither has been studied in pregnancy. Given that, risk factors shown in Table 51-3 should prompt consideration for hospitalization.

TABLE 51-3

Criteria for Severe Community-Acquired Pneumonia[a]

Respiratory rate ≥30/min
Pao_2/Fio_2 ratio ≤250
Multilobular infiltrates
Confusion/disorientation
Uremia
Leukopenia: WBC <4000/μL
Thrombocytopenia—platelets <100,000/μL
Hypothermia—core temperature <36°C
Hypotension requiring aggressive fluid resuscitation

[a]Criteria of the Infectious Diseases Society of America/American Thoracic Society.

Pao_2/Fio_2 = partial pressure oxygen in arterial blood/fraction of inspired oxygen; WBC = white blood cell.

Adapted from Mandell, 2007.

With severe disease, admission to an intensive or intermediate care unit is advisable. Approximately 20 percent of pregnant women admitted to Parkland Hospital for pneumonia require this level of care (Zeeman, 2003). Severe pneumonia is a relatively common cause of acute respiratory distress syndrome (ARDS) during pregnancy, and mechanical ventilation may become necessary (Chap. 47, Clinical Course). Indeed, of the 51 gravidas who required mechanical ventilation in the review by Jenkins and coworkers (2003), 12 percent had pneumonia.

Initial antimicrobial and antiviral treatment is empirical (Mandell, 2015). Because most adult bacterial pneumonias are caused by pneumococci, mycoplasma, or chlamydophila, monotherapy initially is with a macrolide—azithromycin, clarithromycin, or erythromycin (Table 51-4). Yost and colleagues (2000) reported that erythromycin monotherapy, given IV and then orally, was effective in all but one of 99 pregnant women with uncomplicated pneumonia. During influenza season, we routinely administer oseltamivir treatment along with empirical therapy for bacterial pneumonia.

TABLE 51-4

Empirical Antimicrobial Treatment for Community-Acquired Pneumonia

Uncomplicated, otherwise healthy[a]
Macrolides[b]: clarithromycin or azithromycin ***PLUS*** Oseltamivir for suspected influenza A infection
Severe pneumonia[c]
Respiratory fluoroquinolones: moxifloxacin, gemifloxacin, or levofloxacin ***or*** β-lactams: amoxicillin/clavulanate, ceftriaxone, cefotaxime, or cefuroxime plus a macrolide ***PLUS*** Oseltamivir for suspected influenza A infection

[a]Use as inpatient or outpatient regimen.

[b]Doxycycline may be given instead if postpartum.

[c]See Table 51-3 for criteria.

For women with severe disease according to criteria in Table 51-3, Mandell and associates (2007) summarized IDSA/ATS guidelines, which call for either: (1) a respiratory fluoroquinolone—levofloxacin, moxifloxacin, or gemifloxacin; or (2) a macrolide plus a preferred β-lactam—either high-dose amoxicillin or amoxicillin-clavulanate. β-Lactam alternatives include ceftriaxone, cefpodoxime, or cefuroxime (see Table 51-4). In areas in which the resistance of pneumococcal isolates to macrolides is great, these latter regimens are preferred. The teratogenicity risk of fluoroquinolones is low, and these should be given if indicated (Briggs, 2015). If CA-MRSA is suspected, then vancomycin or linezolid is added (Mandell, 2015; Moran, 2013; Wunderink, 2013).

Clinical improvement is usually evident in 48 to 72 hours with resolution of fever in 2 to 4 days. Radiographic abnormalities may take up to 6 weeks to completely resolve (Torres, 2008). Worsening disease is a poor prognostic feature, and subsequent radiography is recommended if fever persists. Even with improvement, however, approximately 20 percent of women develop a pleural effusion. Treatment of uncomplicated pneumonia is recommended for 5 to 7 days (Musher, 2014). Treatment failure may occur in up to 15 percent of cases, and a wider antimicrobial regimen and more extensive diagnostic testing is warranted.

Pregnancy Outcome

During the preantimicrobial era, as many as a third of pregnant women with pneumonia died (Finland, 1939). Although much improved, maternal and perinatal morbidity and mortality remain formidable. In five studies with a total of 632 women published after 1990, almost 7 percent required intubation and mechanical ventilation, and the maternal mortality rate was 0.8 percent.

Prematurely ruptured membranes and preterm delivery are frequent complications and have been reported in up to a third of cases of acute lung infection (Getahun, 2007; Shariatzadeh, 2006). Likely related are older studies reporting a twofold increase in low-birthweight neonates (Sheffield, 2009). In one population-based study from Taiwan of nearly 219,000 births, incidences of preterm and growth-restricted newborns and of preeclampsia and cesarean delivery were significantly increased (Chen, 2012).

Prevention

Two pneumococcal vaccines, a 23-serotype older preparation and a newer 13-serotype vaccine, are used in children (Swamy, 2015). The 23-serotype vaccine is 60- to 70-percent protective, and its use lowers emergence of drug-resistant pneumococci (Kyaw, 2006). The 13-serotype vaccine is not recommended for otherwise healthy pregnant women. It is, however, recommended for women who are immunocompromised, including those with HIV infection; significant smoking history; diabetes; cardiac, pulmonary, or renal disease; and asplenia, such as with sickle-cell disease (Table 9-7). Protection against pneumococcal infection in women with chronic diseases may be less efficacious than in healthy patients (Moberley, 2013).

Influenza Pneumonia

Clinical Presentation

Each year, 10 percent of pregnant women develop influenza (Cantu, 2013). Influenza A and B are RNA viruses that cause respiratory infection, including pneumonitis, that is epidemic in the winter months. The virus is spread by aerosolized droplets and quickly infects ciliated columnar epithelium, alveolar cells, mucus gland cells, and macrophages. Disease onset is 1 to 4 days following exposure. Common symptoms include fever, cough, myalgia, and chills (Sokolow, 2015). In most healthy adults, infection is self-limited.

Pneumonia is the most frequent complication of influenza and mimics bacterial pneumonia. According to the CDC (2010a), infected pregnant women are more likely to be hospitalized and admitted to an ICU. Others have corroborated these observations (Mertz, 2017). At Parkland Hospital during the 2003 to 2004 influenza season, pneumonia developed in 12 percent of gravidas with influenza (Rogers, 2010).

The 2009 to 2010 pandemic with the influenza (A/H1N1)pdm09 strain was particularly severe (Rasmussen, 2014). In an MFMU Network study, 10 percent of pregnant or postpartum women admitted with H1N1 influenza were cared for in an ICU, and 11 percent of these patients died (Varner, 2011). Risk factors included late pregnancy, smoking, and chronic hypertension. Overall, influenza accounted for 12 percent of pregnancy-related deaths during the 2009 to 2010 pandemic (Callaghan, 2015). During the 2013 to 2014 influenza season, a fourth of pregnant women admitted to California ICUs died (Louie, 2015). Of 865 pregnant women with influenza, Oboho and coworkers (2016) noted that 7 percent of their cohort had severe disease, and four women died. If influenza causes ARDS, extracorporeal membrane oxygenation (ECMO) may be lifesaving (Anselmi, 2015; Saad, 2016).

Primary influenza pneumonitis is characterized by sparse sputum production and radiographic interstitial infiltrates (Cohen, 2015). More commonly, either secondary or mixed pneumonia develop from bacterial superinfection by streptococci or staphylococci after 2 to 3 days of initial clinical improvement. The CDC (2007) reported several cases in which CA-MRSA caused influenza-associated pneumonitis with a case-fatality rate of 25 percent. Other possible adverse effects of influenza A and B on pregnancy outcome are discussed in Chapter 64 (Influenza Virus).

Management

Supportive treatment is recommended for uncomplicated influenza, and early antiviral treatment is effective (Jamieson, 2011; Oboho, 2016). Hospitalization is considered for severely ill women, and for those with pneumonia. As discussed, influenza hospitalization rates for those with advanced pregnancy are increased compared with nonpregnant women (Dodds, 2007; Schanzer, 2007). The CDC (2016b) recommends neuraminidase inhibitors given within 2 days of symptom onset for chemoprophylaxis and treatment of influenza A and B (Chap. 64, Mumps Virus). The drugs interfere with release of progeny virus from infected host cells and thus prevent infection of new host cells (Cohen, 2015). Oseltamivir is given orally, 75 mg twice daily, or zanamivir is given by inhalation, 10 mg twice daily. Recommended treatment duration with either is 5 days. The drugs shorten the course of illness by 1 to 2 days, and they probably reduce the risk for pneumonitis (Belgi, 2014; Muthuri, 2014). Our practice is to treat all pregnant women with influenza whether or not pneumonitis is identified (Rasmussen, 2014). Few data guide use of these agents in pregnant women, but the drugs are not teratogenic in animal studies and are considered low risk (Briggs, 2015).

A major potential concern for viral resistance comes from avian influenza isolates. “Bird flu” with HPAI, H5N8, H5N2, and H5N1 isolates has been reported in the United States by the CDC (Jhung, 2015). In Asia, human infection has been documented with some of these, and mortality rates are high.

Preventively, vaccination for influenza A is recommended by the American College of Obstetricians and Gynecologists (2016b) and the CDC (2016b). Vaccination is discussed in detail in Chapter 64 (Mumps Virus). Prenatal vaccination also affords some temporary protection for infants (Madhi, 2014; Tita, 2016). During the 2014 to 2015 flu season, the CDC reported that only half of pregnant women received influenza vaccine (Ding, 2015).

Varicella Pneumonia

Infection with varicella-zoster virus, the same agent responsible for chicken pox, results in pneumonitis in 5 percent of gravidas (Harger, 2002). Diagnosis and management are considered in Chapter 64 (Varicella-Zoster Virus).

Fungal and Parasitic Pneumonia

Pneumocystis Pneumonia

Fungal and parasitic pulmonary infections are usually of greatest consequence in immunocompromised hosts, especially in women with acquired immunodeficiency syndrome (AIDS). Of these, lung infection with *Pneumocystis jiroveci*, formerly called *Pneumocystis carinii*, is a common complication. The opportunistic fungus causes interstitial pneumonia characterized by dry cough, tachypnea, dyspnea, and diffuse radiographic infiltrates. Although this organism can be identified by sputum culture, bronchoscopy with lavage or biopsy may be necessary.

In an earlier report from the AIDS Clinical Trials Centers, Stratton and colleagues (1992) described pneumocystis pneumonia as the most frequent HIV-related disorder in pregnant women. In some cases, tracheal intubation and mechanical ventilation may be required. Ahmad and coworkers (2001) reviewed 22 cases during pregnancy and cited a 50-percent mortality rate. Treatment is with trimethoprim-sulfamethoxazole for 14 to 21 days (Masur, 2015). Alternative agents include the more toxic pentamidine (Walzer, 2005).

For prophylaxis, several international health agencies recommend one double-strength trimethoprim-sulfamethoxazole tablet orally daily for certain groups of HIV-infected pregnant women. These include women with $CD4^+$ T-lymphocyte counts <200/µL, those whose $CD4^+$ T lymphocytes constitute <14 percent, or if there is an AIDS-defining illness, particularly oropharyngeal candidiasis (Centers for Disease Control and Prevention, 2016a).

Fungal Pneumonia

Any of several fungi can cause pneumonia. In pregnancy, this is usually seen in women with HIV infection or who are otherwise immunocompromised. Infection is usually mild and self-limited. It is characterized initially by cough and fever, and dissemination is infrequent (Mansour, 2015).

Histoplasmosis and *blastomycosis* do not appear to be more frequent or more severe during pregnancy (Youssef, 2013). Data concerning *coccidioidomycosis* are conflicting (Bercovitch, 2011; Patel, 2013). In a case-control study from an endemic area, Rosenstein and associates (2001) reported that pregnancy was a significant risk factor for disseminated disease. In another study, however, Caldwell and coworkers (2000) identified 32 serologically confirmed cases during pregnancy and documented dissemination in only three cases. Women with associated erythema nodosum have a better prognosis, whereas mediastinal lymphadenopathy may more likely reflect disseminated disease (Caldwell, 2000; Mayer, 2013). Finally, Crum and Ballon-Landa (2006) reviewed 80 cases of antepartum coccidioidomycosis and found that almost all women diagnosed in the third trimester had disseminated disease. Although the overall maternal mortality rate was 40 percent, it was only 20 percent for 29 cases reported since 1973. Spinello (2007) and Bercovitch (2011) with their colleagues have provided reviews of coccidioidomycosis in pregnancy.

Most cases of *cryptococcosis* reported during pregnancy manifest as meningitis. Otherwise healthy pregnant women occasionally have cryptococcal pneumonia (Asadi Gharabaghi, 2014; Ely, 1998). Diagnosis is difficult because clinical presentation is similar to that of other community-acquired pneumonias.

Treatment

The 2007 IDSA/ATS guidelines recommend itraconazole as preferred therapy for disseminated fungal infections (Mandell, 2007). Pregnant women have also been given IV amphotericin B or ketoconazole (Paranyuk, 2006; Pilmis, 2015). Amphotericin B has been used extensively in pregnancy with no embryofetal effects. Because of evidence that fluconazole, itraconazole, and ketoconazole may be embryotoxic in large doses in early pregnancy, Briggs and coworkers (2015) recommend that first-trimester use should be avoided if possible.

Three echinocandin derivatives—*caspofungin*, *micafungin*, and *anidulafungin*—are effective for invasive candidiasis (Pilmis, 2015; Reboli, 2007). They are embryotoxic and teratogenic in laboratory animals, and use in human pregnancies has not been reported (Briggs, 2015).

Severe Acute Respiratory Syndrome (SARS)

This coronaviral respiratory infection was first identified in China in 2002, but no new cases have been reported since 2005. It caused atypical pneumonitis with a case-fatality rate of approximately 10 percent (Dolin, 2012). SARS in pregnancy had a case-fatality rate of up to 25 percent (Lam, 2004; Wong, 2004). Ng and coworkers (2006) reported that the placentas from 7 of 19 cases showed abnormal intervillous or subchorionic fibrin deposition in three, and extensive fetal thrombotic vasculopathy in two.

TUBERCULOSIS

Tuberculosis is still a major worldwide concern. Indeed, it is estimated that a third of the world population is infected (Getahun, 2015). However, it is uncommon in the United States. The incidence of *active tuberculosis* in this country has plateaued since 2000 (Scott, 2015). More than half of active cases are in immigrants (Centers for Disease Control and Prevention, 2009b). Persons born in the United States have newly acquired infection, whereas foreign-born persons usually have reactivation of latent infection. In this country, tuberculosis is a disease of the elderly, the urban poor, minority groups—especially black Americans, and patients with HIV infection (Khan, 2013; Raviglione, 2015).

Infection is via inhalation of *Mycobacterium tuberculosis*, which incites a granulomatous pulmonary reaction. In more than 90 percent of patients, infection is contained and is dormant for long periods (Getahun, 2015; Zumla, 2013). In some, especially those who are immunocompromised or who have other diseases, tuberculosis becomes reactivated to cause clinical disease. Manifestations usually include cough with minimal sputum production, low-grade fever, hemoptysis, and weight loss. Various infiltrative patterns are seen on chest radiograph, and cavitation or mediastinal lymphadenopathy may be associated. Acid-fast bacilli are seen on stained smears of sputum in approximately two thirds of culture-positive individuals. Forms of extrapulmonary tuberculosis include lymphadenitis, pleural, genitourinary, skeletal, meningeal, gastrointestinal, and miliary or disseminated (Raviglione, 2015).

Treatment

Resistance to antituberculosis drugs in the United States in the early 1990s was associated with emergence of strains of *multidrug-resistant tuberculosis* (*MDR-TB*). Because of this, the CDC (2009a) now recommends a multidrug regimen for initial empirical treatment of patients with symptomatic tuberculosis. Isoniazid, rifampin, pyrazinamide, and ethambutol are given until susceptibility studies are performed (Horsburgh, 2015). Cure rates with 6-

month short-course *directly observed therapy*—DOT—approach 90 percent for new infections (Raviglione, 2015). Other second-line drugs may need to be added. Drug susceptibility is performed on all first isolates.

Tuberculosis and Pregnancy

The considerable influx of women into the United States from Asia, Africa, Mexico, and Central America has been accompanied by an increased frequency of tuberculosis in pregnancy. Sackoff and coworkers (2006) reported positive tuberculin test results in half of 678 foreign-born women attending prenatal clinics in New York City. Almost 60 percent were newly diagnosed. Pillay and colleagues (2004) stress the prevalence of tuberculosis in HIV-positive pregnant women. At Jackson Memorial Hospital in Miami, Schulte and associates (2002) reported that 21 percent of 207 HIV-infected pregnant women had a positive skin test result. Recall also that silent endometrial tuberculosis can cause tubal infertility (Levison, 2010; Raviglione, 2015).

Without therapy, active tuberculosis appears to have adverse effects on pregnancy (Mnyani, 2011). Several studies indicate that outcomes are dependent on the site of infection and gestational age at diagnosis. Jana and colleagues (1994) from India and Figueroa-Damian and Arrendondo-Garcia (1998) from Mexico City noted that active pulmonary tuberculosis was associated with increased incidences of preterm delivery, low-birthweight and growth-restricted newborns, and perinatal mortality. Others have found similar effects (El-Messidi, 2016; Lin, 2010; Sobhy, 2017). From her review, Efferen (2007) cited twofold greater rates of low birthweight, preterm delivery, and preeclampsia. The perinatal mortality rate was increased almost tenfold. Adverse outcomes correlate with late diagnosis, incomplete or irregular treatment, and advanced pulmonary lesions. Conversely, treated tuberculosis is associated with good pregnancy outcomes (Nguyen, 2014; Taylor, 2013).

Extrapulmonary tuberculosis is less common. Jana and coworkers (1999) reported outcomes in 33 pregnant women with renal, intestinal, and skeletal tuberculosis, and a third had low-birthweight newborns. Llewelyn and associates (2000) reported that nine of 13 pregnant women with extrapulmonary disease had delayed diagnoses. Prevost and Fung Kee Fung (1999) reviewed 56 cases of tuberculous meningitis in which a third of mothers died. Spinal tuberculosis may cause paraplegia, but vertebral fusion may prevent it from becoming permanent (Badve, 2011; Nanda, 2002). Psoas abscess develops in 5 percent of those with spinal infections (Nigam, 2013). Other presentations include widespread intraperitoneal tuberculosis simulating ovarian carcinomatosis and degenerating leiomyoma, and hyperemesis gravidarum from tubercular meningitis (Kutlu, 2007; Moore, 2008; Sherer, 2005).

Diagnosis

Two types of tests are used to detect latent or active tuberculosis. One is the time-honored *tuberculin skin test (TST),* and the others are *interferon-gamma release assays (IGRAs),* which are becoming preferred (Getahun, 2015; Horsburgh, 2011). IGRAs are blood tests that measure interferon-gamma release in response to antigens present in *M tuberculosis*, but not *bacille Calmette-Guérin (BCG)* vaccine (Levison, 2010). The CDC (2005b, 2010b) recommends either skin testing or IGRA testing of gravidas who are in any of the high-risk groups. For those who have received BCG vaccination, IGRA testing is used (Mazurek, 2010).

For skin testing, the preferred antigen is purified protein derivative (PPD) of intermediate strength of 5 tuberculin units. If the intracutaneously applied test result is negative, no further evaluation is needed. A positive skin test result measures ≥5 mm in diameter and requires evaluation for active disease, including a chest radiograph.

Two IGRAs are available: *QuantiFERON-TB Gold* and *T-SPOT.TB* tests are recommended by the CDC (2005a,b) for the same indications as skin testing. Although these tests have not been evaluated as extensively as tuberculin skin testing, Kowada (2014) concluded that the tests are cost effective.

Other essential laboratory methods for detection or verification of infection—both active and latent—include microscopy, culture, nucleic acid amplification assay, and drug-susceptibility testing (Horsburgh, 2015; Raviglione, 2015).

Treatment

Latent Infection

In nonpregnant tuberculin-positive patients with latent infection who are younger than 35 years and who have no evidence of active disease, isoniazid, 300 mg orally daily, is given for 9 months. Isoniazid has been used for decades, and it is considered safe in pregnancy (Briggs, 2015; Taylor, 2013). Compliance is a major problem, and Sackoff (2006) and Cruz (2005) and their associates reported a disappointing 10-percent treatment completion. One obvious disconnect is that care for tuberculosis is given in different health systems than prenatal care (Zenner, 2012). These observations are important because most recommend that isoniazid therapy be delayed until after delivery. Because of possibly increased isoniazid-induced hepatitis risk in postpartum women, some even recommend withholding treatment until 3 to 6 months after delivery. That said, neither method is as effective as antepartum treatment to prevent active infection. Boggess and colleagues (2000) reported that only 42 percent of 167 tuberculin-positive asymptomatic women delivered at San Francisco General Hospital completed 6-month therapy that was not begun until the first postpartum visit.

There are exceptions to delayed treatment for latent infection in pregnancy. Known recent skin-test convertors are treated antepartum because the incidence of active infection is 5 percent in the first year (Zumla, 2013). Skin-test-positive women exposed to active infection are also treated because the incidence of infection is 0.5 percent per year. Finally, HIV-positive women are treated because they have an approximate 10-percent annual risk of active disease.

Active Infection

Recommended initial treatment for active tuberculosis in pregnant women is a four-drug regimen with isoniazid, rifampin, ethambutol, and pyrazinamide, along with pyridoxine. For meningitis, levofloxacin may be added (Kalita, 2014). In the first 2-month phase, all four drugs are given—*bactericidal phase*. This is followed by a 4-month phase of isoniazid and rifampin—*continuation phase* (Raviglione, 2015; Zumla, 2013). A few reports describe MDR-TB during pregnancy, and treatment options have been reviewed (Horsburgh, 2015; Lessnau, 2003). Breastfeeding is not prohibited during antituberculous therapy.

Treatment of active disease is of special concern if there is antiretroviral naiveté. In these circumstances, beginning concomitant therapy with antituberculosis and antiretroviral therapy can cause the *immune reconstitution inflammatory syndrome (IRIS)* with toxic drug effects (Lai, 2016; Török, 2011). That said, recent studies support earlier administration of highly active antiretroviral therapy (HAART)—within 2 to 4 weeks—after beginning antituberculosis therapy (Blanc, 2011; Havlir, 2011; Karim, 2011). Also, for HIV-infected women, rifampin or rifabutin use may be contraindicated if certain protease inhibitors or nonnucleoside reverse transcriptase inhibitors are being administered. If there is resistance to rifabutin or rifampin, then pyrazinamide therapy is given. Of the second-line regimens, the aminoglycosides—streptomycin, kanamycin, amikacin, and capreomycin—are ototoxic to the fetus and are contraindicated (Briggs, 2015).

Neonatal Tuberculosis

Tubercular bacillemia can infect the placenta, but the fetus infrequently becomes infected—*congenital tuberculosis*. The term also applies to newborns who are infected by aspiration of infected secretions at delivery. Each route of infection constitutes approximately half of the cases. Neonatal tuberculosis simulates other congenital infections and manifests with hepatosplenomegaly, respiratory distress, fever, and lymphadenopathy (Dewan, 2014; Osowicki, 2016).

Cantwell and associates (1994) reviewed 29 cases of congenital tuberculosis reported since 1980. Only 12 of the mothers had active infection, and tuberculosis was frequently demonstrated by postpartum endometrial biopsy. Adhikari and colleagues (1997) described 11 South African postpartum women whose endometrial biopsy was culture-positive. Six of their neonates had congenital tuberculosis.

Neonatal infection is unlikely if the mother with active disease has been treated before delivery or if her sputum culture is negative. Because the newborn is susceptible to tuberculosis, most experts recommend isolation from the mother suspected of having active disease. If untreated, the risk of disease in the infant born to a woman with active infection is 50 percent in the first year (Jacobs, 1988).

SARCOIDOSIS

This is a chronic, multisystem inflammatory disease of unknown etiology characterized by an accumulation of T-helper lymphocytes and phagocytes within noncaseating granulomas (Baughman, 2015; Celada, 2015). Predisposition to the disease is genetically determined and characterized by an exaggerated response of helper T lymphocytes to environmental triggers. Pulmonary involvement is most common, followed by skin, eyes, lymph nodes, and then all other organ systems. The prevalence of sarcoid in the United States is 20 to 60 per 100,000, with equal sex distribution. It is more than 10 times more common for blacks than for whites (Baughman, 2015). Most patients are between 20 and 40 years. Clinical presentation varies, but more than half of patients have dyspnea and a dry cough without constitutional symptoms that develop insidiously over months. Disease onset is abrupt in approximately 25 percent of patients, and 10 to 20 percent are asymptomatic at discovery.

Pulmonary symptoms are dominant, and more than 90 percent of patients have an abnormal chest radiograph at some point. *Interstitial pneumonitis* is the hallmark of pulmonary involvement, and half of affected patients develop permanent radiological changes. *Lymphadenopathy*, especially of the mediastinum, is present in 75 to 90 percent of cases. A fourth each have uveitis and skin involvement, the latter usually manifest as *erythema nodosum*. In women, sarcoid causes approximately 10 percent of cases of erythema nodosum (Mert, 2007). Importantly, any other organ system may be involved (Kandolin, 2015; Powe, 2015; Wallmüller, 2012). Confirmation of the diagnosis is with biopsy—preferably a lymph node. However, because the lung may be the only obviously involved organ, tissue acquisition is often difficult.

The overall prognosis for sarcoidosis is good, and it resolves without treatment in 50 percent of patients. Still, quality of life is diminished (de Vries, 2007). In the other 50 percent, permanent organ dysfunction, albeit mild and nonprogressive, persists. Approximately 10 percent die because of their disease.

Glucocorticoids are the most widely used treatment for symptomatic disease. Permanent organ derangement is seldom reversed by their use (Paramothayan, 2002). Thus, the decision to treat is based on symptoms, physical findings, chest radiograph, and pulmonary function tests. Unless respiratory symptoms are prominent, therapy is usually withheld for a several-month observation period. If inflammation does not subside, then prednisone, 1 mg/kg, is given daily and tapered to <10 mg by 6 months (Baughman, 2015). For those with an inadequate response, immunosuppressive or cytotoxic agents and cytokine modulators can be used.

Sarcoidosis and Pregnancy

Because it is uncommon and frequently benign, sarcoidosis is not often seen in pregnancy. Although it seldom affects pregnancy adversely, meningitis, heart failure, and neurosarcoidosis have been described (Cardonick, 2000; Maisel, 1996; Wallmüller, 2012). In a study of the Nationwide Inpatient Sample of 678 cases of sarcoidosis in pregnancy, incidences of preeclampsia, preterm delivery, and thromboembolism were increased (Hadid, 2015). Selroos

(1990) studied 252 women with sarcoidosis in Finland, and 15 percent had sarcoidosis during pregnancy. Disease did not progress in the 26 pregnancies in women with active disease. Three aborted spontaneously, and the other 23 women were delivered at term. Agha and coworkers (1982) reported similar experiences with 35 pregnancies at the University of Michigan.

Active sarcoidosis is treated using the same guidelines as for the woman who is not pregnant. Severe disease warrants serial determination of pulmonary function. Symptomatic uveitis, constitutional symptoms, and pulmonary symptoms are treated with prednisone, 1 mg/kg orally per day.

CYSTIC FIBROSIS

This autosomal recessive exocrinopathy is one of the most common fatal genetic disorders in whites. Cystic fibrosis is caused by one of more than 2000 mutations in a 230-kb gene on the long arm of chromosome 7 that encodes an amino acid polypeptide (Patel, 2015; Sorscher, 2015). This peptide functions as a chloride channel and is termed the *cystic fibrosis transmembrane conductance regulator (CFTR)*. As discussed in Chapter 14 (Cystic Fibrosis), phenotypes vary widely, even among homozygotes for the common ΔF508 mutation (Rowntree, 2003). Approximately 10 to 20 percent of affected newborns are diagnosed shortly after birth because of *meconium peritonitis* (Boczar, 2015; Sorscher, 2015). Currently, the median predicted survival is 37 years, and nearly 80 percent of females with cystic fibrosis now survive to adulthood (Gillet, 2002; Patel, 2015).

Pathophysiology

Mutations in the chloride channel cause altered epithelial cell membrane transport of electrolytes. This affects all sites in which epithelium expresses CFTR-secretory cells. These include the sinuses, lung, pancreas, liver, and reproductive tract. Disease severity depends on which two alleles are inherited, and approximately 10 percent are disease-causing mutations (Sorscher, 2015). Homozygosity for Phe508del (ΔF508) is one of the most severe, and 90 percent of individuals with clinical disease carry at least one F508 allele.

Exocrine gland ductal obstruction develops from thick, viscid secretions (Rowe, 2005). In the lung, submucosal glandular ducts are affected. Eccrine sweat gland abnormalities are the basis for the diagnostic *sweat test*, characterized by elevated sodium, potassium, and chloride levels in sweat.

Lung involvement is commonplace and is usually the cause of death. Bronchial gland hypertrophy with mucous plugging and small-airway obstruction leads to subsequent infection that ultimately causes chronic bronchitis and bronchiectasis. For complex and not completely explicable reasons, chronic inflammation from *Pseudomonas aeruginosa* occurs in more than 90 percent of patients. In a minority, *S aureus, H influenzae,* and *Burkholderia cepacia* are recovered (Rowe, 2005). Colonization with the last has been reported to signify a worse prognosis, especially in pregnancy (Gillet, 2002). Acute and chronic parenchymal inflammation ultimately causes extensive fibrosis, and along with airway obstruction, ventilation–perfusion mismatch develops. Pulmonary insufficiency is the end result. Lung or heart–lung transplantation has a 5-year survival rate of only 50 to 60 percent (Sorscher, 2015). A few women have successfully undergone pregnancy following lung transplantation (Kruszka, 2002; Shaner, 2012).

Preconceptional Counseling

This CFTR2 resource delineates gene variants with a clear etiological role—http://www.cftr2.org. Women with clinical cystic fibrosis are subfertile because of tenacious cervical mucus. Males have oligospermia or aspermia from vas deferens obstruction, and 98 percent are infertile (Ahmad, 2013). Despite this, the North American Cystic Fibrosis Foundation estimated that 4 percent of affected women become pregnant every year (Edenborough, 1995). The endometrium and tubes express some CFTR but are functionally normal, and the ovaries do not express the *CFTR* gene (Edenborough, 2001). Both intrauterine insemination and in vitro fertilization can be successful for affected women (Rodgers, 2000). Several ethical considerations regarding plans for pregnancy by these women were reviewed by Wexler and colleagues (2007). One important factor is the long-term prognosis for the mother. For male infertility, Sobczyńska-Tomaszewska and associates (2006) have emphasized the importance of molecular diagnosis.

Screening

The American College of Obstetricians and Gynecologists (2017) recommends that carrier screening be offered to all women currently pregnant or considering conception (Chap. 14, Cystic Fibrosis). The CDC also added cystic fibrosis to newborn screening programs (Southern, 2009) (Chap. 32, Routine Newborn Care).

Prenatal Care

Pregnancy outcome is inversely related to severity of lung dysfunction. Advanced chronic lung disease, hypoxia, and frequent infections may prove deleterious. At least in the past, *cor pulmonale* was common, but even that does not preclude successful pregnancy (Cameron, 2005). In some women, *pancreatic dysfunction* may cause poor maternal nutrition. Otherwise normal pregnancy-induced insulin resistance frequently results in gestational diabetes after midpregnancy (Hardin, 2005). In one study of 48 pregnancies, half had pancreatic insufficiency and a third required insulin (Thorpe-Beeston, 2013). Up to 25 percent of patients develop diabetes by age 20, and diabetes is most frequent with the Phe508del homozygous mutation (Giacobbe, 2012; Patel, 2015).

Cystic fibrosis per se is not affected by pregnancy (Schechter, 2013). Early reports of a deleterious effect on the course of cystic fibrosis were related to severe disease (Olson, 1997). When matched with nonpregnant women by disease severity, recent reports indicate no deleterious effects on long-term survival (Schechter, 2013).

Management

Prepregnancy counseling is imperative. Women who choose to become pregnant require close surveillance for development of superimposed infection, diabetes, and heart failure. Serial pulmonary function testing assists management and estimating prognosis. When the FEV_1 is at least 70 percent, women usually tolerate pregnancy well. Emphasis is placed on postural drainage, bronchodilator therapy, and infection control.

β-Adrenergic bronchodilators help control airway constriction. Inhaled recombinant human deoxyribonuclease I improves lung function by reducing sputum viscosity (Sorscher, 2015). Inhaled 7-percent saline produces short- and long-term benefits (Elkins, 2006). Nutritional status is assessed and appropriate dietary counseling given. Pancreatic insufficiency requires replacement of oral pancreatic enzymes. Promising new therapy to correct CFTR protein dysfunction was recently described by Wainwright and colleagues (2015). Using a combination of lumacaftor and ivacaftor, these investigators showed that patients homozygous for the Phe508del mutation were significantly benefitted. No reports of either drug are available regarding pregnant women.

Infection is heralded by increasing cough and mucus production. Oral semisynthetic penicillins or cephalosporins usually suffice to treat staphylococcal infections. *Pseudomonas* infection is problematic, and inhaled tobramycin and colistin have been used successfully to control this organism. Immediate hospitalization and aggressive therapy are warranted for serious pulmonary infections. The threshold for hospitalization with other complications is low. For labor and delivery, epidural analgesia is recommended (Deighan, 2014).

Pregnancy Outcome

Earlier reports chronicled the poor maternal and perinatal outcomes of women with cystic fibrosis (Cohen, 1980; Kent, 1993). More recent reports describe better outcomes, but there still are serious complications. Disease severity is now quantified by pulmonary function studies, which are the best predictor of pregnancy and long-term maternal outcome. Edenborough and colleagues (2000) reported 69 pregnancies and found that if prepregnancy FEV_1 was <60 percent of predicted, the risk for preterm delivery, respiratory complications, and death of the mother within a few years of childbirth was substantive. Thorpe-Beeston (2013) and Fitzsimmons (1996) and their associates reported similar findings. Gillet and colleagues (2002) reported 75 pregnancies from the French Cystic Fibrosis Registry. Almost 20 percent of newborns were delivered preterm, and 30 percent had growth restriction. The one maternal death was due to *Pseudomonas* sepsis in a woman whose prepregnancy FEV_1 was 60 percent. Long-term, however, 17 percent of women died, and four infants had confirmed cystic fibrosis.

Maternal complications are daunting. Patel and coworkers (2015) recently queried the National Inpatient Sample database and reported that the prevalence of cystic fibrosis in pregnancy had a significant linear increase from 2000 to 2010. They analyzed 1119 affected women in more than 12 million births and reported a litany of risks (Table 51-5). In contrast, perinatal outcomes were surprisingly good.

TABLE 51-5

Odds Ratios for Maternal Complications in 1119 Pregnant Women with Cystic Fibrosis Compared with Controls

Complication	Odds Ratio
Asthma	5
Diabetes	14
Thrombophilia	6
Mechanical ventilation	32
Pneumonia	69
Respiratory failure	30
Acute kidney injury	16
Death	125

Data from Patel, 2015.

Lung Transplantation

Cystic fibrosis is a common antecedent disease leading to lung transplantation. Gyi and coworkers (2006) reviewed 10 pregnancies in such women and reported nine liveborn neonates. Maternal outcomes were less favorable. Of the three gravidas who developed rejection during pregnancy, all had progressively declining pulmonary function and died of chronic rejection by 38 months after delivery.

CARBON MONOXIDE POISONING

Carbon monoxide is a ubiquitous gas, and most nonsmoking adults have a carbon monoxyhemoglobin saturation of 1 to 3 percent. In cigarette smokers, levels may be as high as 5 to 10 percent. Carbon monoxide is the most frequent cause of poisoning worldwide (Stoller, 2007). Toxic levels are often encountered in inadequately ventilated areas warmed by space heaters.

Carbon monoxide is particularly toxic because it is odorless and tasteless and has a high affinity for hemoglobin binding. Thus, it displaces oxygen and impedes its transfer with resultant hypoxia. Besides acute sequelae including death and anoxic encephalopathy, cognitive defects develop in as many as half of patients following loss of consciousness or in those with carbon monoxide levels >25 percent (Weaver, 2002). Hypoxic brain damage has a predilection for the cerebral cortex and white matter and for the basal ganglia (Lo, 2007; Prockop, 2007). A Parkinson syndrome sometimes follows after recovery (Hemphill, 2015).

Pregnancy and Carbon Monoxide Poisoning

Through several physiological alterations, the rate of endogenous carbon monoxide production almost doubles in normal pregnancy (Longo, 1977). Although the pregnant woman is not more susceptible to carbon monoxide poisoning, the fetus does not tolerate excessive exposure (Friedman, 2015). With chronic exposure, maternal symptoms usually appear when the carboxyhemoglobin concentration is 5 to 20 percent. Symptoms include headache, weakness, dizziness, physical and visual impairment, palpitations, and nausea and vomiting. With acute exposure, concentrations of 30 to 50 percent produce symptoms of impending cardiovascular collapse. Levels >50 percent may be fatal for the mother.

Because hemoglobin F has an even higher affinity for carbon monoxide, fetal carboxyhemoglobin levels are 10 to 15 percent higher than those in the mother. This may be due to facilitated diffusion (Longo, 1977). Importantly, the half-life of carboxyhemoglobin is 2 hours in the mother but 7 hours in the fetus. Because carbon monoxide is bound so tightly to hemoglobin F, the fetus may be hypoxic even before maternal carbon monoxide levels are appreciably elevated. Several anomalies are associated with embryonic exposure, and anoxic encephalopathy is the primary sequela of later fetal exposure (Alehan, 2007; Aubard, 2000).

Treatment

For all victims, treatment of carbon monoxide poisoning is supportive along with immediate administration of 100-percent inspired oxygen. Indications for hyperbaric oxygen treatment in nonpregnant individuals are unclear (Kao, 2005). Weaver and associates (2002) reported that hyperbaric oxygen treatment minimized the incidence of cognitive defects in adults at both 6 weeks and 1 year compared with that with normobaric oxygen. Hyperbaric oxygen is generally recommended in pregnancy if carbon monoxide exposure has been "significant" (Aubard, 2000; Ernst, 1998). The problem is how to define significant exposure (Friedman, 2015). Although maternal carbon monoxide levels are not accurately predictive of those in the fetus, some clinicians recommend hyperbaric therapy if maternal levels exceed 15 to 20 percent. With fetal heart rate pattern evaluation, Towers and Corcoran (2009) described affected fetuses to have an elevated baseline, diminished variability, and absent accelerations and decelerations. Treatment of the affected newborn with hyperbaric oxygen is also controversial (Bar, 2007).

Elkharrat and colleagues (1991) reported successful hyperbaric treatments in 44 pregnant women. Silverman and Montano (1997) reported successful management of a woman whose abnormal neurological and cardiopulmonary findings abated in a parallel fashion with resolution of associated variable decelerations in fetal heart rate. Greingor and coworkers (2001) used 2.5-atm hyperbaric 100-percent oxygen for 90 minutes in a 21-week pregnant woman who was delivered of a healthy infant at term. According to the Divers Alert Network—DAN (2016)—at Duke University, 700 chambers are located in North and Central America. Emergency consultation from the Network is available at 919–684–9111.

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CHAPTER 52: Thromboembolic Disorders

The patient complains of intense and sudden precordial pain, becomes livid in appearance, and presents symptoms of profound dyspnea and eventually of air hunger. These embolisms, however, are not always fatal, a small proportion of the patients recovering. The treatment is purely palliative.

—J. Whitridge Williams (1903)

INTRODUCTION

During the past century, the frequency of venous thromboembolism (VTE) during the puerperium decreased remarkably as early ambulation became more widely practiced. Despite this and other advances in prevention and treatment, however, thromboembolism remains a leading cause of maternal morbidity and mortality. Indeed, thrombotic pulmonary embolism accounted for 9.2 percent of pregnancy-related deaths in the United States between 2011 and 2013 (Creanga, 2017).

The absolute incidence of VTE during pregnancy is low—1 or 2 cases per 1000 pregnancies. However, the risk is approximately five times higher than that among women who are not pregnant (Greer, 2015). Approximately equal numbers of cases are identified antepartum and in the puerperium. Deep-vein thrombosis alone is more frequent antepartum, and pulmonary embolism is more common in the first 6 weeks postpartum (Jacobsen, 2008). During the puerperium, the estimated incidence of a thromboembolic complication is 22 events per 100,000 deliveries. Although still elevated, the risk falls to approximately 3 cases per 100,000 deliveries during the second 6-week postpartum period (Kamel, 2014).

PATHOPHYSIOLOGY

Rudolf Virchow (1856) postulated that stasis, local trauma to the vessel wall, and hypercoagulability predisposed to venous thrombosis. During normal pregnancy, the risk for each of these rises. Compression of the pelvic veins and inferior vena cava by the enlarging uterus renders the lower extremity venous system particularly vulnerable to stasis. From their review, Marik and Plante (2008) cite a 50-percent reduction in venous flow velocity in the legs that lasts from the early third trimester until 6 weeks postpartum. This stasis is the most constant predisposing risk factor for venous thrombosis. Venous stasis and delivery may also contribute to endothelial cell injury. Last, as listed in the Appendix (Serum and Blood Constituents), the synthesis of most clotting factors is markedly enhanced during pregnancy and favors coagulation.

Characteristics for developing thromboembolism during pregnancy are shown in Table 52-1. The most important of these is a personal history of thrombosis. Specifically, 15 to 25 percent of all VTE cases during pregnancy are recurrent events (American College of Obstetricians and Gynecologists, 2017b). In one study, the magnitude of other risks was estimated from 7177 VTE cases during pregnancy and 7158 events during the postpartum period (James, 2006). Calculated risks for thromboembolism were approximately doubled in women with multifetal gestation, anemia, hyperemesis, hemorrhage, and cesarean delivery. The risk was even greater in pregnancies complicated by postpartum infection. Waldman and associates (2013) found that the risk of VTE was slightly higher in women with advanced maternal age and approximately doubled in women with great parity, a hypertensive disorder, cesarean delivery, or obesity. Risks were significantly higher among women who had a stillbirth or who underwent peripartum hysterectomy.

TABLE 52-1

Some Risk Factors Associated with an Increased Risk for Thromboembolism

Obstetrical	General
Cesarean delivery	Age 35 years or older
Cesarean hysterectomy	Anatomical anomaly[a]
Diabetes	Cancer
Hemorrhage and anemia	Connective tissue disease
Hyperemesis	Dehydration
Immobility—prolonged bed rest	Immobility—long-distance travel
Multifetal gestation	Infection and inflammatory disease
Multiparity	Myeloproliferative disease
Preeclampsia	Nephrotic syndrome
Puerperal infection	Obesity
Stillbirth	Oral contraceptive use
	Orthopedic surgery
	Paraplegia
	Prior thromboembolism
	Sickle-cell disease
	Smoking
	Thrombophilia

[a]Includes May-Thurner syndrome (iliac vein compression syndrome).

The next most important individual risk factor is a genetically determined thrombophilia. An estimated 20 to 50 percent of women who develop a venous thrombosis during pregnancy or postpartum have an identifiable underlying genetic disorder (American College of Obstetricians and Gynecologists, 2017b).

THROMBOPHILIAS

Several important regulatory proteins act as inhibitors in the coagulation cascade (Fig. 52-1). Normal values for many of these proteins during pregnancy are found in the Appendix (Serum and Blood Constituents). Inherited or acquired deficiencies of these inhibitory proteins are collectively referred to as *thrombophilias*. These can lead to hypercoagulability and recurrent VTE (Connors, 2017). Although these disorders are collectively present in approximately 15 percent of white European populations, they are responsible for approximately 50 percent of all thromboembolic events during pregnancy (Lockwood, 2002; Pierangeli, 2011). Some aspects of the more common inherited thrombophilias are summarized in Table 52-2.

TABLE 52-2

Inherited Thrombophilias and Their Association with Venous Thromboembolism (VTE) in Pregnancy

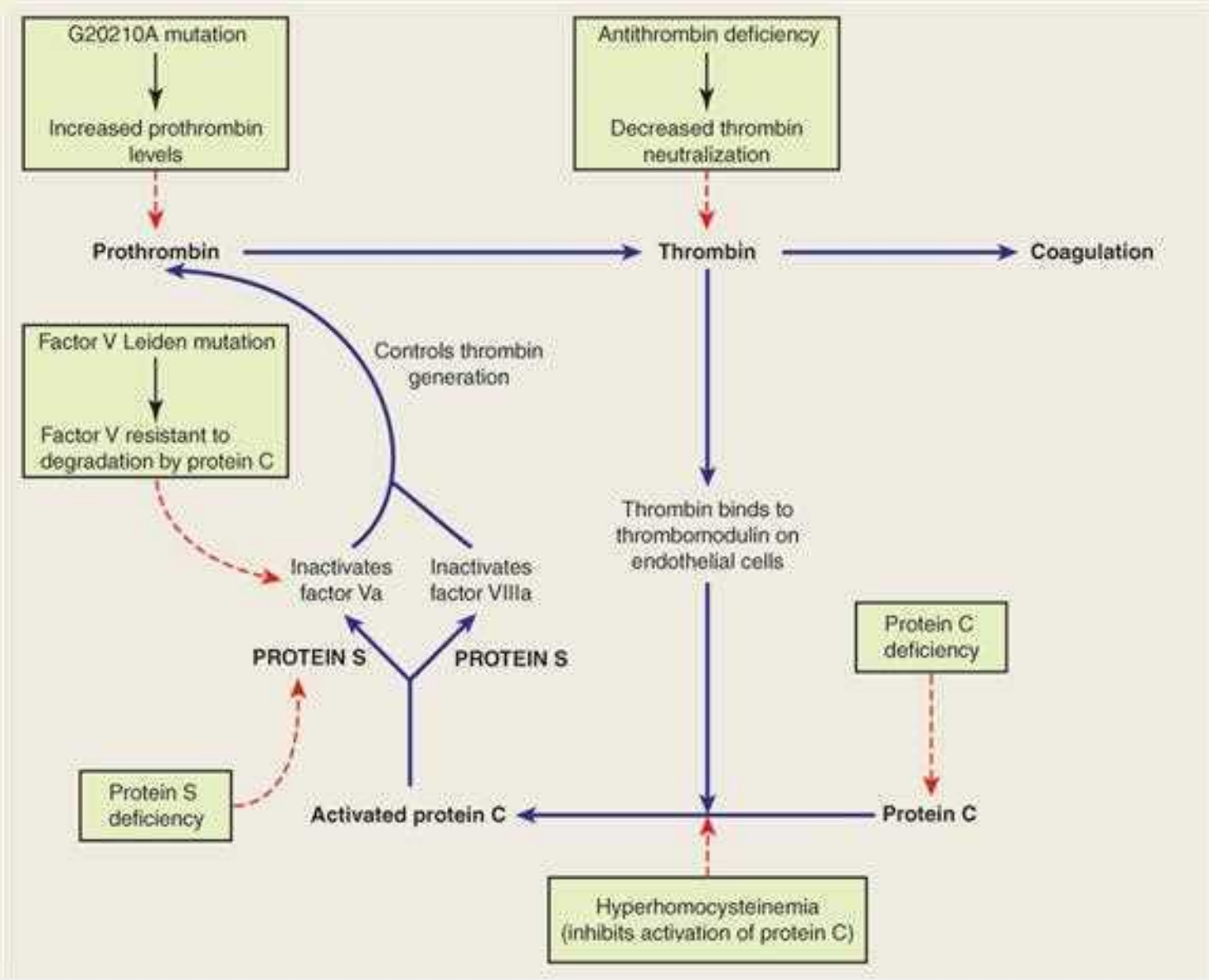
Mutation	VTE Risk per Pregnancy (No History) (%)	VTE Risk per Pregnancy (Prior VTE) (%)	VTE Odds Ratio[a]
Factor V Leiden heterozygote	0.5–1.2	10	6.4
Factor V Leiden homozygote	4	17	35.8
Prothrombin gene heterozygote	<0.5	>10	5.1
Prothrombin gene homozygote	2–4	>17	21.1
Factor V Leiden/prothrombin double heterozygote	4–5	>20	21.2
Antithrombin deficiency	3–7	40	9.5
Protein C deficiency	0.1–0.8	4–17	9.3
Protein S deficiency	0.1	0–22	7.0

[a]Odds ratio for pregnancy-associated VTE compared with gravid noncarriers.

Data from the American College of Obstetricians and Gynecologists, 2017c; Croles, 2017.

FIGURE 52-1

Inherited thrombophilias and their effect(s) on the coagulation cascade. (Data from Seligsohn, 2001.)



Inherited Thrombophilias

Patients with inherited thrombophilic disorders often have a family history of thrombosis. Inherited thrombophilias are also found in up to half of all patients who present with VTE before the age of 45 years, particularly in those whose event occurred in the absence of well-recognized risk factors. Of greatest significance is a family history of sudden death due to pulmonary embolism or a history of multiple family members requiring long-term anticoagulation therapy because of recurrent thrombosis (Anderson, 2011).

Antithrombin Deficiency

Synthesized in the liver, antithrombin is one of the most important inhibitors of thrombin and inactivates thrombin and factor Xa (Rhéaume, 2016). Notably, the rate of antithrombin interaction with its target is accelerated by heparin (Anderson, 2011). Antithrombin deficiency may result from hundreds of different mutations that are almost always autosomal dominant. Type I deficiency results from reduced synthesis of biologically normal antithrombin, and type II deficiency is characterized by normal levels of antithrombin with reduced functional activity (Anderson, 2011). Homozygous antithrombin deficiency is lethal.

Antithrombin deficiency is rare—it affects approximately 1 in 500 to 5000 individuals (Ilonczai, 2015; Rhéaume, 2016). It is the most thrombogenic of the heritable coagulopathies. Indeed, antithrombin deficiency is associated with a 25- to 50-fold higher relative risk of VTE in the general population and a sixfold increased risk of thromboembolic complications during pregnancy (Ilonczai, 2015). Those affected have approximately a 50-percent lifetime risk of VTE (Duhl, 2007).

Sabadell and associates (2010) studied the outcomes of 18 pregnancies complicated by antithrombin deficiency. Twelve of these women were treated with therapeutic doses of low-molecular-weight heparin (LMWH), and six were not treated because antithrombin deficiency had not yet been diagnosed. Three of the untreated patients suffered a thromboembolic episode compared with none in the treated group. Untreated women also had a 50-percent risk of stillbirth and fetal-growth restriction. By comparison, none of the treated women had a stillbirth, but a fourth developed fetal-growth restriction. Similar results were reported by Ilonczai and colleagues (2015). García-Botella and associates (2016) described a mesenteric vein thrombosis in a pregnant woman with antithrombin deficiency. In one review of outcomes in 23 newborns with antithrombin deficiency, there were 11 cases of thrombosis and 10 infant deaths (Seguin, 1994).

Given such risk, affected women are treated during pregnancy with heparin regardless of whether they have had a prior thrombosis. When anticoagulation is necessarily withheld, such as during surgery or delivery, Paidas and colleagues (2016) found that treatment with recombinant human antithrombin protected against VTE development. Sharpe and associates (2011) described successful use of antithrombin concentrate infusions plus therapeutic anticoagulation in a pregnant woman with antithrombin deficiency who developed a thrombosis during the third trimester despite therapeutic LMWH.

Protein C Deficiency

When thrombin is bound to thrombomodulin on endothelial cells of small vessels, its procoagulant activities are neutralized. This binding also activates protein C, a natural anticoagulant that in the presence of protein S controls thrombin generation, in part, by inactivating factors Va and VIIIa (see Fig. 52-1). Protein C activity increases modestly but significantly throughout the first half of pregnancy, and some have speculated that this augmentation may play a role in maintaining early pregnancy through both anticoagulant and inflammatory regulatory pathways (Said, 2010b).

More than 160 different autosomal dominant mutations for the protein C gene have been described (Louis-Jacques, 2016). The prevalence of protein C deficiency is 2 to 3 per 1000, but many of these individuals do not have a thrombosis history because the phenotypic expression is highly variable (Anderson, 2011). These prevalence estimates correspond with functional activity threshold values of 50 to 60 percent, which are used by most laboratories and which are associated with a six- to 12-fold higher risk for VTE (Lockwood, 2012).

Protein S Deficiency

This circulating anticoagulant is activated by protein C, which enhances the capacity of protein S to inactivate factors Va and VIIIa (see Fig. 52-1). Protein S deficiency may be caused by more than 130 different mutations, with an aggregate prevalence of approximately 0.3 to 1.3 per 1000 individuals (Louis-Jacques, 2016). Protein S deficiency may be measured by antigenically determined free, functional, and total S levels. All three decline substantively during normal gestation (Appendix, Serum and Blood Constituents). Thus, the diagnosis in pregnant women—as well as in those taking certain oral contraceptives—is difficult (Archer, 1999). If screening during pregnancy is necessary, threshold values for free protein S antigen levels in the second and third trimesters have been identified at <30 percent and <24 percent, respectively. Among those with a positive family history, the VTE risk in pregnancy is 6 to 7 percent (American College of Obstetricians and Gynecologists, 2017c).

Conard and coworkers (1990) described thrombosis in five of 29 pregnant women with protein S deficiency. They, as well as Burneo and colleagues (2002), reported maternal cerebral vein thrombosis. Neonatal homozygous protein C or S deficiency is usually associated with a fatal clinical phenotype known as *purpura fulminans* (Shanbhag, 2015).

Activated Protein C Resistance—Factor V Leiden Mutation

This is the most prevalent of the known thrombophilia syndromes and is characterized by resistance of plasma to the anticoagulant effects of activated protein C. There are several mutations that create this resistance, but the most common is the factor V Leiden mutation, which was named after the city in which it was described. This missense mutation in the factor V gene results from a substitution of glutamine for arginine at position 506 in the factor V polypeptide. As a result of this mutation, activated factor V is neutralized approximately tenfold more slowly by activated protein C (see Fig. 52-1). This leads to enhanced thrombin generation (MacCallum, 2014).

Heterozygous inheritance of factor V Leiden is the most common heritable thrombophilia. Found in 3 to 15 percent of select European populations and 3 percent of African Americans, it is virtually absent in African blacks and Asians (Lockwood, 2012). One theory for its relatively high prevalence suggests that the heterozygous state may confer a survival advantage, possibly because of reduced bleeding with childbirth or trauma (MacCallum, 2014).

Women who are heterozygous for factor V Leiden account for approximately 40 percent of VTE cases during pregnancy. However, the actual risk among pregnant women who are heterozygous and who do not have a personal history or a first-degree relative with a thrombotic episode before age 50 years is 5 to 12 events per 1000 gravidas (see Table 52-2). In contrast, this risk rises to at least 10 percent among pregnant women with a personal or family history. Pregnant women who are homozygous without a personal or family history have a 1- to 4-percent risk for VTE, whereas those with such a history have an approximately 17-percent risk (American College of Obstetricians and Gynecologists, 2017c).

Diagnosis during pregnancy is performed by DNA analysis for the mutant factor V gene. Bioassay is not used because of the normal resistance that develops after early pregnancy from alterations in other coagulation protein concentrations (Walker, 1997). Of note, activated protein C resistance can also be caused by antiphospholipid syndrome, which is described in Acquired Thrombophilias and also detailed in Chapter 59, Antiphospholipid Syndrome.

To assess the prognostic significance of maternal factor V Leiden mutation during pregnancy, Kjellberg and colleagues (2010) compared the outcomes of 491 carriers with those of 1055 controls. All three of the thromboembolic events occurred among the carriers. But, preterm birth rates, birthweights, or hypertensive complication rates did not differ between the two groups. In a prospective observational study of approximately 5000 women conducted by the Maternal-Fetal Medicine Units Network, the heterozygous mutant gene incidence was 2.7 percent (Dizon-Townson, 2005). Of three pulmonary emboli and one deep-vein thrombosis cases—a rate of 0.8 per 1000 pregnancies—none were among these carriers. Moreover, in the heterozygous women, the risks of preeclampsia, placental abruption, fetal-growth restriction, or pregnancy loss were not elevated. The investigators concluded that universal prenatal screening for the Leiden mutation and prophylaxis for carriers without a prior VTE is not indicated.

Prothrombin G20210A Mutation

This missense mutation in the prothrombin gene leads to excessive accumulation of prothrombin, which then may be converted to thrombin. Prothrombin levels are increased approximately 30 percent in heterozygotes and 70 percent in homozygotes (MacCallum, 2014). As with factor V Leiden, a personal or family history of VTE in a first-degree relative before age 50 years raises the risk of VTE during pregnancy (see Table 52-2). For a heterozygous carrier with such a history, the risk exceeds 10 percent. Without such a history, heterozygous carriers of the mutation have less than a 1-percent risk of VTE during pregnancy (American College of Obstetricians and Gynecologists, 2017c).

Silver and coworkers (2010) tested nearly 4200 women for the prothrombin G20210A mutation. A total of 157—or 3.8 percent—of the women carried the mutation, and only one of these was homozygous. Carriers had similar rates of pregnancy loss, preeclampsia, fetal-growth restriction, and placental abruption compared with noncarriers. Three thromboembolic events occurred in women who tested negative for the mutation.

Homozygous patients, or those who coinherit a G20210A mutation with a factor V Leiden mutation, have a greater thromboembolism risk than heterozygous carriers (Connors, 2017). Lim and associates (2016) have provided detailed information on pregnancy outcomes in women with such rare compound thrombophilias.

Hyperhomocysteinemia

The most common cause of elevated homocysteine is the C667T thermolabile mutation of the 5,10-methylene-tetrahydrofolate reductase (MTHFR) enzyme. Inheritance is autosomal recessive. Elevated homocysteine levels may also result from deficiency of one of several enzymes involved in methionine metabolism and from correctible nutritional deficiencies of folic acid, vitamin B_6, or vitamin B_{12} (Hague, 2003). During normal pregnancy, mean homocysteine plasma concentrations decline (López-Quesada, 2003). Thus, to make a diagnosis during pregnancy, Lockwood (2002) recommends a fasting threshold >12 µmol/L to define hyperhomocysteinemia.

In an interesting metaanalysis, Den Heijer and associates (2005) found that international studies of MTHFR polymorphisms were collectively associated with slightly greater risks for thrombosis. In contrast, studies conducted in North America collectively demonstrated no such association. The authors speculated that folic acid supplementation could explain the difference. Recall that folic acid serves as a cofactor in the remethylation reaction of homocysteine to methionine. Similarly, the American College of Chest Physicians concluded that the lack of an association with thromboembolism could reflect the physiological reductions in homocysteine levels associated with pregnancy and the effects of widespread prenatal folic acid supplementation (Bates, 2012). The American College of Obstetricians and Gynecologists (2017c) has concluded that there is insufficient evidence to support assessment of MTHFR polymorphisms or measurement of fasting homocysteine levels in the evaluation for VTE.

Other Thrombophilia Mutations

Potentially thrombophilic polymorphisms are being discovered at an ever-increasing rate. Unfortunately, information regarding the prognostic significance of such newly discovered mutations is limited. For example, *protein Z* is a vitamin K-dependent protein that serves as a cofactor in factor Xa inactivation. Studies have found that low protein Z levels are associated with an elevated thromboembolism risk in nonpregnant patients and may be implicated in the pathogenesis of poor pregnancy outcomes (Almawi, 2013). Similarly, *plasminogen activator inhibitor type 1 (PAI-1)* is an important regulator of fibrinolysis. Certain polymorphisms in the gene promoter have been associated with slightly greater VTE risks. Although these thrombophilias may exacerbate risk among patients when coinherited with other thrombophilias, the American College of Obstetricians and Gynecologists (2017c) has concluded that evidence to recommend screening is insufficient.

As an interesting aside, Galanaud and coworkers (2010) hypothesized that a paternal thrombophilia could increase the risk of maternal thromboembolism. Specifically, these investigators found that a paternal thrombophilia—the PROCR 6936G allele—affects the endothelial protein C receptor. This receptor is expressed by villous trophoblast and thus is exposed to maternal blood. Although this research is preliminary, it could help explain the pathogenesis of recurrent idiopathic thromboses in pregnant women.

Acquired Thrombophilias

Some examples of acquired hypercoagulable states include antiphospholipid syndrome (APS), heparin-induced thrombocytopenia (Newer Agents), and cancer.

Antiphospholipid Syndrome

This prothrombotic disorder can affect both the venous and arterial circulations. The deeper veins of the lower limbs and the cerebral arterial circulation are the most frequent sites of venous and arterial thrombosis, respectively (Connors, 2017; Giannakopoulos, 2013). Besides thrombosis, the other major clinical manifestations of the APS are obstetrical (Table 18-5). Criteria include: (1) at least one otherwise unexplained fetal death at or beyond 10 weeks; (2) at least one preterm birth before 34 weeks' gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or (3) at least three unexplained consecutive spontaneous abortions before 10 weeks.

Once one of the above clinical criteria—thrombosis or obstetrical—is met, antiphospholipid antibody testing should be performed to diagnose APS. These patients should be tested for the presence of three factors: (1) lupus anticoagulant, (2) anticardiolipin immunoglobulin G and M (IgG and IgM) antibodies, and (3) anti-β_2-glycoprotein I IgG and IgM antibodies. If any of these laboratory test results are positive, a confirmatory test is performed 12 weeks later (Connors, 2017).

Based on their study of 750 singleton pregnancies complicated by APS, Saccone and associates (2017) found that anticardiolipin antibody is the most common sole antiphospholipid antibody present; but anti-β_2-glycoprotein I is associated with the lowest live birth rate and highest incidences of preeclampsia, fetal-growth restriction, and stillbirth compared with anticardiolipin antibodies or lupus anticoagulant alone. These investigators also observed that despite therapy with low-dose aspirin and prophylactic LMWH heparin, the chance of a liveborn neonate was only 30 percent for women with positive test results for all three antibodies.

The thrombosis risk rises significantly during pregnancy in women with APS. Indeed, up to 25 percent of thrombotic events in women with APS occur during pregnancy or in the puerperium. Looking at this a different way, women with APS have a 5- to 12-percent risk of thrombosis during pregnancy or the puerperium (American College of Obstetricians and Gynecologists, 2017a). This syndrome is discussed in more detail in Chapter 59 (Antiphospholipid Syndrome).

Thrombophilias and Pregnancy Complications

Attention has been directed toward possible relationships between inherited thrombophilias and pregnancy complications other than thromboses. Summarized in Table 52-3 are the findings of 25 studies systematically reviewed by Robertson and associates (2005) and incorporated into the recommendations of the American College of Chest Physicians (Bates, 2012). Importantly, the considerable heterogeneity and wide confidence intervals illustrate the uncertainty of these associations.

TABLE 52-3

Association between Pregnancy Complications and Thrombophilia

Type of Thrombophilia	Early Loss	Recurrent First-Trimester Loss	Nonrecurrent Second-Trimester Loss	Late Loss	Preeclampsia	Placental Abruption	Fetal-Growth Restriction
Factor V Leiden (homozygous)	**2.71(1.32–5.58)**	—[a]	—[a]	1.98 (0.40–9.69)	1.87 (0.44–7.88)	8.43 (0.41–171.20)	4.64 (0.19–115.68)
Factor V Leiden (heterozygous)	**1.68(1.09–2.58)**	**1.91 (1.01–3.61)**[a]	**4.12 (1.91–8.81)**[a]	**2.06 (1.10–3.86)**	**2.19 (1.46–3.27)**	**4.70 (1.13–19.59)**	2.68 (0.59–12.13)
Prothrombin gene mutation (heterozygous)	**2.49(1.24–5.00)**	**2.70 (1.37–5.34)**	**8.60 (2.18–33.95)**	**2.66 (1.28–5.53)**	**2.54 (1.52–4.23)**	**7.71 (3.01–19.76)**	2.92 (0.62–13.70)
MTHFR C677T (homozygous)	1.40(0.77–2.55)	0.86 (0.44–1.69)	NA	1.31 (0.89–1.91)	**1.37 (1.07–1.76)**	1.47 (0.40–5.35)	1.24 (0.84–1.82)
Antithrombin deficiency	0.88(0.17–4.48)	NA	NA	7.63 (0.30–196.36)	3.89 (0.16–97.19)	1.08 (0.06–18.12)	NA
Protein C deficiency	2.29(0.20–26.43)	NA	NA	3.05 (0.24–38.51)	5.15 (0.26–102.22)	5.93 (0.23–151.58)	NA
Protein S deficiency	3.55(0.35–35.72)	NA	NA	**20.09 (3.70–109.15)**	2.83 (0.76–10.57)	2.11 (0.47–9.34)	NA
Anticardiolipin antibodies	**3.40(1.33–8.68)**	**5.05 (1.82–14.01)**	NA	**3.30 (1.62–6.70)**	**2.73 (1.65–4.51)**	1.42 (0.42–4.77)	**6.91 (2.70–17.68)**
Lupus anticoagulants (nonspecific inhibitor)	**2.97 (1.03–9.76)**	NA	**14.28 (4.72–43.20)**	2.38 (0.81–6.98)	1.45 (0.70–4.61)	NA	NA
Hyper-homocysteinemia	**6.25 (1.37–28.42)**	**4.21 (1.28–13.87)**	NA	0.98 (0.17–5.55)	**3.49 (1.21–10.11)**	2.40 (0.36–15.89)	NA

[a]Homozygous and heterozygous carriers were grouped together; it is not possible to extract data for each state.

Data are presented as odds ratio (OR [95% CI]) and are derived from Robertson, 2005. Bolded numbers are statistically significant.

MTHFR = methylene tetrahydrofolate reductase variant; NA = not available.

Reproduced with permission from Bates SM, Greer IA, Middledorp S, et al: VTE, thrombophilia, antithrombotic therapy, and pregnancy. Chest 141:e691S, 2012.

Other investigations underscore the heterogeneity of results. For example, Kahn and coworkers (2009) found no higher risk for early-onset or severe preeclampsia in women with factor V Leiden mutation, prothrombin G20210A mutation, MTHFR C677T polymorphism, or hyperhomocysteinemia. Said and associates (2010a) prospectively screened more than 2000 healthy nulliparous women for factor V Leiden, prothrombin gene mutation, MTHFR C677T, MTHFR A1298C, and thrombomodulin polymorphism. Women who carried the prothrombin gene mutation had a 3.6-fold greater risk of adverse pregnancy outcome, including severe preeclampsia, fetal-growth restriction, placental abruption, or stillbirth. But, none of the other polymorphisms conferred an elevated risk of these adverse outcomes. From the Stillbirth Collaborative Research Network, Silver and associates (2016) found a weak association between maternal factor V Leiden and stillbirth. There was no association between stillbirth and the other inherited thrombophilias. Based on their prospective study of 750 pregnancies complicated by stillbirth, Korteweg and colleagues (2010) concluded that routine thrombophilia testing after fetal death is inadvisable.

The American College of Obstetricians and Gynecologists (2017c) notes that a definitive causal link cannot be made between inherited thrombophilias and adverse pregnancy outcomes. Moreover, in one randomized trial, Rodger and associates (2014) found that antepartum prophylactic LMWH did not reduce a composite outcome of pregnancy loss, severe or early-onset preeclampsia, small-for-gestational age neonates, and VTE in thrombophilic women.

Thus, because of uncertainties in the magnitude of risk and in the benefits of prophylaxis given to prevent pregnancy complications in women with heritable thrombophilias, it remains unproven that universal screening is indicated (Louis-Jacques, 2016). In contrast, the association between APS and adverse pregnancy outcomes—including fetal loss, recurrent pregnancy loss, and preeclampsia—is much stronger.

Thrombophilia Screening

Given the relatively high incidence of thrombophilia in the population and the low incidence of VTE, universal screening during pregnancy is not cost effective (Carbone, 2010). Thus, a selective screening strategy is required. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend that thrombophilia screening be considered in the following clinical circumstances: (1) a personal history of VTE that was associated with a nonrecurrent risk factor such as fractures, surgery, and/or prolonged immobilization; and (2) a first-degree relative (parent or sibling) with a history of high-risk thrombophilia or VTE before age 50 years in the absence of other risk factors.

The American College of Obstetricians and Gynecologists (2017c) notes that testing for inherited thrombophilias in women who have experienced recurrent fetal loss or placental abruption is not recommended because clinical evidence that antepartum heparin prophylaxis prevents recurrence is insufficient. Similarly, testing is not recommended for women with a history of fetal-growth restriction or preeclampsia. The American College of Chest Physicians also recommends against screening women with prior pregnancy complications (Bates, 2012). However, screening for antiphospholipid antibodies may be appropriate in women who have experienced a fetal loss or early-onset preeclampsia (Berks, 2015).

Methods of screening for the more common inherited thrombophilias are shown in Table 52-4. Whenever possible, laboratory testing is performed at least 6 weeks after the thrombotic event, while the patient is not pregnant, and when she is not receiving anticoagulation or hormonal therapy. Screening for hyperhomocysteinemia is not recommended (American College of Obstetricians and Gynecologists, 2017c).

TABLE 52-4

How to Test for Thrombophilias

Thrombophilia	Testing Method	Is Testing Reliable During Pregnancy?	Is Testing Reliable During Acute Thrombosis?	Is Testing Reliable with Anticoagulation?
Factor V Leiden mutation	Activated protein C resistance assay (second generation) If abnormal: DNA analysis	Yes Yes	Yes Yes	No Yes
Prothrombin gene mutation G20210A	DNA analysis	Yes	Yes	Yes
Protein C deficiency	Protein C activity (<60%)	Yes	No	No
Protein S deficiency	Functional assay (<55%)	No[a]	No	No
Antithrombin deficiency	Antithrombin activity (<60%)	Yes	No	No

[a]If screening in pregnancy is necessary, cutoff values for free protein S antigen levels in the second and third trimesters have been identified at less than 30% and less than 24%, respectively.

Reproduced with permission from American College of Obstetricians and Gynecologists Women's Health Care Physicians: ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy, Obstet Gynecol. 2013 Sep;122(3):706–717.

DEEP-VEIN THROMBOSIS

Clinical Presentation

During pregnancy, most venous thromboses are confined to the deep veins of the lower extremity. Approximately 70 percent of cases are located in the iliofemoral veins without involvement of the calf veins. Isolated iliac vein and calf vein thromboses occur in approximately 17 and 6 percent of cases, respectively (Chan, 2010). In contrast, in the general population, more than 80 percent of deep-vein thromboses involve calf veins, and iliofemoral or isolated iliac vein thromboses are uncommon (Huisman, 2015).

The signs and symptoms vary greatly and depend on the degree of occlusion and the intensity of the inflammatory response. Ginsberg and coworkers (1992) reported that 58 of 60 antepartum women—97 percent—had left leg thromboses. Blanco-Molina and coworkers (2007) reported left-leg involvement in 78 percent. Greer (2003) hypothesizes that this results from compression of the left iliac vein by the right iliac and ovarian artery, both of which cross the vein only on the left side. Yet, as described in Chapter 53 (Urinary Tract Infections), the ureter is compressed more on the right side.

Classically, thrombosis involving the lower extremity is abrupt in onset, and there is pain and edema of the leg and thigh. The thrombus typically involves much of the deep-venous system to the iliofemoral region. Occasionally, reflex arterial spasm causes a pale, cool extremity with diminished pulsations.

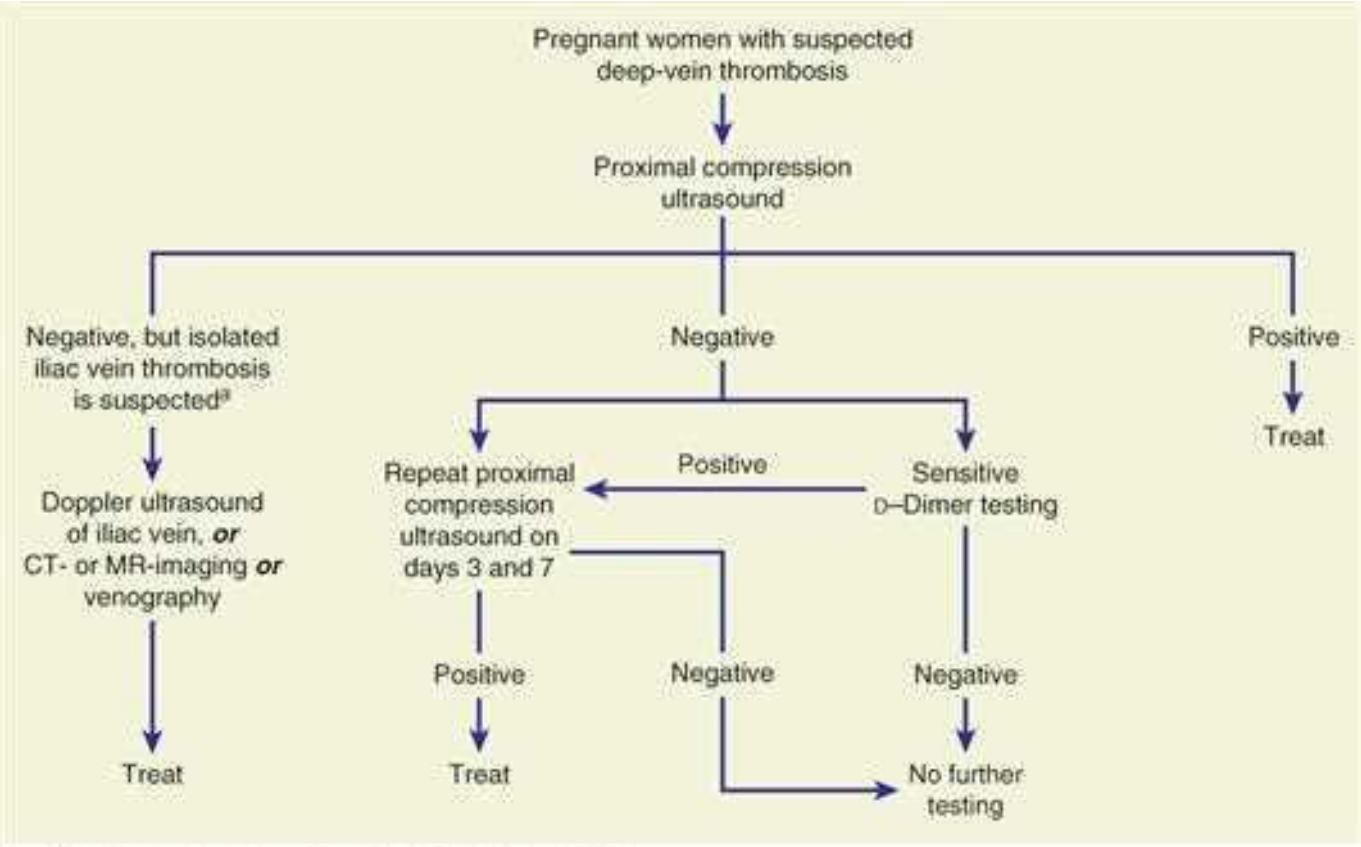
Alternatively, there may be appreciable clot, yet little pain, heat, or swelling. Importantly, calf pain, either spontaneous or in response to squeezing or to Achilles tendon stretching—*Homans sign*—may be caused by a strained muscle or contusion. Between 30 and 60 percent of women with a confirmed lower-extremity acute deep-vein thrombosis have an asymptomatic pulmonary embolism (Superficial Venous Thrombophlebitis).

Diagnosis

Clinical diagnosis of deep-vein thrombosis is difficult, and in an earlier study of pregnant women, the clinical diagnosis was confirmed in only 10 percent (Hull, 1990). Another challenge is that many of the common diagnostic tests that have been investigated extensively in nonpregnant patients have not been validated appropriately in pregnancy (Huisman, 2015). Shown in Figure 52-2 is one diagnostic algorithm recommended by the American College of Chest Physicians that can be used for evaluation of pregnant women (Guyatt, 2012). With a few modifications, we follow a similar evaluation at Parkland Hospital.

FIGURE 52-2

Algorithm for evaluation of suspected deep-vein thrombosis in pregnancy. CT = computed tomography; MR = magnetic resonance. [a]Signs and symptoms include swelling of the entire leg, with or without flank, buttock, or back pain. (Data from Guyatt GH, Akl EA, Crowther M, et al: Executive summary: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, Chest. 2012 Feb;141(2 Suppl):7S-47S.)



Compression Ultrasonography

In pregnant women with suspected deep-vein thrombosis, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend compression ultrasonography of the proximal veins as the initial diagnostic test. According to the American College of Chest Physicians, this noninvasive technique is currently the most-used first-line test to detect deep-vein thrombosis (Guyatt, 2012). The diagnosis is based on the noncompressibility and typical echoarchitecture of a thrombosed vein.

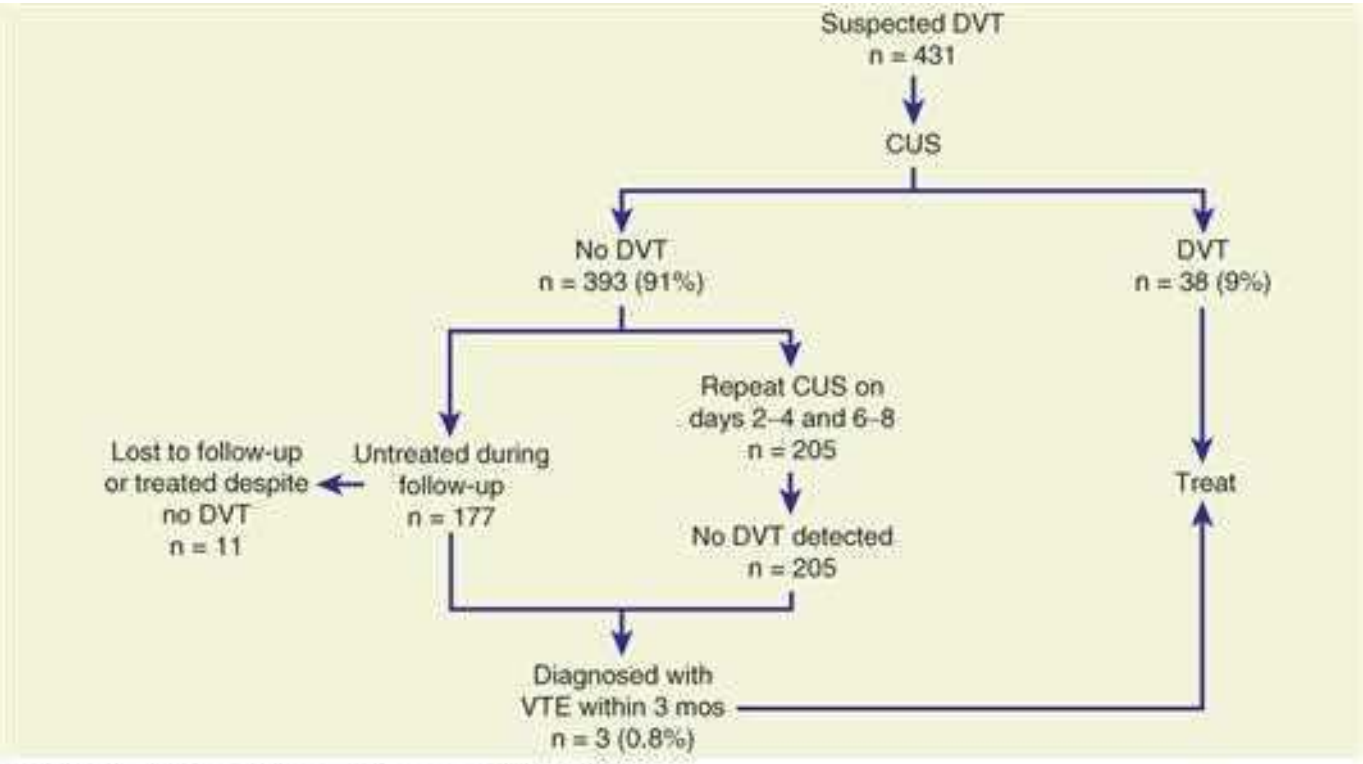
For *nonpregnant* patients with suspected thrombosis, the safety of withholding anticoagulation for 1 week has been established for those who have a compression ultrasound examination that is initially normal (Birdwell, 1998; Heijboer, 1993). Serial compression examinations are then performed because isolated undetected calf thromboses that ultimately extend into the proximal veins will do so within 1 to 2 weeks of presentation in approximately a fourth of patients.

In *pregnant* women, the important caveat is that normal findings with venous ultrasonography do not always exclude a pulmonary embolism. This is because the thrombosis may have already embolized or because it arose from iliac or other deep-pelvic veins, which are less accessible to ultrasound evaluation (Goldhaber, 2004). As discussed, thrombosis associated with pulmonary embolism during pregnancy commonly originates in the iliac veins.

The results of two studies are helpful for evaluating the need for serial examinations in pregnant women suspected of having a deep-vein thrombosis but who have a negative initial compression ultrasound examination. The combined results are depicted in Figure 52-3. Chan and coworkers (2013) studied 221 pregnant and postpartum women presenting with a suspected deep-vein thrombosis. The 205 women with a negative initial study result underwent serial testing, which was negative in all cases. Of these, one woman with normal serial testing had a pulmonary embolism 7 weeks later. Le Gal and colleagues (2012) studied 210 pregnant and postpartum women with a suspected deep-vein thrombosis. Of these, 177 women without a deep-vein thrombosis were not anticoagulated and did not undergo serial testing. Two had an objectively confirmed thrombosis diagnosed within 3 months. In sum, these preliminary data suggest that a negative single complete compression ultrasonography study may safely exclude the diagnosis of deep-vein thrombosis in most pregnant women.

FIGURE 52-3

Findings from two studies of serial and nonserial compression ultrasound examinations in pregnant and postpartum women. CUS = compression ultrasonography. DVT = deep vein thrombosis. VTE = venous thromboembolism. (Data from Chan, 2013; Le Gal, 2012.)



Magnetic Resonance Imaging

This imaging technique allows excellent delineation of anatomical detail above the inguinal ligament. Thus, in many cases, magnetic resonance (MR) imaging is immensely useful for diagnosis of iliofemoral and pelvic vein thrombosis. The venous system can also be reconstructed using MR venography (Chap. 46, Imaging During Pregnancy). Erdman and associates (1990) reported that MR imaging was 100-percent sensitive and 90-percent specific for detection of venographically proven deep-vein thrombosis in nonpregnant patients. Importantly, almost half of those without deep-vein thrombosis were found to have nonthrombotic conditions that included cellulitis, myositis, edema, hematomas, and superficial phlebitis.

Khalil and coworkers (2012) used MR venography to study the natural history of pelvic vein thrombosis after vaginal delivery. Among the 30 *asymptomatic* patients who were all within four days of delivery, 30 percent had a definitive thrombosis in either the iliac or ovarian veins, and another 37 percent had a suspected thrombosis. Our experiences with hundreds of postpartum MR scans do not support these findings. Thus, although the clinical significance of their findings is uncertain, it seems clear that some degree of pelvic vein intraluminal filling defect may be a normal finding.

d-Dimer Screening Tests

These specific fibrin degradation products are generated when fibrinolysin degrades fibrin, as occurs in thromboembolism (Chap. 41, Pregnancy-Induced Coagulation Changes). Their measurement is frequently incorporated into diagnostic algorithms for VTE in nonpregnant patients (Wells, 2003). Screening with the d-dimer test in pregnancy, however, is problematic for several reasons. As shown in the Appendix (Serum and Blood Constituents), depending on assay sensitivity, d-dimer serum levels rise with gestational age along with substantively elevated plasma fibrinogen concentrations (Murphy, 2015). Levels are also affected by multifetal gestation and cesarean delivery (Morikawa, 2011). d-Dimer concentrations can also be elevated in certain pregnancy complications such as placental abruption, preeclampsia, and sepsis syndrome. Moreover, higher levels have been observed in sickle-cell carriers and in

women of African and South Asian racial origin (Grossman, 2016). For all these reasons, their use during pregnancy remains uncertain, but a negative d-dimer test should be considered reassuring (Lockwood, 2012; Marik, 2008).

Management

Optimal management of VTE during pregnancy has not undergone major clinical study to provide evidence-based practices. There is, however, consensus for treatment with anticoagulation and limited activity. If thrombophilia testing is performed, it is done before anticoagulation. Heparin induces a decline in antithrombin levels, and warfarin lowers protein C and S concentrations. The results of these tests do not change treatment (Connors, 2017).

Anticoagulation is initiated with either unfractionated heparin (UFH) or LMWH. Although either type is acceptable, most recommend one of the LMWHs (Bates, 2016; Kearon, 2016). For example, the American College of Chest Physicians suggests preferential use of LMWH during pregnancy because of better bioavailability, longer plasma half-life, more predictable dose response, reduced risks of osteoporosis and thrombocytopenia, and less frequent dosing (Bates, 2012). Dosages are shown in Table 52-5.

TABLE 52-5

Anticoagulation Regimen Definitions

Anticoagulation Regimen	Definition
Prophylactic LMWH[a]	Enoxaparin, 40 mg SC once daily Dalteparin, 5,000 units SC once daily Tinzaparin, 4,500 units SC once daily
Therapeutic LMWH[b]	Enoxaparin, 1 mg/kg every 12 hours Dalteparin, 200 units/kg once daily Tinzaparin, 175 units/kg once daily Dalteparin, 100 units/kg every 12 hours May target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL for twice daily regimen; slightly higher doses may be needed for a once-daily regimen.
Minidose prophylactic UFH	UFH, 5,000 units SC every 12 hours
Prophylactic UFH	UFH, 5,000–10,000 units SC every 12 hours UFH, 5,000–7,500 units SC every 12 hours in first trimester UFH 7,500–10,000 units SC every 12 hours in the second trimester UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Therapeutic UFH[b]	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5) 6 hours after injection
Postpartum anticoagulation	Prophylactic LMWH/UFH for 4–6 weeks or vitamin K antagonists for 4–6 weeks with a target INR of 2.0–3.0, with initial UFH or LMWH therapy overlap until the INR is 2.0 or more for 2 days
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep-vein thrombosis or pulmonary embolism

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.

[a]Although at extremes of body weight, modification of dose may be required.

[b]Also referred to as weight adjusted, full treatment dose.

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TABLE 52-6

Some Recommendations for Thromboprophylaxis during Pregnancy

	Pregnancy		Postpartum	
Clinical Scenario	**ACOG[a]**	**ACCP[b]**	**ACOG[a]**	**ACCP[b]**
Prior single VTE				
Risk factor no longer present	Surveillance only	Surveillance only	Postpartum anticoagulation[c] "Surveillance only acknowledged by some experts."	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Pregnancy- or estrogen-related or no known association (idiopathic) ***and*** not receiving long-term therapy	Prophylactic UFH or LMWH ***or*** "Surveillance only acknowledged by some experts"	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Receiving long-term warfarin	NSS	Adjusted-dose LMWH ***or*** 75% of a therapeutic dose of LMWH	NSS	Resume long-term anticoagulation
Associated with a high-risk thrombophilia[d] ***and*** not receiving long-term anticoagulation or an affected first-degree relative	Prophylactic, intermediate-, or adjusted-dose LMWH or UFH	NSS	Postpartum anticoagulation[c] ***or*** intermediate- or adjusted-dose LMWH or UFH × 6 weeks[c]	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Associated with a low-risk thrombophilia[e] and not receiving treatment	Prophylactic or intermediate-dose LMWH or UFH ***or*** surveillance only	NSS	Postpartum anticoagulation[c] ***or*** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Two or more prior VTEs with or without thrombophilia				
Not receiving long-term therapy	Prophylactic or therapeutic-dose UFH or LMWH	NSS	Postpartum anticoagulation[c] ***or*** therapeutic-dose LMWH or UFH × 6 weeks	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Receiving long-term anticoagulation	Therapeutic-dose LMWH or UFH	Adjusted-dose LMWH ***or*** 75% of a therapeutic dose of LMWH	Resumption of long- term anticoagulation	Resumption of long-term anticoagulation
No prior VTE				
High-risk thrombophilia[d]	Surveillance only ***or*** prophylactic or intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE ***and*** homozygous factor V Leiden or prothrombin 20210A mutation	NSS	Prophylactic or intermediate-dose LMWH	NSS	Prophylactic or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks

	Pregnancy		Postpartum	
Clinical Scenario	**ACOG[a]**	**ACCP[b]**	**ACOG[a]**	**ACCP[b]**
Negative family history VTE and homozygous factor V Leiden or prothrombin 20210A mutation	Surveillance only ***or*** prophylactic LMWH or UFH	Surveillance only	Postpartum anticoagulation[c]	Prophylactic- or intermediate-dose LMWH ***or*** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE and low-risk thrombophilias[e]	Surveillance only	Surveillance only	Postpartum anticoagulation[c] ***or*** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH ***or*** in women not protein C or S deficient, warfarin target INR 2.0–3.0
Low-risk thrombophilia[e]	Surveillance only	Surveillance only if no family history	Surveillance only; postpartum anticoagulation with additional risk factors[f]	Surveillance only if no family history
Antiphospholipid antibodies				
History of VTE	Prophylactic anticoagulation with UFH or LMWH (?plus low-dose aspirin)	NSS	Prophylactic anticoagulation[c]; referral to specialist[g]	NSS
No prior VTE	Surveillance only ***or*** prophylactic LMWH or UFH ***or*** prophylactic LMWH or UFH plus low-dose aspirin if prior recurrent pregnancy loss or stillbirth	Prophylactic- or intermediate-dose UFH ***or*** prophylactic-dose LMWH, both given with 75–100 mg/day aspirin[h]	Prophylactic heparin plus low-dose aspirin × 6 weeks if prior recurrent pregnancy loss or stillbirth[g]	NSS

[a] American College of Obstetricians and Gynecologists, 2017a, c.

[b] American College of Chest Physicians (Bates, 2012).

[c] Postpartum treatment levels should be ≥ antepartum treatment.

[d] Antithrombin deficiency; doubly heterozygous or homozygous for prothrombin 20210A and factor V Leiden.

[e] Heterozygous factor V Leiden or prothrombin 20210A; protein S or C deficiency.

[f] First-degree relative with VTE at <50 years; other major thrombotic risk factors, e.g., obesity, prolonged immobility.

[g] Women with antiphospholipid syndrome should not use estrogen-containing contraceptives.

[h] Treatment is recommended if the diagnosis of antiphospholipid syndrome is based on three or more prior pregnancy losses.

LMWH = low-molecular-weight heparin; NSS = not specifically stated; UFH = unfractionated heparin; VTE = venous thromboembolism.

Prophylactic, intermediate-, and adjusted-dose regimens are listed in Table 52-5.

During pregnancy, heparin therapy is continued, and for postpartum women, anticoagulation is begun simultaneously with warfarin. Recall that pulmonary embolism develops in as many as 60 percent of patients with untreated venous thrombosis, and anticoagulation decreases this risk to less than 5 percent. In nonpregnant patients, the mortality rate with a pulmonary embolism approximates 1 percent (Douketis, 1998; Pollack, 2011).

Over several days, leg pain dissipates. After symptoms have abated, graded ambulation is begun. Elastic stockings are fitted, and anticoagulation is continued. Recovery to this stage usually takes 7 to 10 days. Graduated compression stockings are continued for 2 years after the diagnosis to reduce the incidence of postthrombotic syndrome (Brandjes, 1997). This syndrome can include chronic leg paresthesias or pain, intractable edema, skin changes, and leg ulcers.

Unfractionated Heparin

This agent should be considered for the initial treatment of thromboembolism and in situations in which delivery, surgery, or thrombolysis may be necessary (American College of Obstetricians and Gynecologists, 2017b). Unfractionated heparin can be administered by one of two alternatives: (1) initial intravenous therapy followed by adjusted-dose subcutaneous UFH given every 12 hours; or (2) twice-daily, adjusted-dose subcutaneous UFH with doses adjusted to prolong the activated partial thromboplastin time (aPTT) into the therapeutic range 6 hours postinjection (Bates, 2012). As shown in Table 52-5, the therapeutic dose for subcutaneous UFH is usually 10,000 units or more every 12 hours.

For intravenous therapy, several protocols are acceptable. In general, if UFH is used, it is initiated with a bolus intravenous dose of 70 to 100 U/kg, which is 5000 to 10,000 U. This is followed by continuous intravenous infusions beginning at 1000 U/hr or 15 to 20 U/kg/hr. This infusion rate is titrated to achieve an aPTT 1.5 to 2.5 times control values (Brown, 2010; Linnemann, 2016). Intravenous anticoagulation is maintained for at least 5 to 7 days, after which treatment is converted to subcutaneous heparin to maintain the aPTT to at least 1.5 to 2.5 times control throughout the dosing interval. For women with lupus anticoagulant, aPTT does not accurately assess heparin anticoagulation, and thus anti-factor Xa levels are preferred.

The duration of full anticoagulation varies, and no studies have defined the optimal duration for pregnancy-related thromboembolism. In nonpregnant patients with VTE, evidence supports a minimum treatment duration of 3 months (Kearon, 2012). For pregnant patients, the American College of Chest Physicians recommends anticoagulation throughout pregnancy and postpartum for a minimum total duration of 3 months (Bates, 2012). Lockwood (2012) recommends that full anticoagulation be continued for at least 20 weeks followed by prophylactic doses if the woman is still pregnant. Prophylactic doses of subcutaneous UFH can range from 5000 to 10,000 U every 12 hours titrated to maintain an anti-factor Xa level of 0.1 to 0.2 U/mL, measured 6 hours after the last injection. If the VTE occurs during the postpartum period, Lockwood (2012) recommends a minimum of 6 months of anticoagulation treatment.

Low-Molecular-Weight Heparin

This is a family of derivatives of unfractionated heparin, and their molecular weights average 4000 to 5000 daltons compared with 12,000 to 16,000 daltons for conventional heparin. None of these heparins cross the placenta, and all exert their anticoagulant activity by activating antithrombin. The primary difference is their relative inhibitory activity against factor Xa and thrombin. Specifically, UFH has equivalent activity against factor Xa and thrombin, but LMWHs have greater activity against factor Xa than against thrombin. They also have a more predictable anticoagulant response and fewer bleeding complications than UFH because of their better bioavailability, longer half-life, dose-independent clearance, and decreased interference with platelets (Tapson, 2008). These LMWH compounds are cleared by the kidneys and must be used cautiously when there is renal dysfunction.

Several studies have shown that VTE is treated effectively with LMWH (Quinlan, 2004; Tapson, 2008). Using serial venograms, Breddin and associates (2001) observed that these compounds were more effective than UFH in reducing thrombus size without increasing mortality rates or major bleeding complications. Several different treatment regimens using adjusted-dose LMWH for treatment of acute VTE are recommended by the American College of Obstetricians and Gynecologists (2017b,c) and are listed in Table 52-5.

Pharmacokinetics in Pregnancy

LMWHs available for use in pregnancy include enoxaparin, tinzaparin, and dalteparin. Enoxaparin (Lovenox) pharmacokinetics were studied in 36 women with VTE during pregnancy or immediately postpartum (Rodie, 2002). The dose was approximately 1 mg/kg given twice daily based on early pregnancy weight. Treatment was monitored by peak anti-factor Xa activity at 3 hours postinjection, with a target therapeutic range of 0.4 to 1.0 U/mL. In 33 women, enoxaparin provided satisfactory anticoagulation. In the other three women, dose reduction was necessary. None developed recurrent thromboembolism or bleeding complications. In postcesarean women with a body mass index (BMI) ≥35, Stephenson and associates (2016) found that weight-based dosing of enoxaparin 0.5 mg/kg twice daily more effectively achieved prophylactic peak anti-Xa levels between 0.2 to 0.6 U/mL than a fixed dose of 40 mg daily. Similar findings were reported by Overcash and colleagues (2015).

For tinzaparin (Innohep), a dosage of 75 to 175 U/kg/d was necessary to achieve peak anti-factor Xa levels of 0.1 to 1.0 U/mL (Smith, 2004). In studies of dalteparin (Fragmin) pharmacokinetics, conventional starting doses of dalteparin—100 U/kg every 12 hours—were likely insufficient to maintain full anticoagulation (Barbour, 2004; Jacobsen, 2003). Thus, slightly higher doses than that shown in Table 52-5 may be required.

Dosing and Monitoring

Standard prophylactic and therapeutic dosages recommended by the American College of Obstetricians and Gynecologists (2017b) for various LMWHs are listed in Table 52-5. Whether such dosages require adjustments during the course of pregnancy is controversial (Berresheim, 2014; Cutts, 2013). Some suggest periodic measurement of anti-factor Xa levels 4 to 6 hours after an injection with dose adjustment to maintain a therapeutic level. Large studies using clinical end points that demonstrate an optimal therapeutic range or show that dose adjustments increase therapy safety or efficacy are lacking.

Accordingly, the American College of Chest Physicians and others note that routine monitoring with anti-Xa levels is difficult to justify (Bates, 2012; McDonnell, 2017).

Safety in Pregnancy

Early reviews concluded that LMWHs were safe and effective (Lepercq, 2001; Sanson, 1999). Despite this, in 2002, the manufacturer of Lovenox warned that its use in pregnancy had been associated with congenital anomalies and a higher risk of hemorrhage. After its own extensive review, the American College of Obstetricians and Gynecologists (2017b) concluded that these risks were rare, that their incidence was not higher than expected, and that no cause-and-effect relationship had been established. It further concluded that enoxaparin and dalteparin could be given safely during pregnancy. Other reports confirm their safety (Andersen, 2010; Bates, 2012; Galambosi, 2012).

Nelson-Piercy and coworkers (2011) assessed the safety of tinzaparin through a comprehensive study of 1267 treated pregnant women. There were no maternal deaths or complications from regional analgesia. Although thrombocytopenia developed in 1.8 percent, there were no cases of heparin-induced thrombocytopenia (Newer Agents). The allergy incidence was 1.3 percent. Osteoporotic fractures in three women (0.2 percent) were judged to be related to tinzaparin (Newer Agents). A total of 43 women (3.4 percent) required medical intervention for bleeding. Of 15 stillbirths, four were judged as possibly being related to tinzaparin use. But, none of the neonatal deaths or congenital abnormalities was attributed to tinzaparin. The authors concluded that tinzaparin during pregnancy was safe for mother and fetus. LMWHs are also safe during breastfeeding (Lim, 2010).

However, LMWHs should be avoided in women with renal failure. Moreover, when given within 2 hours of cesarean delivery, these agents raise the risk of wound hematoma (van Wijk, 2002).

Labor and Delivery

Women receiving either therapeutic or prophylactic anticoagulation should be converted from LMWH to the shorter half-life UFH in the last month of pregnancy or sooner if delivery appears imminent. The purpose of conversion to UFH has less to do with any risk of maternal bleeding at the time of delivery, but rather with neuraxial blockade complicated by an epidural or spinal hematoma (Chap. 25, Safety). The American College of Chest Physicians recommends that women scheduled for a planned delivery who are receiving twice-daily adjusted-dose subcutaneous UFH or LMWH discontinue their heparin 24 hours before labor induction or cesarean delivery (Bates, 2012). Patients receiving once-daily LMWH should take only 50 percent of their normal dose on the morning of the day before delivery. The American College of Obstetricians and Gynecologists (2017c) advises that adjusted-dose subcutaneous LMWH or UFH can be discontinued 24 to 36 hours before an induction of labor or scheduled cesarean delivery. The American Society of Regional Anesthesia and Pain Medicine advises withholding neuraxial blockade for 10 to 12 hours after the last prophylactic dose of LMWH or 24 hours after the last therapeutic dose (Horlocker, 2010).

If a woman begins labor while taking UFH, clearance can be verified by an aPTT. Reversal of heparin with protamine sulfate is rarely required and is not indicated with a prophylactic dose of heparin. For women in whom anticoagulation therapy has temporarily been discontinued, pneumatic compression devices are recommended.

Anticoagulation with Warfarin Compounds

Vitamin K antagonists are generally contraindicated because they readily cross the placenta and may cause fetal death and malformations from hemorrhages (Chap. 12, Warfarin). They do not accumulate in breast milk and are thus safe during breastfeeding.

Postpartum venous thrombosis is usually treated with intravenous heparin and oral warfarin initiated simultaneously. The initial dose of warfarin is usually 5 to 10 mg for the first 2 days. Subsequent doses are titrated to achieve an international normalized ratio (INR) of 2 to 3. To avoid paradoxical thrombosis and skin necrosis from the early anti-protein C effect of warfarin, these women are maintained on therapeutic doses of UFH or LMWH for 5 days and until the INR is in a therapeutic range for 2 consecutive days (American College of Obstetricians and Gynecologists, 2017c; Stewart, 2010).

Treatment in the puerperium may require larger doses of anticoagulant. Brooks and colleagues (2002) compared anticoagulation in postpartum women with that of age-matched nonpregnant controls. The former required a significantly larger median total dose of warfarin—45 versus 24 mg—and a longer time—7 versus 4 days—to achieve the target INR.

Newer Agents

Of newer oral anticoagulants, dabigatran (Pradaxal) inhibits thrombin. Rivaroxaban (Xarelto) and apixaban (Eliquis) inhibit factor Xa. Currently, very few reports address these newer agents during pregnancy, and thus the human reproductive risks are essentially unknown (Bates, 2012). Dabigatran crosses the human placenta (Bapat, 2014). However, it is unknown whether any of these agents are excreted in breast milk. Because of the potential for infant harm, a decision should be made to either avoid breastfeeding or use an alternative anticoagulant, such as warfarin, in postpartum women (Burnett, 2016).

Complications of Anticoagulation

Three significant complications associated with anticoagulation are hemorrhage, thrombocytopenia, and osteoporosis. The latter two are unique to heparin, and their risk may be reduced with LMWHs. The most serious complication is hemorrhage, which is more likely if there has been recent surgery or lacerations. Troublesome bleeding also is more likely if the heparin dosage is excessive. Unfortunately, management schemes using laboratory testing to identify when a heparin dosage is sufficient to inhibit further thrombosis, yet not cause serious hemorrhage, have been discouraging.

Heparin-Induced Thrombocytopenia

There are two types—the most common is a nonimmune, benign, reversible thrombocytopenia that develops within the first few days of therapy and resolves in approximately 5 days without therapy cessation. The second is the severe form of heparin-induced thrombocytopenia (HIT), which results from an immune reaction involving IgG antibodies directed against complexes of platelet factor 4 and heparin. The diagnosis of HIT is based on a drop in the platelet count of more than 50 percent or thrombosis beginning 5 to 10 days after the start of heparin in association with the appearance of platelet-activating HIT antibodies. The fall in platelet count in HIT occurs rapidly—over a period of 1 to 3 days—and is assessed relative to the highest platelet count after the start of heparin. The typical nadir is 40,000 to 80,000 platelets per microliter (Greinacher, 2015).

Although the incidence of HIT is approximately 3 to 5 percent in nonpregnant individuals, it is <0.1 percent in obstetrical patients (Linkins, 2012). Fausett and coworkers (2001) reported no cases among 244 heparin-treated gravidas compared with 10 among 244 nonpregnant patients. Accordingly, the American College of Chest Physicians recommends against platelet count monitoring when the risk of HIT is considered to be less than 1 percent. In others, they suggest monitoring every 2 or 3 days from day 4 until day 14 (Linkins, 2012).

When HIT is diagnosed, heparin therapy is stopped and alternative anticoagulation initiated. Platelet transfusions are avoided (Greinacher, 2015). LMWH may not be entirely safe because it has some cross reactivity with UFH. The American College of Chest Physicians recommends danaparoid (Orgaran)—a sulfated glycosaminoglycan heparinoid (Bates, 2012; Linkins, 2012). In a review of nearly 50 pregnant women with either HIT or a skin rash, Lindhoff-Last and associates (2005) concluded that danaparoid was a reasonable alternative. However, they reported two fatal maternal hemorrhages and three fetal deaths. Magnani (2010) reviewed case reports of 83 pregnant women treated with danaparoid. Although it was generally effective, two patients died related to bleeding, three patients suffered nonfatal major bleeds, and three women developed thromboembolic events unresponsive to danaparoid. The drug has been removed from the U.S. market.

Other agents are *fondaparinux* (Arixtra)—a pentasaccharide factor Xa inhibitor and *argatroban* (Novastan)—a direct thrombin inhibitor (Kelton, 2013; Linkins, 2012). Successful use in pregnancy has been reported (Elsaigh, 2015; Knol, 2010). Tanimura and coworkers (2012) successfully used argatroban, and later fondaparinux, to manage HIT in a pregnant woman with hereditary antithrombin deficiency.

Heparin-Induced Osteoporosis

Bone loss may develop with long-term heparin administration—usually 6 months or longer—and is more prevalent in cigarette smokers. UFH can cause osteopenia, and this is less likely with LMWHs (Deruelle, 2007). Women treated with any heparin should be encouraged to take an oral daily 1500-mg calcium supplement (Cunningham, 2005; Lockwood, 2012). In one study, Rodger and colleagues (2007) found that long-term use of dalteparin for a mean of 212 days was not associated with a significant decline in bone mineral density.

Anticoagulation and Abortion

The treatment of deep-vein thrombosis with heparin does not preclude pregnancy termination by careful curettage. After the products are removed without trauma to the reproductive tract, full-dose heparin can be restarted in several hours.

Anticoagulation and Delivery

The effects of heparin on blood loss at delivery depend on several variables: (1) dose, route, and timing of administration; (2) number and depth of incisions and lacerations; (3) intensity of postpartum myometrial contractions; and (4) presence of other coagulation defects. Blood loss should not be greatly increased with vaginal delivery if the episiotomy is modest in depth, there are no lacerations, and the uterus promptly contracts. Unfortunately, such ideal circumstances do not always prevail. For example, Mueller and Lebherz (1969) described 10 women with antepartum thrombophlebitis treated with heparin. Three women who continued to receive heparin during labor and delivery bled remarkably and developed large hematomas. Thus, heparin therapy generally is stopped during labor and delivery. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) recommend restarting UFH or LMWH no sooner than 4 to 6 hours after vaginal delivery or 6 to 12 hours after cesarean delivery. We wait at least 24 hours to restart therapy after cesarean delivery or after vaginal delivery with significant lacerations.

Slow intravenous administration of protamine sulfate generally reverses the effect of heparin promptly and effectively. It should not be given in excess of the amount needed to neutralize the heparin, because it also has an anticoagulant effect.

SUPERFICIAL VENOUS THROMBOPHLEBITIS

Thrombosis limited strictly to the superficial veins of the saphenous system is treated with analgesia, elastic support, heat, and rest. If it does not soon subside or if deep-vein involvement is suspected, appropriate diagnostic measures are performed. Superficial vein thrombosis raises the risk of deep-vein

thrombosis four- to sixfold. Heparin is given if deep-vein involvement is confirmed (Roach, 2013). Superficial thrombophlebitis is typically seen in association with varicosities or as a sequela of an indwelling intravenous catheter.

PULMONARY EMBOLISM

Although it causes approximately 10 percent of maternal deaths, pulmonary embolism is relatively uncommon during pregnancy and the puerperium. The incidence averages 1 in 7000 pregnancies. According to Marik and Plante (2008), 70 percent of gravidas presenting with a pulmonary embolism have associated clinical evidence of deep-vein thrombosis. And recall that between 30 and 60 percent of women with a deep-vein thrombosis will have a coexisting silent pulmonary embolism.

Clinical Presentation

In almost 2500 nonpregnant patients with a proven pulmonary embolism, symptoms included dyspnea in 82 percent, chest pain in 49 percent, cough in 20 percent, syncope in 14 percent, and hemoptysis in 7 percent (Goldhaber, 1999). Pollack and coworkers (2011) found similar symptoms. Other predominant clinical findings typically include tachypnea, apprehension, and tachycardia. In some cases, an accentuated pulmonic closure sound, rales, and/or friction rub is heard.

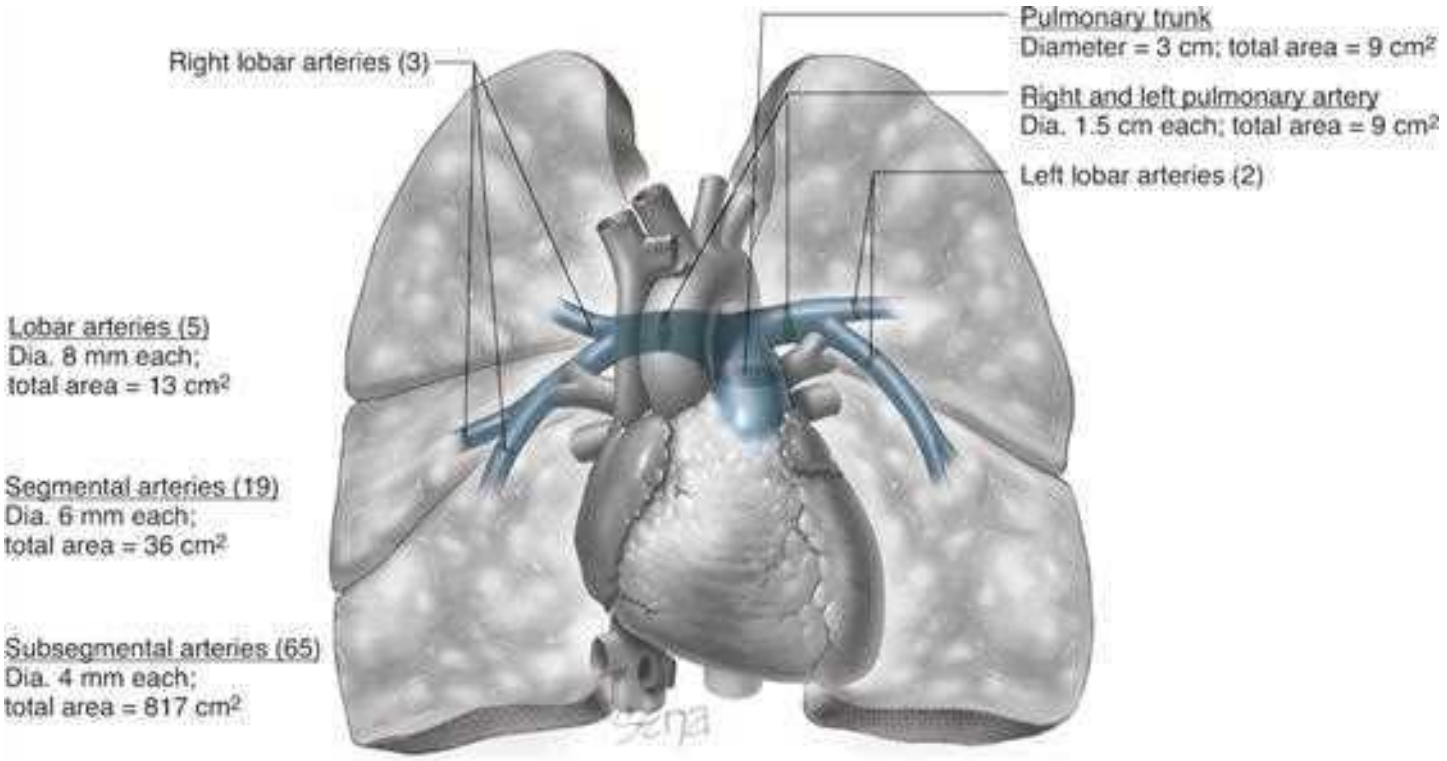
Right axis deviation and T-wave inversion in the anterior chest leads may be evident on the electrocardiogram. In at least 40 percent, chest radiography results are normal. In others, nonspecific findings may include atelectasis, an infiltrate, cardiomegaly, or an effusion (Pollack, 2011). Vascular markings in the lung region supplied by the obstructed artery can be lost. Although most women are hypoxemic, a normal arterial blood gas analysis does not exclude pulmonary embolism. Approximately a third of young patients have P_{O_2} values >80 mm Hg. Thus, the alveolar-arterial oxygen tension difference is a more useful indicator of disease. More than 86 percent of patients with acute pulmonary embolism will have an alveolar-arterial difference >20 mm Hg (Lockwood, 2012). Even with massive pulmonary embolism, signs, symptoms, and laboratory data to support the diagnosis may be deceptively nonspecific.

Massive Pulmonary Embolism

This is defined as embolism causing hemodynamic instability (Tapson, 2008). Acute mechanical obstruction of the pulmonary vasculature causes increased vascular resistance and pulmonary hypertension followed by acute right ventricular dilation. In otherwise healthy patients, significant pulmonary hypertension does not develop until 60 to 75 percent of the pulmonary vascular tree is occluded (Guyton, 1954). Moreover, circulatory collapse requires 75- to 80-percent obstruction. This is depicted schematically in Figure 52-4 and emphasizes that most acutely symptomatic emboli are large and likely a saddle embolism. These are suspected when the pulmonary artery pressure is substantively increased as estimated by echocardiography.

FIGURE 52-4

Schematic of pulmonary arterial circulation. Note that the cross-sectional area of the pulmonary trunk and the combined pulmonary arteries is 9 cm^2. A large saddle embolism could occlude 50 to 90 percent of the pulmonary tree, causing hemodynamic instability. As the arteries give off distal branches, the total surface area rapidly increases, that is, 13 cm^2 for the combined five lobar arteries, 36 cm^2 for the combined 19 segmental arteries, and more than 800 cm^2 for the total 65 subsegmental arterial branches. Thus, hemodynamic instability is less likely with emboli past the lobar arteries. (Data from Singhal S, Henderson R, Horsfield K, et al: Morphometry of the human pulmonary arterial tree, Circ Res. 1973 Aug;33(2):190–197.)



If there is evidence of right ventricular dysfunction, the mortality rate approaches 25 percent. This compares with a 1-percent rate without such dysfunction (Kinane, 2008). It is important in these cases to infuse crystalloids carefully and to support blood pressure with vasopressors. As discussed in Management, oxygen treatment, endotracheal intubation, and mechanical ventilation are completed preparatory to thrombolysis, filter placement, or embolectomy (Tapson, 2008).

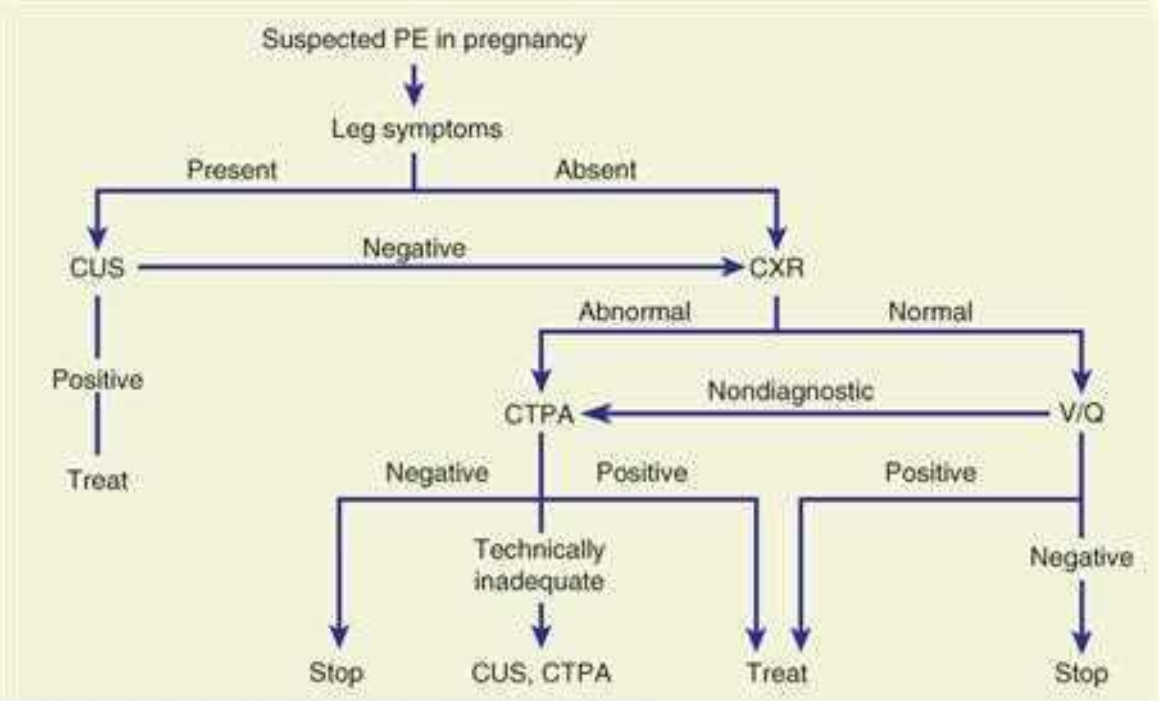
Diagnosis

In most cases, recognition of a pulmonary embolism requires a high index of suspicion that prompts objective evaluation. Exposure of the mother and fetus to ionizing radiation is a concern when investigating a suspected pulmonary embolism during pregnancy. However, this concern is largely overruled by the hazards of missing a potentially fatal diagnosis. Moveover, erroneously assigning a diagnosis of pulmonary embolism to a pregnant woman is also fraught with problems. It unnecessarily exposes the mother and fetus to the risks of anticoagulation treatment and will impact delivery plans, future contraception, and thromboprophylaxis during subsequent pregnancies. Therefore, investigations should aim at diagnostic certainty (Konstantinides, 2014).

In 2011, the American Thoracic Society and the Society of Thoracic Radiology developed an algorithm—shown in Figure 52-5 for the diagnosis of pulmonary embolism during pregnancy (Leung, 2011). In addition to compression ultrasonography, which was previously discussed (Deep-Vein Thrombosis), the algorithm includes computed-tomographic pulmonary angiography (CTPA) and ventilation-perfusion scintigraphy.

FIGURE 52-5

The American Thoracic Society and Society of Thoracic Radiology diagnostic algorithm for suspected pulmonary embolism during pregnancy. CTPA = computed tomographic pulmonary angiography; CUS = compression ultrasonography; CXR = chest x-ray; PE = pulmonary embolism; V/Q = ventilation/perfusion scintigraphy. (Modified with permission from Leung AN, Bull TM, Jaeschke R, et al: An official American Thoracic Society/Society of Thoracic Radiology Clinical Practice Guideline: Evaluation of suspected pulmonary embolism in pregnancy, Am J Respir Crit Care Med. 2011 Nov 15;184(10):1200–1208.)

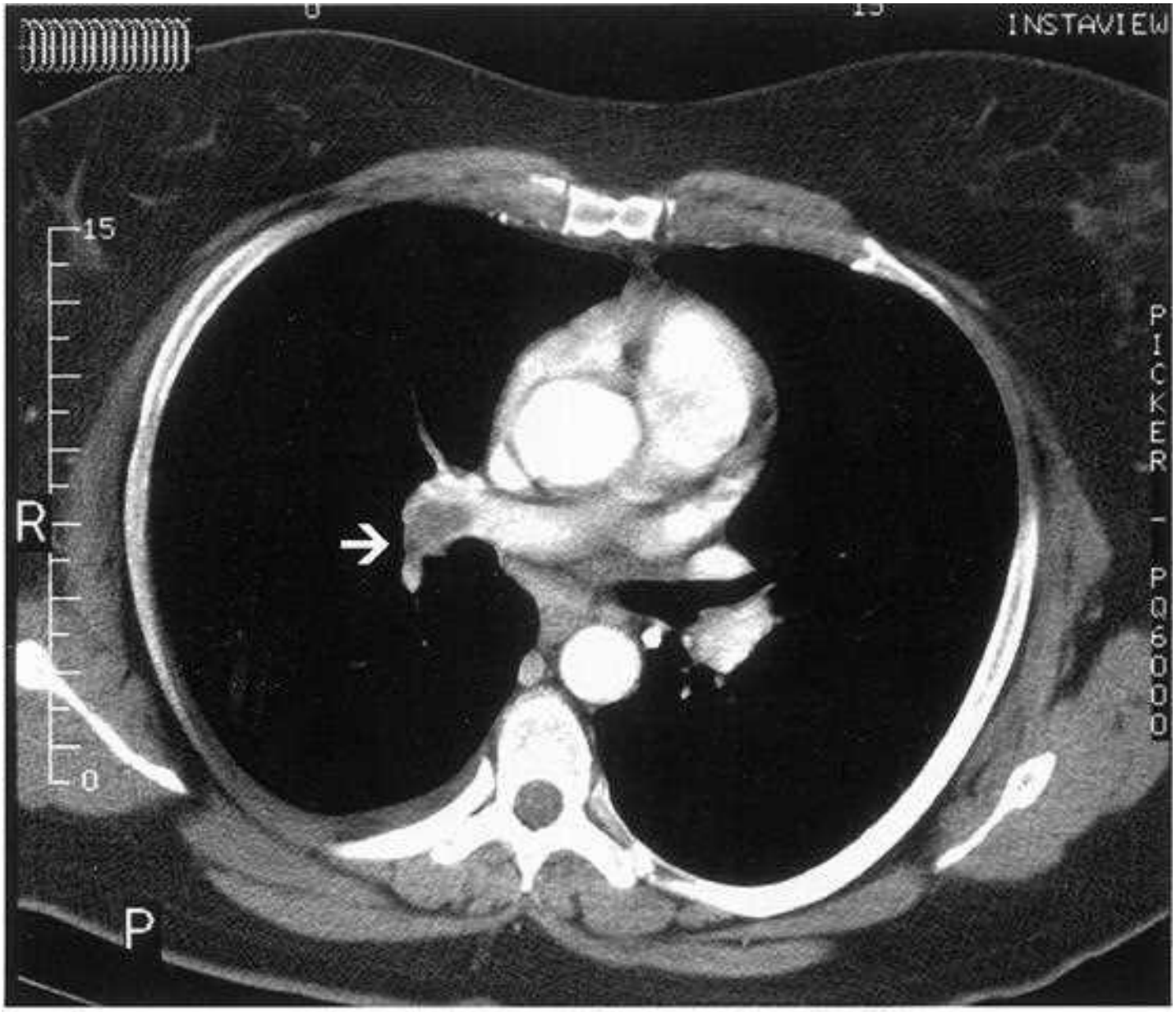


Computed Tomographic Pulmonary Angiography

Multidetector computed tomography with pulmonary angiography is currently the most commonly employed technique used for pulmonary embolism diagnosis in nonpregnant patients (Bourjeily, 2012; Pollack, 2011). The technique is described further in Chapter 46 (Computed Tomography), and an imaging example is shown in Figure 52-6. The estimated fetal radiation exposure averages 0.45 to 0.6 mGy. The estimated maternal breast dose is 10 to 70 mGy (Waksmonski, 2014).

FIGURE 52-6

Axial image of the chest from a four-channel multidetector spiral computed tomographic scan performed after administration of intravenous contrast. There is enhancement of the pulmonary artery with a large thrombus on the right (*arrow*) consistent with pulmonary embolism. (Reproduced with permission from Dr. Michael Landay.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

Bourjeily and colleagues (2012) performed a follow-up study of 318 pregnant women who had a negative CTPA performed for a suspected pulmonary embolism. All were seen 3 months following their initial presentation or at 6 weeks postpartum. None of these women were subsequently diagnosed with a thromboembolism.

CTPA has many advantages, but we find that the higher resolution allows detection of previously inaccessible smaller distal emboli that have uncertain clinical significance. Similar observations have been reported by others (Anderson, 2007; Hall, 2009). Also, the hyperdynamic circulation and augmented plasma volume associated with pregnancy leads to a higher number of nondiagnostic studies compared with nonpregnant patients (Ridge, 2011; Scarsbrook, 2006).

Ventilation–Perfusion Scintigraphy—Lung Scan

This technique involves a small dose of radiotracer such as intravenously administered technetium-99m–macroaggregated albumin. There is negligible fetal and maternal breast radiation exposure—0.1 to 0.4 mGy. The scan may not provide a definite diagnosis because many other conditions can cause perfusion defects. Examples are pneumonia or local bronchospasm. Chan and coworkers (2002) found that a fourth of ventilation-perfusion scans in pregnant women were nondiagnostic. In these instances, CTPA is preferred (Tromeur, 2017).

To compare the performance of lung scintigraphy and CTPA, Revel and colleagues (2011) evaluated 137 pregnant women with suspected pulmonary embolism. The two modalities performed comparably and had no significant differences between the proportions of positive, negative, or indeterminate results. Specifically, the proportion of indeterminate results for both approximated 20 percent. By way of comparison, about a fourth of the nonpregnant

population had indeterminate studies. The investigators attributed this difference to the younger age of the pregnant patients. Similarly, one systematic review concluded that both CTPA and lung scintigraphy seem appropriate for exclusion of pulmonary embolism during pregnancy (van Mens, 2017).

Intravascular Pulmonary Angiography

This requires catheterization of the right side of the heart and is considered the reference test for pulmonary embolism. With newer generation multidetector CT scanners, however, the role of invasive pulmonary angiography has been questioned. This is especially true given the higher radiation exposure for the fetus (Konstantinides, 2014; Kuriakose, 2010). Other detractions are that it can be time consuming, uncomfortable, and associated with dye-induced allergy and renal failure. Indeed, the procedure-related mortality rate approximates 1 in 200 (Stein, 1992). It is reserved for confirmation when less invasive tests are equivocal.

Management

Immediate treatment for pulmonary embolism is full anticoagulation similar to that for deep-vein thrombosis as discussed in Unfractionated Heparin. Several complementary procedures may be indicated.

Vena Caval Filters

The woman who has very recently suffered a pulmonary embolism and who must undergo cesarean delivery presents a particularly serious problem. Reversal of anticoagulation may be followed by another embolus, and surgery while fully anticoagulated frequently results in life-threatening hemorrhage or troublesome hematomas. In these cases, placement of a vena caval filter should be considered before surgery (Marik, 2008). Moreover, in the very infrequent circumstances in which heparin therapy fails to prevent recurrent pulmonary embolism from the pelvis or legs, or when embolism develops from these sites despite heparin treatment, a vena caval filter may also be indicated. Such filters can also be used following massive emboli in patients who are not candidates for thrombolysis (Deshpande, 2002).

The device is inserted through either the jugular or femoral vein and can be inserted during labor (Jamjute, 2006). Routine filter placement has no added advantage to heparin given alone (Decousus, 1998). Retrievable filters may be used as short-term protection and then removed 1 to 2 weeks later (Liu, 2012). From their systematic review, Harris and associates (2016) found that complication rates in pregnant women with vena caval filters are comparable to those in nonpregnant patients.

Thrombolysis

Compared with heparin, thrombolytic agents provide more rapid lysis of pulmonary clots and improvement of pulmonary hypertension (Tapson, 2008). Konstantinides and coworkers (2002) studied 256 nonpregnant patients receiving heparin for an acute submassive pulmonary embolism. They also were randomly assigned to a placebo or the recombinant tissue plasminogen activator *alteplase*. Those given the placebo had a threefold greater risk of death or treatment escalation compared with those given alteplase. Agnelli and associates (2002) performed a metaanalysis of trials involving 461 nonpregnant patients. They reported that the risk of recurrence or death was significantly lower in patients given thrombolytic agents and heparin compared with those given heparin alone—10 versus 17 percent. Importantly, however, there were five—2 percent—fatal bleeding episodes in the thrombolysis group and none in the heparin-only group.

In their review, Leonhardt and colleagues (2006) identified 28 reports of tissue plasminogen activator use during pregnancy. Ten cases were for thromboembolism. Complication rates were similar to those in nonpregnant patients, and the authors concluded that such therapy should not be withheld during pregnancy if indicated. However, Akazawa and Nishida (2017) reviewed 13 cases of systemic thrombolytic therapy administered during the first 48 hours after delivery. Blood transfusion was required in five of the eight cesarean deliveries, including three cases of hysterectomy and two cases of hematoma removal.

Embolectomy

Given the efficacy of thrombolysis and filters, surgical embolectomy is uncommonly indicated. Published experience with emergency embolectomy during pregnancy is limited to case reports (Colombier, 2015; Saeed, 2014). From their review, Ahearn and associates (2002) found that although the operative risk to the mother is reasonable, the stillbirth rate is 20 to 40 percent.

THROMBOPROPHYLAXIS

Most recommendations regarding thromboprophylaxis during pregnancy stem from consensus guidelines. In one review of guidelines for thromboprophylaxis in pregnancy, the authors concluded that there is a lack of overall agreement about which women should be offered thromboprophylaxis or offered testing for thrombophilias (Okoroh, 2012). Bates and associates (2016) also conducted a review of guidelines for obstetrically associated VTE. They summarized that evidence-based recommendations are based largely on observational studies and extrapolated from data in nonpregnant patients. Similarly, a Cochrane review concluded that evidence is insufficient for firm recommendations regarding thromboprophylaxis during pregnancy (Bain, 2014).

The confusion that has ensued has provided fertile ground for litigators. Cleary-Goldman and associates (2007) surveyed 151 fellows of the American College of Obstetricians and Gynecologists and reported that intervention without a clear indication is common. Table 52-6 lists several consensus recommendations for thromboprophylaxis. In some cases, more than one option is listed, thus illustrating the confusion that currently reigns.

Prior Venous Thromboembolism

In general, either antepartum surveillance or heparin prophylaxis is recommended for women with prior VTE but without a recurrent risk factor, including no known thrombophilia. The study by Tengborn and coworkers (1989), however, suggested that such management may not be effective. They reported outcomes in 87 pregnant Swedish women who had prior thromboembolic disease and were not tested for thrombophilias. Despite unfractionated heparin prophylaxis, which was usually 5000 U twice daily, three of 20 women (15 percent) developed antepartum recurrence. This compared with eight of 67 women (12 percent) not given heparin.

Brill-Edwards and colleagues (2000) prospectively studied 125 pregnant women with a single prior VTE. Antepartum heparin was not given, but anticoagulant therapy was given for 4 to 6 weeks postpartum. Six women had a recurrent venous thrombosis—three antepartum and three postpartum. There were no recurrences in the 44 women without a known thrombophilia or whose prior thrombosis was associated with a temporary risk factor. These findings imply that prophylactic heparin may not be required for these two groups of women. In contrast, and as shown in Table 52-6, women with a prior thrombosis in association with a thrombophilia or in the absence of a temporary risk factor generally should be given both antepartum and postpartum prophylaxis (Connors, 2017).

De Stefano and coworkers (2006) studied 1104 nonpregnant women who had a first-episode VTE before the age of 40 years. After excluding those with antiphospholipid antibodies, 88 women were identified who subsequently had a total of 155 pregnancies and who were not given antithrombotic prophylaxis. There were 19 women (22 percent) who had a subsequent pregnancy- or puerperium-related VTE. Of 20 women whose original thrombosis was associated with a transient risk factor—not including pregnancy or oral contraceptive use—there were no recurrences during pregnancy, but two during the puerperium. These data also suggest that for women with a prior VTE, antithrombotic prophylaxis during pregnancy could be tailored according to the circumstances of the original event.

It is important to emphasize that VTE may recur despite antithrombotic prophylaxis. Galambosi and associates (2014) studied 270 women during 369 pregnancies who had at least one previous VTE. A total of 28 women (10.4 percent) suffered a recurrent VTE. Twelve of these recurrences occurred early in pregnancy before the initiation of antithrombotic prophylaxis, and 16 occurred despite prophylactic use of LMWH.

Our practice at Parkland Hospital for many years for women with a history of prior VTE was to administer subcutaneous UFH, 5000 to 7500 units two to three times daily. With this regimen, the recurrence of documented deep-vein thrombosis embolization was rare. Beginning approximately 10 years ago, we have successfully used 40 mg enoxaparin given subcutaneously daily for thromboprophylaxis.

Cesarean Delivery

The risk for deep-vein thrombosis and especially for fatal thromboembolism rises manyfold in women following cesarean compared with that after vaginal delivery. When considering that a third of women giving birth in the United States yearly undergo cesarean delivery, pulmonary embolism is understandably a major cause of maternal mortality (Creanga, 2017). That said, the “lack of high quality data” described earlier by Bates and colleagues (2016) creates considerable variation in the current recommendations promulgated by the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians, and the American College of Chest Physicians (Palmerola, 2016).

In 2011, the American College of Obstetricians and Gynecologists (2017b) recommended placement of pneumatic compression devices before cesarean delivery for all women not already receiving thromboprophylaxis. This recommendation was based primarily on consensus and expert opinion. For patients undergoing cesarean delivery with additional risk factors for thromboembolism, both pneumatic compression devices and UFH or LMWH may be recommended. The College stipulated that cesarean delivery in an emergency setting should not be delayed because of the time necessary to implement thromboprophylaxis. Implementation of this strategy by the Hospital Corporation of America, the largest for-profit obstetrical health care delivery system in the United States, was associated with a reduction in deaths from pulmonary embolism from 7 of 458,097 cesarean births to 1 of 465,880 cesarean births (Clark, 2011, 2014).

In 2016, the National Partnership for Maternal Safety published several consensus recommendations for the prevention of maternal VTE (D’Alton, 2016). These recommendations included expanded use of antenatal prophylaxis for women hospitalized 3 days or longer, expanded use of prophylaxis during and after vaginal delivery, and expanded use of pharmacological prophylaxis to most women after cesarean delivery. In response, Sibai and Rouse (2016) expressed concern that these new recommendations derive from sparse data of questionable applicability to obstetrical patients. They called for better quality evidence to measure the benefits, harms, and costs of increased pharmacological thromboprophylaxis. As aptly expressed by Macones (2017), “an intervention, such as increased postcesarean pharmacologic thromboprophylaxis, where there are legitimate concerns about efficacy and safety, requires a much higher degree of evidence before a national guideline is implemented.” We agree with these sentiments.

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CHAPTER 53: Renal and Urinary Tract Disorders

In rare instances in patients suffering from pyelitis, the pregnant uterus may so compress the ureter as to cause a damming back of the purulent discharge, and thus give rise to a pyelonephritis.

—J. Whitridge Williams (1903)

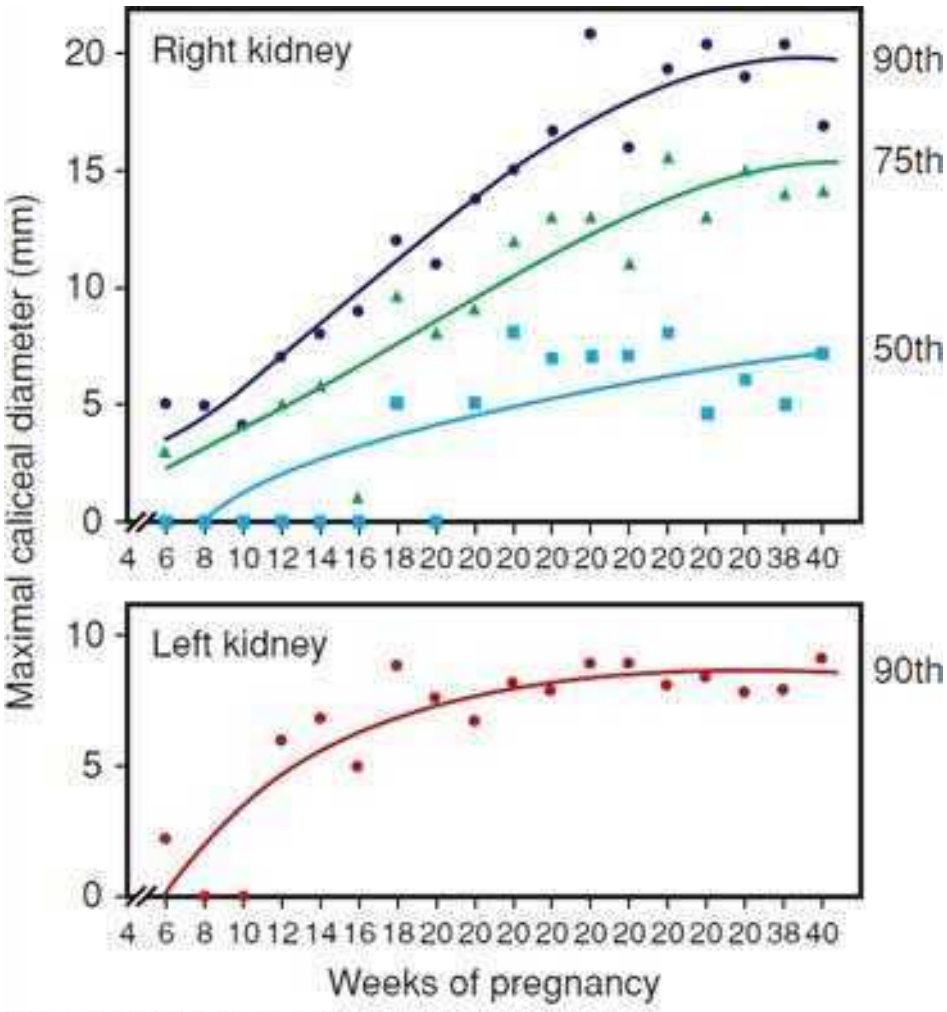
INTRODUCTION

Renal and urinary tract disorders are frequently encountered in pregnancy. Some precede pregnancy—one example being nephrolithiasis. In some women, pregnancy-induced changes may predispose to development or worsening of urinary tract disorders—an example is the markedly increased risk for pyelonephritis, described above by Williams. Finally, some renal pathology is unique to pregnancy, such as preeclampsia. With good prenatal care, however, most women with these disorders will likely have no long-term sequelae.

PREGNANCY-INDUCED URINARY TRACT CHANGES

Significant changes in both structure and function within the urinary tract during normal pregnancy are discussed in Chapter 4 (Urinary System). The kidneys become larger, and dilatation of the right renal calyces and ureters can be striking (Fig. 53-1). Some dilatation develops before 14 weeks and likely stems from progesterone-induced relaxation of the muscularis. More marked dilatation is apparent beginning in midpregnancy because of more distal ureteral compression, especially on the right side (Faúndes, 1998). There is also some *vesicoureteral reflux* during pregnancy. Because of these physiological changes, the risk of upper urinary infection rises. Also, imaging studies done to evaluate urinary tract obstruction may occasionally be erroneously interpreted.

FIGURE 53-1
The 50th, 75th, and 90th percentiles for maternal renal caliceal diameters measured using sonography in 1395 pregnant women from 4 to 42 weeks' gestation. (Redrawn and modified from Faúndes A, Bricola-Filho M, Pinto e Silva JC: Dilatation of the urinary tract during pregnancy: proposal of a curve of maximal caliceal diameter by gestational age. Am J Obstet Gynecol 178:1082, 1998.)



Evidence of functional renal hypertrophy becomes apparent very soon after conception. Glomeruli are larger, although cell numbers do not grow (Strevens, 2003). Pregnancy-induced intrarenal vasodilatation develops, and both afferent and efferent resistances decline. This leads to greater effective renal plasma flow and glomerular filtration (Helal, 2012; Hussein, 2014). By 12 weeks' gestation, the glomerular filtration rate (GFR) is already augmented 20 percent above nonpregnant values (Hladunewich, 2004). Ultimately, plasma flow and GFR rise by 40 and 65 percent, respectively. Consequently, serum concentrations of creatinine and urea drop substantively across pregnancy, and values within a nonpregnant normal range may be abnormal for pregnancy (Appendix, Serum and Blood Constituents). Other alterations include those related to maintaining normal acid-base homeostasis, osmoregulation, and fluid and electrolyte retention.

Assessment of Renal Function During Pregnancy

Urinalysis results are essentially unchanged during pregnancy, except for occasional glucosuria. Although protein excretion normally rises, it seldom reaches levels that are detected by usual screening methods. Higby and colleagues (1994) reported 24-hour protein excretion in pregnancy to be 115 mg/d with a 95-percent confidence level of 260 mg/d. Values did not significantly differ by trimester (Fig. 4-14). Albumin constitutes only a small part of total protein excretion and ranges from 5 to 30 mg/d. Airoldi and Weinstein (2007) concluded that proteinuria must exceed 300 mg/d to be considered abnormal. Many consider 500 mg/d to be important with gestational hypertension. Investigators have correlated a urinary protein-to-creatinine ratio of ≥0.3 in a spot urine sample—ideally from a first morning void—with a 24-hour protein excretion rate of ≥300 mg (Kuper, 2016).

In one study, 3 percent of 4589 nulliparas screened before 20 weeks had *idiopathic hematuria*, defined as 1+ or greater blood on urine dipstick (Stehman-Breen, 2002). These women had a twofold risk of developing preeclampsia. In another study of 1000 women screened during pregnancy, the incidence of dipstick hematuria was 15 percent (Brown, 2005). Most women had only trace levels of hematuria, and the false-positive rate was 40 percent.

If the serum creatinine level in pregnancy persistently exceeds 0.9 mg/dL (75 µmol/L), then intrinsic renal disease is suspected. In these cases, some determine the creatinine clearance as an estimate of the GFR. Of other assessment tools, s*onography* provides imaging of renal size, relative consistency, and elements of obstruction (see Fig. 53-1). *Magnetic resonance (MR) imaging* of renal masses provides excellent anatomic information (Putra, 2009). Full-sequence *intravenous pyelography* is not done routinely, but injection of contrast media with one or two abdominal radiographs may be indicated by the clinical situation. The usual clinical indications for *cystoscopy* are followed. *Ureteroscopy* is another available tool when indicated.

Although *renal biopsy* is relatively safely performed during pregnancy, it usually is postponed unless results may change therapy. From a review of 243 biopsies in pregnant women, the incidence of complications was 7 percent—this compares with 1 percent in postpartum women (Piccoli, 2013). Some consider biopsy for rapid deterioration of renal function with no obvious cause or for symptomatic nephrotic syndrome (Lindheimer, 2007a). We and others have found biopsy helpful in

selected cases to direct management (Chen, 2001; Piccoli, 2013). In one series, renal biopsy in 12 *normal* pregnant volunteers showed that five had slight to moderate glomerular endotheliosis (Strevens, 2003). Recall this is the histopathological lesion that is putatively typical of preeclampsia and is characterized by fibrin deposition within the glomerular endothelium leading to capillary occlusion. In contrast, all 27 women with proteinuric hypertension had endotheliosis, and in all but one, it was moderate to severe.

Pregnancy after Unilateral Nephrectomy

In these cases, if the remaining kidney is normal, renal function becomes augmented. However, women who have donated a kidney have a higher frequency of gestational hypertension or preeclampsia in subsequent pregnancy—11 versus 5 percent compared with non-donors (Garg, 2015). Otherwise, women with one normal kidney most often have no difficulty in pregnancy. Moreover, kidney donation does not lead to long-term adverse consequences. That said, thorough functional evaluation of the remaining kidney is essential (Ibrahim, 2009).

URINARY TRACT INFECTIONS

These infections are the most frequent bacterial infections complicating pregnancy. Although *asymptomatic bacteriuria* is the most common, symptomatic infection includes *cystitis*, or it may involve the renal calyces, pelvis, and parenchyma to cause *pyelonephritis*. Organisms that cause urinary infections are those from the normal perineal flora. Approximately 90 percent of *Escherichia coli* strains that cause nonobstructive pyelonephritis have adhesins such as P- and S-fimbriae. These are cell-surface protein structures that enhance bacterial adherence and, thereby, virulence (Foxman, 2010; Hooton, 2012). Data suggest that pregnant women have more severe sequelae from urosepsis. One possible underlying factor is the T-helper cell—Th1/Th2 ratio—reversal of normal pregnancy, which is discussed in Chapter 4 (Leukocytes and Lymphocytes). Other perturbations of cytokine or of adhesin expression may be contributory (Chaemsaithong, 2013; Sledzińska, 2011). But even if pregnancy itself does not enhance these virulence factors, urinary stasis, vesicoureteral reflux, and diabetes predispose to symptomatic upper urinary infections (Czaja, 2009).

In the puerperium, several risk factors predispose to urinary infections. Bladder sensitivity to intravesical fluid tension is often diminished due to labor trauma or epidural analgesia. Bladder sensations can also be obscured by discomfort from vaginal or perineal injury. Normal postpartum diuresis may worsen bladder overdistention, and catheterization to relieve retention often leads to urinary infection. Postpartum pyelonephritis is treated in the same manner as antepartum renal infections (McDonnold, 2012).

Asymptomatic Bacteriuria

This refers to persistent, actively multiplying bacteria within the urinary tract in asymptomatic women. The incidence during pregnancy is similar to that in nonpregnant women. It varies from 2 to 7 percent, and it is characteristically population dependent. The highest incidence is in African-American multiparas with sickle-cell trait, and the lowest is in affluent white women of low parity. Asymptomatic infection is also more common in diabetics (Schneeberger, 2014).

Bacteriuria is typically present at the first antepartum visit. An initial positive urine culture result done as a part of prenatal care should prompt treatment. After this, fewer than 1 percent of women develop a urinary tract infection (Whalley, 1967). A clean-voided specimen containing more than 100,000 organisms/mL is diagnostic. It may be prudent to treat when lower concentrations are identified, because pyelonephritis develops in some women despite colony counts of only 20,000 to 50,000 organisms/mL (Lucas, 1993).

Most studies indicate that if asymptomatic bacteriuria is not treated, approximately 25 percent of infected women will develop symptomatic infection during pregnancy (Smaill, 2015). In a more recent study, only 2.4 percent of *treated* women developed pyelonephritis (Kazemier, 2015). Eradication of bacteriuria with antimicrobial agents prevents most of these serious infections. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017), as well as the U.S. Preventive Services Task Force (2008), recommend screening for bacteriuria at the first prenatal visit. Standard urine cultures may not be cost effective when the prevalence is low. Less expensive screening tests such as the leukocyte esterase/nitrite dipstick are cost effective when the prevalence is ≤2 percent (Rogozinska, 2016; Rouse, 1995). Also, a dipstick culture technique has excellent positive- and negative-predictive values (Mignini, 2009). With this, a special agar-coated dipstick is first placed into urine and then also serves as the culture plate. Because of a high prevalence—5 to 8 percent—at Parkland Hospital, most women are screened by traditional urine culture. Susceptibility determination is not necessary because initial treatment is empirical (Hooton, 2012).

In some but not all studies, covert bacteriuria has been associated with preterm or low-birthweight infants. It is even more controversial whether eradication of bacteriuria decreases these complications. Evaluating a cohort of 25,746 mother-infant pairs, Schieve and coworkers (1994) reported urinary tract infection to be associated with greater risks for low-birthweight infants, preterm delivery, pregnancy-associated hypertension, and anemia. These findings vary from those of others (Gilstrap, 1981b; Whalley, 1967). Notably, in most studies, cohorts with asymptomatic infection are not evaluated separately from those with acute renal infection (Banhidy, 2007). One Cochrane database review noted insufficient data to answer this question (Smaill, 2015).

Treatment

Bacteriuria responds to empirical treatment with any of several antimicrobial regimens listed in Table 53-1. Although selection can be based on in vitro susceptibilities, in our extensive experience, empirical oral treatment for 10 days with nitrofurantoin macrocrystals, 100 mg at bedtime, is usually effective. Satisfactory results are also achieved with a 7-day oral course of nitrofurantoin, 100 mg given twice daily (Lumbiganon, 2009). Single-dose antimicrobial therapy is less successful (Widmer, 2015). *The important caveat is that, regardless of regimen given, the recurrence rate is approximately 30 percent.* This may indicate covert upper tract infection and the need for longer therapy. Thus, after initial therapy, periodic surveillance is necessary to prevent recurrent urinary infections (Schneeberger, 2015).

TABLE 53-1

Oral Antimicrobial Agents Used for Treatment of Pregnant Women with Asymptomatic Bacteriuria

Single-dose treatment
Amoxicillin, 3 g
Ampicillin, 2 g
Cephalosporin, 2 g
Nitrofurantoin, 200 mg
Trimethoprim-sulfamethoxazole, 320/1600 mg
3-day course
Amoxicillin, 500 mg three times daily
Ampicillin, 250 mg four times daily
Cephalosporin, 250 mg four times daily
Ciprofloxacin, 250 mg twice daily
Levofloxacin, 250 or 500 mg daily
Nitrofurantoin, 50 to 100 mg four times daily or 100 mg twice daily
Trimethoprim-sulfamethoxazole, 160/800 mg twice daily
Other
Nitrofurantoin, 100 mg four times daily for 10 days
Nitrofurantoin, 100 mg twice daily for 5 to 7 days
Nitrofurantoin, 100 mg at bedtime for 10 days
Treatment failures
Nitrofurantoin, 100 mg four times daily for 21 days
Suppression for bacterial persistence or recurrence
Nitrofurantoin, 100 mg at bedtime for pregnancy remainder

For recurrent bacteriuria, we have had success with nitrofurantoin, 100 mg orally at bedtime for 21 days (Lucas, 1994). For women with persistent or frequent bacteriuria recurrences, suppressive therapy for the remainder of pregnancy can be given. We routinely use nitrofurantoin, 100 mg orally at bedtime. This drug may rarely cause an acute pulmonary reaction that dissipates on its withdrawal (Boggess, 1996).

Cystitis and Urethritis

Lower urinary infection during pregnancy may develop without antecedent covert bacteriuria (Harris, 1981). Cystitis produces dysuria, urgency, and frequency, but with few associated systemic findings. Pyuria and bacteriuria are usually found. Microscopic hematuria is common, and occasionally there is gross hematuria from hemorrhagic cystitis. Although cystitis is usually uncomplicated, the upper urinary tract may become involved by ascending infection. Almost 40 percent of pregnant women with acute pyelonephritis have preceding symptoms of lower tract infection (Gilstrap, 1981a).

Women with cystitis respond readily to any of several regimens. Most of the 3-day regimens listed in Table 53-1 are usually 90-percent effective (Fihn, 2003). Single-dose therapy is less effective, and if it is used, concomitant pyelonephritis must be confidently excluded.

Lower urinary tract symptoms with pyuria accompanied by a sterile urine culture may stem from urethritis caused by *Chlamydia trachomatis*. Mucopurulent cervicitis usually coexists, and azithromycin therapy is effective (Chap. 65, Chlamydial Infections).

Acute Pyelonephritis

Renal infection is one of the most frequent serious medical complications of pregnancy. Data from the 2006 Nationwide Inpatient Sample showed that nearly 29,000 pregnancy-associated hospitalizations were for acute pyelonephritis (Jolley, 2012). In one hospital-system database of nearly 550,000 births, its incidence was 0.5 percent (Wing, 2014). Importantly, pyelonephritis is a leading cause of septic shock during pregnancy (Snyder, 2013). In one Parkland Hospital Obstetrical Intensive Care Unit review, 12 percent of antepartum admissions were for sepsis syndrome caused by renal infections (Zeeman, 2003). Urosepsis may be related to an increased incidence of cerebral palsy in preterm infants (Jacobsson, 2002). Fortunately, affected mothers suffer no serious long-term sequelae (Raz, 2003).

Clinical Findings

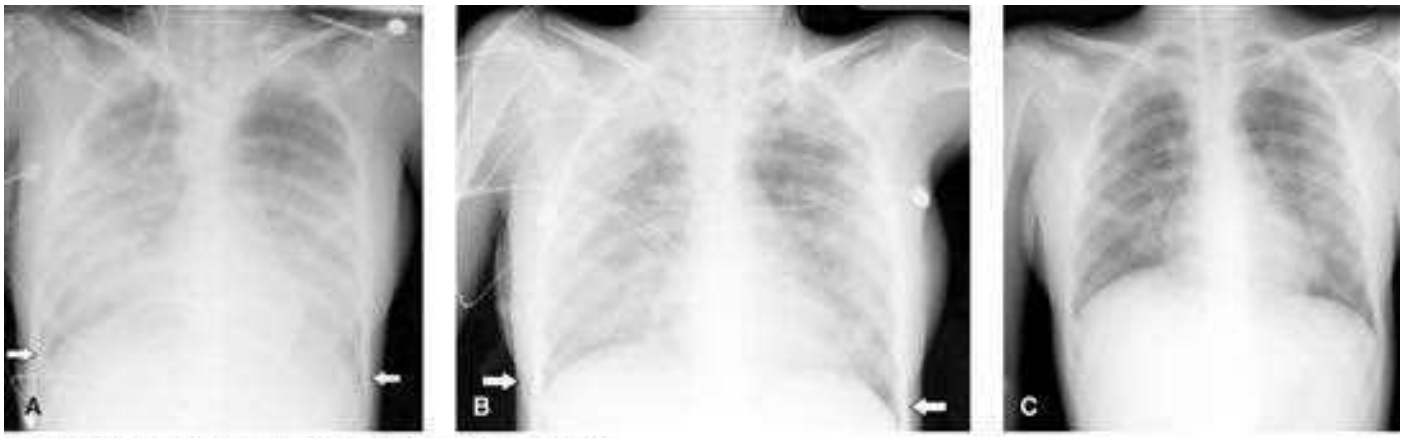
Renal infection develops more frequently in the second trimester, and nulliparity and young age are risks (Hill, 2005). Pyelonephritis is unilateral and right-sided in more than half of cases, and it is bilateral in a fourth. Fever and shaking chills usually develop rather abruptly, and patients have aching pain in one or both lumbar regions. Anorexia, nausea, and vomiting may worsen dehydration. Tenderness usually can be elicited by percussion in one or both costovertebral angles. The differential diagnosis includes, among others, labor, chorioamnionitis, adnexal torsion, appendicitis, placental abruption, or infarcted leiomyoma. Evidence of the sepsis syndrome is common (Chap. 47, Sepsis Syndrome).

If this infection is suspected, a urine sample obtained by catheterization may be preferred to avoid obscuring contamination from the lower genital tract. The urinary sediment contains many leukocytes, frequently in clumps, and numerous bacteria. Bacteremia is demonstrated in 15 to 20 percent of these women. *E coli* is isolated from urine or blood in 70 to 80 percent of infections, *Klebsiella pneumoniae* in 3 to 5 percent, *Enterobacter* or *Proteus* species in 3 to 5 percent, and gram-positive organisms, including group B *Streptococcus* and *Staphylococcus aureus*, in up to 10 percent of cases (Hill, 2005; Wing, 2000).

Plasma creatinine is monitored because early studies reported that 20 percent of pregnant women developed acute kidney injury. More recent findings, however, show this to be only 5 percent if aggressive fluid resuscitation is provided (Hill, 2005). Follow-up studies have demonstrated that this endotoxin-induced damage is reversible long term. As shown in Figure 53-2, varying degrees of *respiratory distress syndrome* from endotoxin-induced alveolar injury are manifest in up to 2 percent of women (Cunningham, 1987; Snyder, 2013; Wing, 2014).

FIGURE 53-2

A series of anterior-posterior projection chest radiographs of improving acute respiratory distress syndrome (ARDS) in a second-trimester pregnant woman with severe pyelonephritis. **A.** An extensive infiltrative process and complete obliteration of the diaphragm (*white arrows*) is seen. **B.** Improved aeration of lung fields bilaterally is noted as pleural disease resolves (*arrows*). **C.** Markedly improved visualization of the lung fields with residual platelike atelectasis and normal appearance of the diaphragm.



Uterine activity from endotoxin is common and is related to fever severity (Graham, 1993). In one study, women with pyelonephritis averaged five contractions per hour at admission, and this decreased to two per hour within 6 hours of intravenous fluid and antimicrobial administration (Millar, 2003). Notably, β-agonist therapy for tocolysis increases the likelihood of respiratory insufficiency from permeability edema (Lamont, 2000). The incidence of pulmonary edema in women with pyelonephritis who were given β-agonists was reported to be 8 percent—a fourfold increase over that expected (Towers, 1991). Endotoxin-induced *hemolysis* is common, and approximately a third of these women with pyelonephritis develop anemia (Cox, 1991). With recovery, hemoglobin regeneration is normal, and acute infection does not affect erythropoietin production (Cavenee, 1994).

Management

One scheme for management of acute pyelonephritis is shown in Table 53-2. Urine cultures are taken, but prospective trials show that blood cultures are of limited clinical utility (Gomi, 2015; Wing, 2000). We obtain blood cultures if the temperature is >39°C. *Intravenous hydration to ensure adequate urinary output is the cornerstone of treatment.* Antimicrobials are also begun promptly with the caveat that they may initially worsen endotoxemia from bacterial lysis. Surveillance for worsening sepsis syndrome includes serial monitoring of urinary output, blood pressure, pulse, temperature, and oxygen saturation. High fevers are lowered with a cooling blanket and acetaminophen. This is especially important in early pregnancy because of possible teratogenic effects from hyperthermia.

TABLE 53-2

Management of the Pregnant Woman with Acute Pyelonephritis

Hospitalize patient
Obtain urine and possibly blood cultures
Evaluate hemogram, serum creatinine, and electrolytes
Monitor vital signs frequently, including urinary output—consider indwelling catheter
Establish urinary output ≥50 mL/hr with intravenous crystalloid solution
Administer intravenous antimicrobial therapy (see text)
Obtain chest radiograph if there is dyspnea or tachypnea
Repeat hematology and chemistry studies in 48 hours
Change to oral antimicrobials when afebrile
Discharge when afebrile 24 hours, consider antimicrobial therapy for 7 to 10 days
Repeat urine culture 1 to 2 weeks after antimicrobial therapy completed

Modified from Lucas, 1994; Sheffield, 2005.

Antimicrobial therapy usually is empirical, and ampicillin plus gentamicin; cefazolin or ceftriaxone; or an extended-spectrum antibiotic are all 95-percent effective in randomized trials (Sanchez-Ramos, 1995; Wing, 1998, 2000). Fewer than half of *E coli* strains are sensitive to ampicillin in vitro, but cephalosporins and gentamicin generally have excellent activity. Serum creatinine levels are monitored if nephrotoxic drugs are given. Initial treatment at Parkland Hospital is ampicillin plus gentamicin. Some recommend suitable substitutes if bacterial studies show in vitro resistance. With any of the regimens discussed, response is usually prompt, and 95 percent of women are afebrile by 72 hours (Hill, 2005; Sheffield, 2005). After discharge, most recommend oral therapy for a total of 7 to 14 days (Hooton, 2012).

Persistent Infection

Generally, intravenous hydration and antimicrobial therapy are followed by stepwise defervescence of approximately 1°F per day. With persistent spiking fever or lack of clinical improvement by 48 to 72 hours, urinary tract obstruction, another complication, or both are considered. In these women, renal sonography is recommended to search for obstruction, which is manifest by abnormal ureteral or pyelocaliceal dilatation (Seidman, 1998). Although most women with continuing infection have no evidence of obstruction, some are found to have calculi. Although renal sonography will detect hydronephrosis, stones are not always seen in pregnancy (Butler, 2000; Maikranz, 1987). If stones are strongly suspected despite a nondiagnostic sonographic examination, a plain abdominal radiograph will identify nearly 90 percent. Another option is the modified *one-shot intravenous pyelogram*—a single radiograph obtained 30 minutes after contrast injection—which usually provides adequate imaging (Butler, 2000).

In some women, MR imaging may disclose the cause of persistent infection (Spencer, 2004). Even without urinary obstruction, persistent infection can be due to an intrarenal or perinephric abscess or phlegmon (Cox, 1988; Rafi, 2012). Obstruction relief is important, and one method is cystoscopic placement of a double-J ureteral stent (Rodriguez, 1988). Because these stents are usually left in place until after delivery, they frequently become encrusted and require replacement. We have found that percutaneous nephrostomy is preferable because the stents are more easily replaced. Finally, surgical removal of stones may be required in some women (Nephrolithiasis).

Outpatient Management

This is sometimes done for nonpregnant women with uncomplicated pyelonephritis (Hooton, 2012). Outpatient management was described in 92 pregnant women who were first given in-hospital intramuscular ceftriaxone, two 1-g doses 24 hours apart (Wing, 1999). After this, only a third of the group was considered suitable for outpatient therapy, and these women were randomly assigned either to discharge home and oral antimicrobials or to continued hospitalization with intravenous therapy. A third of the outpatient management group was unable to adhere to the treatment regimen and required readmission. This suggests that outpatient management is applicable to very few gravidas.

Recurrent urinary tract infection—either covert or symptomatic—develops in 30 to 40 percent of women following completion of pyelonephritis treatment (Cunningham, 1973). Unless other measures are taken to ensure urine sterility, nitrofurantoin, 100 mg orally at bedtime given for the remainder of the pregnancy, reduces bacteriuria recurrence (Van Dorsten, 1987).

Reflux Nephropathy

Vesicoureteral reflux in early childhood can cause recurrent urinary tract infections, and subsequent chronic interstitial nephritis is attributed to *chronic pyelonephritis*. Moreover, high-pressure sterile reflux impairs normal renal growth. Combined, this leads to patchy interstitial scarring, tubular atrophy, and loss of

nephron mass and is termed *reflux nephropathy*. In some cases—especially those with staghorn calculi—*xanthogranulomatous pyelonephritis* causes suppurative destruction of renal tissue. In adults, long-term complications of chronic pyelonephritis include hypertension, which may be severe (Beck, 2015; Diamond, 2012).

Perhaps half of women with reflux nephropathy were treated during childhood for renal infections. Many also had surgical correction of reflux as children, and these women commonly have bacteriuria when pregnant (Mor, 2003). In the other half of women with reflux nephropathy, a clear history of recurrent cystitis, acute pyelonephritis, or obstructive disease is lacking. Reports describing 939 pregnancies in 379 women with reflux nephropathy indicate that impaired renal function and bilateral renal scarring were associated with increased maternal complications (El-Khatib, 1994; Jungers, 1996; Köhler, 2003). Chronic renal disease and pregnancy outcome are discussed in Chronic Kidney Disease.

NEPHROLITHIASIS

Kidney stones develop in up to 9 percent of women during their lifetime with an average age of onset in the third decade (Curhan, 2015). Calcium salts make up approximately 90 percent of stones, and hyperparathyroidism should be excluded. Although calcium oxalate stones in young nonpregnant women are most common, most stones in pregnancy—65 to 75 percent—are calcium phosphate or hydroxyapatite (Ross, 2008; Tan, 2013). Patients who have a stone typically form another one every 2 to 3 years. One study found pregnancy was a risk factor for stone formation (Reinstatler, 2017).

Contrary to past teachings, a low-calcium diet *promotes* stone formation. Thiazide diuretics diminish stone formation. In general, obstruction, infection, intractable pain, and heavy bleeding are indications for stone removal, discussed later.

Stone Disease During Pregnancy

The incidence of stone disease complicating pregnancy varies. At the low end, the incidence was 0.3 admissions per 1000 pregnancies at Parkland Hospital (Butler, 2000). In an Israeli study, the incidence in nearly 220,000 pregnancies was 0.8 per 1000 (Rosenberg, 2011). In Washington state, the incidence was 1.7 per 1000 pregnancies (Swartz, 2007). Bladder stones are rare, but recurrent infection and labor obstructed by stones have been reported (Ait Benkaddour, 2006; Ruan, 2011).

Data are conflicting whether women with kidney stones have an increased risk for low-birthweight and preterm newborns. In one study of 2239 women with nephrolithiasis compared with normal controls, stones were associated with a significantly elevated preterm delivery rate—10.6 versus 6.4 percent (Swartz, 2007). The more recent nationwide study from Taiwan also found 20- to 40-percent increases in rates of low birthweight and preterm birth (Chung, 2013). In contrast, a study from Hungary reported that pregnancy outcomes, including preterm delivery, were similar in women with stones and normal controls (Banhidy, 2007). Comparable conclusions were drawn from the Israeli study discussed above (Rosenberg, 2011).

Diagnosis

Pregnant women may have fewer symptoms with stone passage because of urinary tract dilatation (Hendricks, 1991; Tan, 2013). That said, more than 90 percent of pregnant women with symptomatic nephrolithiasis present with pain. Gross hematuria is less common than in affected nonpregnant women. It was a presenting symptom in 23 percent of women described by Butler and associates (2000). In another study, however, only 2 percent had gross hematuria (Lewis, 2003). Sonography is usually selected to visualize stones, but many are not detected because hydronephrosis may obscure findings (McAleer, 2004). Transabdominal color Doppler sonography to detect presence or absence of ureteral "jets" of urine into the bladder may exclude obstruction (Asrat, 1998).

If the ureter is abnormally dilated but no stone is seen, then other imaging studies are indicated. While helical computed tomography (CT) scanning is the preferred imaging method for nonpregnant individuals, the associated x-ray exposure has led some to recommend MR imaging as a second-line test in pregnancy (Masselli, 2015). Thus CT scanning is usually avoided during pregnancy if possible (Curhan, 2015; Masselli, 2015). If it is used, the slices can be tailored as needed. White and colleagues (2007) recommend unenhanced helical CT and cite an average fetal radiation dose to be 7 mGy.

Management

Treatment depends on symptoms and gestational age (Semins, 2014). Intravenous hydration and analgesics are given. In up to half of women with symptomatic stones, infection will be identified, and this is treated vigorously as described earlier (Reflux Nephropathy). Although stones infrequently cause symptomatic obstruction during pregnancy, persistent pyelonephritis should prompt a search for obstruction due to nephrolithiasis. Urinary obstruction with concomitant infection is an emergency—"pus under pressure" (Curhan, 2015).

Approximately 65 to 80 percent of symptomatic women will improve with conservative therapy, and the stone usually passes spontaneously (Tan, 2013). Others require an invasive procedure such as ureteral stenting, ureteroscopy, percutaneous nephrostomy, transurethral laser lithotripsy, or basket extraction (Butler, 2000; Johnson, 2012; Semins, 2014). Removal by a flexible basket via cystoscopy, although used less often than in the past, is still a reasonable consideration for pregnant women. In one study, 623 various procedures were performed in 2239 symptomatic pregnant women, but less than 2 percent required surgical exploration (Swartz, 2007). Of other treatments, the need for fluoroscopy limits the utility of percutaneous nephrolithotomy (Toth, 2005). Extracorporeal shock-wave lithotripsy is contraindicated in pregnancy.

PREGNANCY AFTER RENAL TRANSPLANTATION

Following transplantation, the 1-year graft survival rate is 95 percent for grafts from living donors and 89 percent for those from deceased donors. Survival rates approximately doubled between 1988 and 1996, due in large part to the introduction of cyclosporine and muromonab-CD3 (OKT3 monoclonal antibody) to prevent and treat organ rejection. Since then, mycophenolate mofetil and tacrolimus have further reduced acute rejection episodes, however, the former is considered teratogenic (Briggs, 2014). The National Transplant Pregnancy Registry reports that 23 percent of fetuses exposed to mycophenolate had birth defects (Coscia, 2010).

Importantly, resumption of renal function after transplantation promptly restores fertility in reproductive-aged women (Hladunewich, 2011; Rao, 2016). But, more than half of transplant recipients in one study reported that they were not counseled regarding contraception (French, 2013).

Pregnancy Outcomes

Women after transplantation do better with pregnancy than those with end-stage renal disease receiving dialysis (Saliem, 2016). In one review of 2000 pregnancies in transplant recipients, most were treated with cyclosporine and tacrolimus, and approximately 75 percent of pregnancies resulted in a live birth (Coscia, 2010). Studies from other countries describe similar outcomes (Bramham, 2013; Wyld, 2013). In a study from Uruguay, 62 percent of liveborns were preterm (Orihuela, 2016). Two other reports also cited a high prevalence of preterm delivery (Erman Akar, 2015; Stoumpos, 2016). Notably, the incidence of fetal malformations was not increased, except in those who took mycophenolate mofetil (Coscia, 2010).

The incidence of preeclampsia is increased in all transplant recipients (Brosens, 2013). In the UK National Cohort Study, the incidence of preeclampsia was 22 percent (Bramham, 2013). From their review, Josephson and McKay (2011) cite an incidence of a third of pregnancies but question the validity of this frequency. Importantly, in some cases, rejection is difficult to distinguish from preeclampsia. That said, the incidence of rejection episodes approximates 2 to 5 percent (Bramham, 2013; Orihuela, 2016). Viral infections—especially those by *polyomavirus hominis 1*, also called *BK virus*, are frequent. In kidney transplant recipients, this virus can cause nephropathy and graft loss, and affected patients generally have an asymptomatic decline in renal function (Wright, 2016). Gestational diabetes is also found in approximately 5 percent of transplant recipients. Both are likely related to immunosuppression therapy. Similar outcomes are reported by other investigators (Al Duraihimh, 2008; Cruz Lemini, 2007; Ghafari, 2008).

Several requisites should be satisfied by renal transplantation patients before attempting pregnancy (Josephson, 2011; López, 2014). First, women should be in good general health for at least 1 to 2 years after transplantation. Also, renal function should be stable and without severe renal insufficiency. Thus, serum creatinine is <2 mg/dL and preferably <1.5 mg/dL, and proteinuria is <500 mg/d. Evidence for graft rejection should be absent for 6 months, and pyelocalyceal distention by urography should not be seen. Moreover, hypertension should be absent or well controlled. And last, women should be taking no teratogenic drugs, and drug therapy should be reduced to maintenance levels.

Cyclosporine, tacrolimus, prednisone, and azathioprine are given routinely to renal transplantation recipients (Jain, 2004; López, 2014). Cyclosporine blood levels decline during pregnancy, although this was not reported to be associated with rejection episodes (Aktürk, 2015; Kim, 2015). Unfortunately, these agents are nephrotoxic and also may cause renal hypertension. In fact, they likely contribute substantively to chronic renal disease that develops in 10 to 20 percent of patients with nonrenal solid-organ transplantation (Goes, 2007). Concern persists regarding the possible late effects in offspring subjected to immunosuppressive therapy in utero. These include malignancy, germ cell dysfunction, and malformations in the children of the offspring. In addition, cyclosporine is secreted in breast milk (Moretti, 2003).

Finally, although pregnancy-induced renal hyperfiltration theoretically may impair long-term graft survival, Sturgiss and Davison (1995) found no evidence for this in a case-control study of 34 allograft recipients followed for a mean of 15 years. Others have reported similar findings (Debska-Ślizień, 2014; Stoumpos, 2016).

Management

Close surveillance is necessary. Covert bacteriuria is treated, and if it is recurrent, suppressive therapy is given for the remainder of the pregnancy. Serial hepatic enzyme concentrations and blood counts are monitored for toxic effects of azathioprine and cyclosporine. Some recommend measurement of serum cyclosporine levels. Gestational diabetes is more common if corticosteroids are taken, and overt diabetes must be excluded with glucose tolerance testing done at approximately 26 weeks' gestation. Surveillance for opportunistic infections from herpesvirus, cytomegalovirus, and toxoplasmosis is important because these infections are common. Some recommend surveillance for BK virus, however, treatment is problematic (Josephson, 2011).

Renal function is monitored, and the GFR usually increases 20 to 25 percent. If a significant rise in the serum creatinine level is detected, then its cause must be determined. Possibilities include acute rejection, cyclosporine toxicity, preeclampsia, infection, and urinary tract obstruction. Evidence of pyelonephritis or graft rejection should prompt aggressive management. Imaging studies and kidney biopsy may be indicated. The woman is carefully monitored for development or worsening of underlying hypertension, and especially superimposed preeclampsia. Management of hypertension during pregnancy is the same as for patients without a transplant.

Because of increased incidences of fetal-growth restriction and preterm delivery, vigilant fetal surveillance is indicated (Chaps. 42, Diagnosis and 44, Fetal-Growth Restriction Recognition). Although cesarean delivery is reserved for obstetrical indications, occasionally the transplanted kidney obstructs labor. In all women with a renal transplant, the cesarean delivery rate exceeds 60 percent (Bramham, 2013; Rocha, 2013).

POLYCYSTIC KIDNEY DISEASE

This usually autosomally dominant systemic disease primarily affects the kidneys. The disease is found in 1 in 800 live births and causes approximately 5 to 10 percent of end-stage renal disease in the United States. Although genetically heterogeneous, almost 85 percent of cases are due to *PKD1* gene mutations on chromosome 16, and the other 15 percent to *PKD2* mutations on chromosome 4 (Zhou, 2015). Prenatal diagnosis is available if the mutation has been identified in a family member or if linkage is established in the family.

Renal complications are more common in men than in women, and symptoms usually appear in the third or fourth decade. Flank pain, hematuria, proteinuria, abdominal masses, and associated calculi and infection are common. Hypertension develops in 75 percent, and progression to renal failure is a major problem. Superimposed acute kidney injury may also develop from infection or obstruction from ureteral angulation by cyst displacement.

Other organs are frequently involved. Asymptomatic *hepatic cysts* coexist in a third of patients with polycystic kidneys. Hepatic involvement is more common and more aggressive in women, and massive polycystic liver disease is almost exclusively found in multiparous women (Zhou, 2015). Approximately 10 percent of patients with polycystic kidney disease die from rupture of an associated *intracranial berry aneurysm.* Up to a fourth of patients have *cardiac valvular lesions* that involve valve prolapse or incompetence.

Pregnancy Outcomes

Because of its generally late onset, adult polycystic kidney disease is uncommon in pregnancy (Banks, 2015). The prognosis for pregnancy in these women depends on the degree of associated hypertension and renal insufficiency. Urinary tract infections are common. One study compared pregnancy outcomes in 235 affected women who had 605 pregnancies with those of 108 unaffected family members who had 244 pregnancies (Chapman, 1994). Composite perinatal complication rates were similar—33 versus 26 percent. However, hypertension, including preeclampsia, was significantly more frequent in women with polycystic kidneys. Pregnancy does not seem to accelerate the natural disease course (Lindheimer, 2007b).

GLOMERULAR DISEASES

The glomerulus and its capillaries are subject to various conditions and stimuli that can lead to acute and chronic diseases. Glomerular damage can be caused by toxins or infections or from systemic diseases that include hypertension, diabetes, or systemic lupus erythematosus (Lewis, 2015). It may also be idiopathic. When there is capillary inflammation, the process is termed g*lomerulonephritis,* and often, an autoimmune process is involved.

Persistent glomerulonephritis eventually leads to worsening renal function. Progression is variable and often does not manifest until chronic renal insufficiency is diagnosed. Lewis and Neilson (2015) group glomerular injuries into six syndromes based on clinical patterns (Table 53-3). Within each of these categories, there are disorders encountered in young women, and thus, these may antedate or first appear during pregnancy.

TABLE 53-3

Patterns of Clinical Glomerulonephritis

Acute Nephritic Syndromes: poststreptococcal, infective endocarditis, SLE, antiglomerular basement membrane disease, IgA nephropathy (Berger disease), ANCA vasculitis, Henoch-Schönlein purpura, cryoglobulinemia, membranoproliferative and mesangioproliferative glomerulonephritis
Pulmonary-Renal Syndromes: Goodpasture, ANCA vasculitis, Henoch-Schönlein purpura, cryoglobulinemia
Nephrotic Syndromes: minimal change disease, focal segmental glomerulosclerosis, membranous glomerulonephritis, diabetes, amyloidosis, others
Basement Membrane Syndromes: anti-GBM disease, others
Glomerular Vascular Syndromes: atherosclerosis, chronic hypertension, sickle-cell disease, thrombotic microangiopathies, antiphospholipid antibody syndrome, ANCA vasculitis, others
Infectious Disease-Associated Syndromes: poststreptococcal, infective endocarditis, HIV, HBV, HCV, syphilis, others

ANCA = antineutrophilic cytoplasmic antibodies; anti-GBM = anti-glomerular basement membrane; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgA = immunoglobulin A; SLE = systemic lupus erythematosus.

Adapted from Lewis, 2015.

Acute Nephritic Syndromes

Acute glomerulonephritis may result from any of several causes (see Table 53-3). The clinical presentation usually includes hypertension, hematuria, red-cell casts, pyuria, and proteinuria. Varying degrees of renal insufficiency and salt and water retention result in edema, hypertension, and circulatory congestion (Lewis, 2015). The prognosis and treatment of nephritic syndromes depends on their etiology. Some recede spontaneously or with treatment. However, in some patients, *rapidly progressive glomerulonephritis* leads to end-stage renal failure, whereas in others, *chronic glomerulonephritis* develops with slowly progressive renal disease.

Lupus nephritis identified before pregnancy has a 50- percent chance of flaring during pregnancy (Koh, 2015). *IgA nephropathy*, also known as *Berger disease*, is the most common form of acute glomerulonephritis worldwide (Wyatt, 2013). The isolated form occurs sporadically, and it may be related to *Henoch-Schönlein purpura* as the systemic form (Donadio, 2002). Isolated nephritis may be due to anti-glomerular basement membrane (anti-GBM) antibodies. These may also involve the lungs to manifest as a pulmonary-renal syndrome with alveolar hemorrhage, which is termed *Goodpasture syndrome* (Friend, 2015; Huser, 2015).

Pregnancy

Acute nephritic syndromes during pregnancy can be difficult to differentiate from severe preeclampsia or eclampsia (Cabiddu, 2016). One example is systemic lupus erythematosus with a flare during the second half of pregnancy (Bramham, 2012; Zhao, 2013). In some of these cases, renal biopsy is sometimes needed to determine etiology and direct management (Lindheimer, 2007a; Ramin, 2006).

Whatever the underlying etiology, acute glomerulonephritis has profound effects on pregnancy outcome. One older study described 395 pregnancies in 238 women with *primary* glomerulonephritis diagnosed before pregnancy (Packham, 1989). The most frequent lesions on biopsy were membranous glomerulonephritis, IgA glomerulonephritis, and diffuse mesangial glomerulonephritis. Although most of these women had normal renal function, half developed hypertension, a fourth were delivered preterm, and the perinatal mortality rate after 28 weeks' gestation was 80 per 1000. As expected, the worst perinatal outcomes were in women with impaired renal function, early or severe hypertension, and nephrotic-range proteinuria. Similar outcomes have been reported for pregnancies in women with IgA nephropathy. From their review of more than 300 such pregnancies, Lindheimer and colleagues (2000) concluded that pregnancy outcome was related to the degree of renal insufficiency and hypertension. Liu and coworkers (2014) reached similar conclusions.

Nephrotic Syndromes

Heavy proteinuria is the hallmark of the nephrotic syndromes. These result from several primary and secondary kidney disorders that cause immunological or toxin-mediated injury with glomerular capillary wall breakdown to allow excessive filtration of plasma proteins. In addition to heavy urine protein excretion, the syndrome is characterized by hypoalbuminemia, hypercholesterolemia, and edema. There frequently is hypertension, and along with albumin nephrotoxicity, renal insufficiency eventually develops.

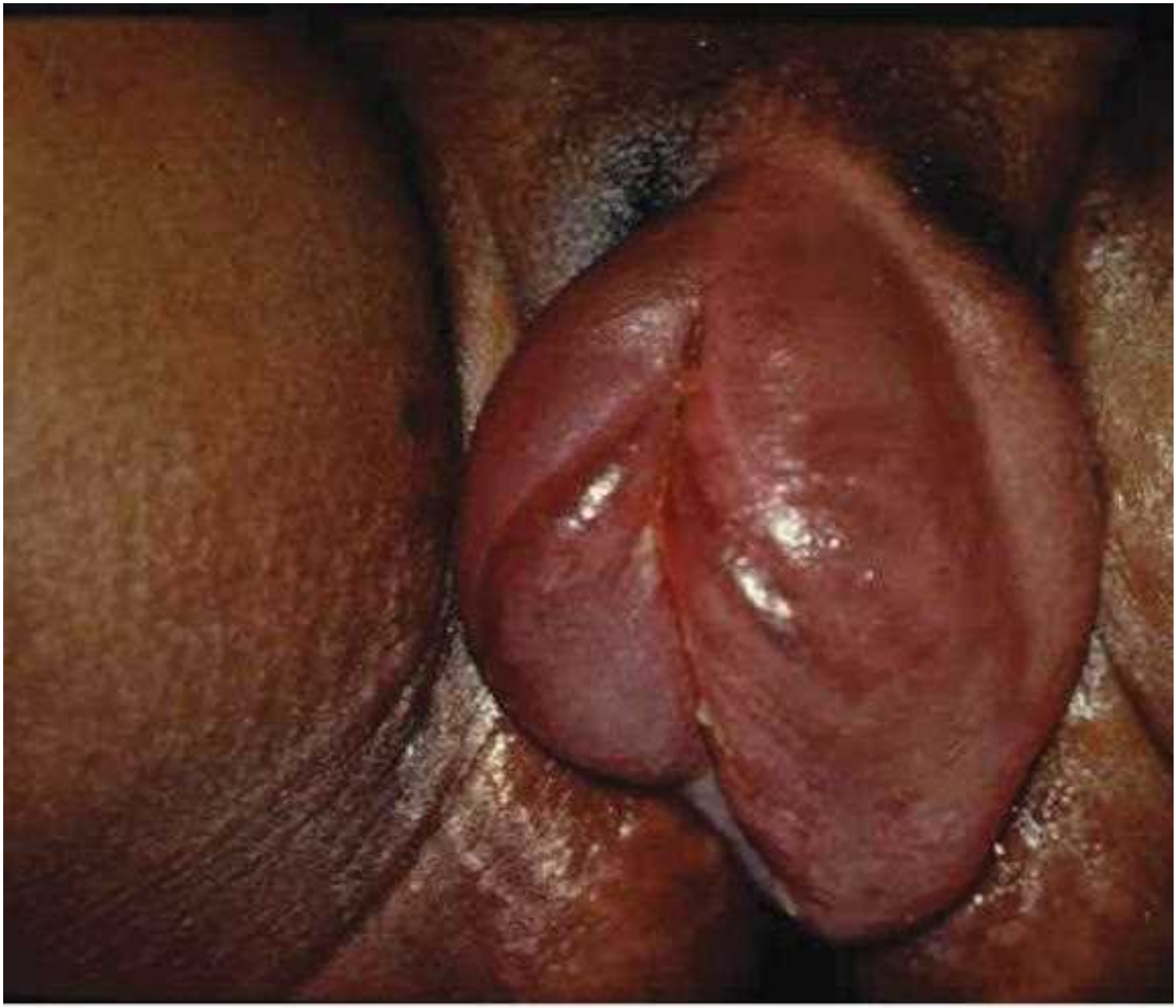
Some of the more frequent causes of the nephrotic syndrome are minimal change disease (10–15 percent), focal segmental glomerulosclerosis (35 percent), membranous glomerulonephritis (30 percent), and diabetic nephropathy. In most cases, renal biopsy will disclose microscopic abnormalities that may help direct treatment (Chen, 2015; Lo, 2014). Edema is problematic, especially during pregnancy. Normal amounts of dietary protein of high biological value are encouraged. The incidence of thromboembolism is increased and varies with the severity of hypertension, proteinuria, and renal insufficiency (Stratta, 2006). Although both arterial and venous thromboses may develop, renal vein thrombosis is particularly worrisome. The value, if any, of prophylactic anticoagulation is unclear. Some cases of nephrosis from primary glomerular disease respond to glucocorticosteroids and other immunosuppressants or cytotoxic drug therapy. In most of those cases caused by infection or drugs, proteinuria recedes when the underlying cause is corrected.

Pregnancy

Maternal and perinatal outcomes in women with the nephrotic syndromes depend on its underlying cause and severity. Whenever possible, these should be ascertained, and renal biopsy may be indicated to determine if the etiology will respond to treatment. Half of women with nephrotic-range proteinuria will have a rise in daily protein excretion as pregnancy progresses (Packham, 1989). In women with nephrosis cared for at Parkland Hospital, we reported that two thirds had protein excretion that exceeded 3 g/d (Stettler, 1992). At the same time, however, if these women had only mild degrees of renal dysfunction, they had normally augmented GFR across pregnancy (Cunningham, 1990).

Management of edema during pregnancy can be particularly challenging as it is intensified by normally increasing hydrostatic pressure in the lower extremities. In some women, massive vulvar edema may develop. An example of massive vulvar edema associated with the nephrotic syndrome caused by secondary syphilis is shown in Figure 53-3. Another major problem is that up to half of these women have chronic hypertension that may require treatment. In these, as well as in previously normotensive women, preeclampsia is common and often develops early in pregnancy.

FIGURE 53-3
Massive vulvar edema in a pregnant woman with the nephrotic syndrome due to secondary syphilis. (Used with permission from Dr. George Wendel, Jr.)



Most women with nephrotic syndromes who do not have severe hypertension or renal insufficiency will have successful pregnancy outcomes. Conversely, if there is renal insufficiency, moderate to severe hypertension, or both, the prognosis is much worse. In a group of such women with 65 pregnancies cared for at Parkland Hospital, complications were frequent (Stettler, 1992). Protein excretion during pregnancy averaged 4 g/d, and a third of the women had classic nephrotic syndrome. There was some degree of renal insufficiency in 75 percent, chronic hypertension in 40 percent, and persistent anemia in 25 percent. Importantly, preeclampsia developed in 60 percent, and 45 percent had preterm deliveries. Even so, after excluding abortions, 53 of 57 neonates were born alive. In another series, fetal-growth restriction was noted in a third of pregnancies in affected women (Stratta, 2006).

Serious long-term adverse outcomes are a risk for women identified to have nephrotic syndromes either before or during pregnancy (Su, 2017). In our series above, at least 20 percent of women followed for 10 years progressed to end-stage renal disease (Stettler, 1992). Similarly, in another group of 15 women, by 2 years postpartum, three had died, three had developed chronic renal failure, and two had progressed to end-stage renal disease (Chen, 2001). Of predictors, serum creatinine level >1.4 mg/dL and 24-hour protein excretion >1 g/d are associated with the shortest renal survival times following pregnancy (Imbasciati, 2007).

CHRONIC KIDNEY DISEASE

This describes a pathophysiological process that can progress to end-stage renal disease. The National Kidney Foundation describes six stages of chronic kidney disease defined by decreasing GFR. It progresses from stage 0—GFR >90 mL/min/1.73 m^2 to stage 5—GFR <15 mL/min/1.73 m^2. Several diseases can worsen renal function, and many result from one of the glomerular diseases discussed earlier. Those that most frequently lead to end-stage disease requiring dialysis and kidney transplantation and their approximate percentages include: diabetes, 35 percent; hypertension, 25 percent; glomerulonephritis, 20 percent; and polycystic kidney disease, 15 percent (Abboud, 2010; Bargman, 2015).

Most reproductive-aged women with these diseases have varying degrees of renal insufficiency, proteinuria, or both. To counsel regarding fertility and pregnancy outcome, the degree of renal functional impairment and of associated hypertension are assessed. Successful pregnancy outcome in general may be more related to these two factors than to the specific underlying renal disorder. A general prognosis can be estimated by considering women with chronic renal disease in arbitrary categories of renal function (Davison, 2011). These include normal or *mild impairment*—defined as a serum creatinine <1.5 mg/dL; *moderate impairment*—defined as a serum creatinine 1.5 to 3.0 mg/dL; and *severe renal insufficiency*—defined as a serum creatinine >3.0 mg/dL. Although some have suggested adopting the classification of the National Kidney Foundation, others recommend using the older categories (Davison, 2011; Piccoli, 2010a, 2011). Thus, the obstetrician is ideally familiar with both.

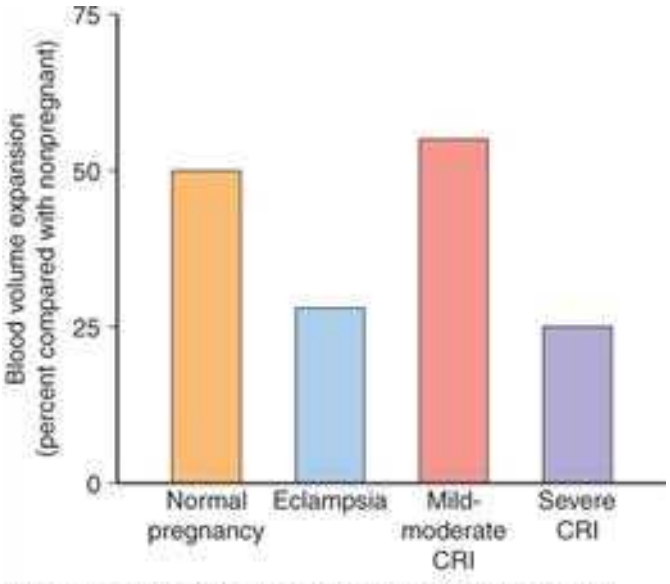
Pregnancy and Chronic Renal Disease

Most women have relatively mild renal insufficiency, and its severity along with any underlying hypertension is prognostic of pregnancy outcome. Renal disease with comorbidities secondary to a systemic disorder—for example, diabetes or systemic lupus erythematosus—portends a worse prognosis (Davison, 2011; Koh, 2015). For all women with chronic renal disease, the incidences of hypertension and preeclampsia, preterm and growth-restricted newborns, and other problems are high (Kendrick, 2015). Despite these, the National High Blood Pressure Education Program (2000) concluded that the prognosis has substantively improved since the 1980s. This has been verified by several reviews (Hladunewich, 2016a; Nevis, 2011; Ramin, 2006).

Loss of renal tissue is associated with compensatory intrarenal vasodilation and hypertrophy of the surviving nephrons. The resultant hyperperfusion and hyperfiltration eventually damage surviving nephrons to cause *nephrosclerosis* and worsening renal function. With mild renal insufficiency, pregnancy causes greater augmentation of renal plasma flow and GFR (Baylis, 2003; Helal, 2012). With progressively declining renal function, there is little, if any, augmented renal plasma flow. In one study, only half of women with moderate renal insufficiency demonstrated a pregnancy-augmented GFR, and women with severe disease had no increase (Cunningham, 1990).*Importantly, severe chronic renal insufficiency curtails normal pregnancy-induced hypervolemia.* Blood volume expansion during pregnancy is related to disease severity and correlates inversely with serum creatinine concentration. As shown in Figure 53-4, women with mild to moderate renal dysfunction have normal blood volume expansion that averages 55 percent. With severe renal insufficiency, however, volume expansion averages only 25 percent, which is similar to that seen with hemoconcentration from eclampsia. In addition, these women have variable degrees of chronic anemia due to intrinsic renal disease.

FIGURE 53-4

Blood volume expansion in 44 normally pregnant women at term compared with 29 who had eclampsia; 10 with moderate chronic renal insufficiency (CRI)—serum creatinine 1.5 to 2.9 mg/dL; and four with severe CRI—serum creatinine ≥3.0 mg/dL. (Data from Cunningham, 1990; Zeeman, 2009.)



Renal Disease with Preserved Function

In some women, although glomerular disease has not yet caused renal dysfunction, incidences of pregnancy complications are still increased. As shown in Table 53-4, these problems are less frequent than in cohorts of women with moderate and severe renal insufficiency. Two earlier studies illustrate this. In one describing 123 pregnancies in women with biopsy-proven glomerular disease, only a few of the women had renal dysfunction, yet 40 percent developed obstetrical or renal complications (Surian, 1984). In another study of 395 pregnancies in women with preexisting glomerulonephritis and minimal renal insufficiency, impaired renal function developed in 15 percent during pregnancy, and 60 percent had worsening proteinuria (Packham, 1989). Only 12 percent had antecedent chronic hypertension, however, more than half of the 395 pregnancies were complicated by hypertension. The perinatal mortality rate was 140 per 1000, but even without early-onset or severe hypertension or nephrotic-range proteinuria, the perinatal death rate was 50 per 1000. Importantly, in 5 percent of these women, worsening renal function was permanent.

TABLE 53-4

Complications (Percent) Associated with Chronic Renal Disease During Pregnancy

		Renal Insufficiency	
Complication	**Preserved Function**	**Moderate and Severe**	**Severe**
Chronic HTN	25	30–70	50
Gestational HTN	20–50	30–50	75
Worsening renal function	8–15	0–43	26–35
Permanent dysfunction	4–5	10–20	35
Preterm delivery	7	30–60	73–89
Fetal-growth restriction	8–14	30–38	57
Perinatal mortality	5–14	4–7	—

HTN = hypertension.

Data from Alsuwaida, 2011; Cunningham, 1990; Farwell, 2013; Feng, 2015; Imbasciati, 2007; Maruotti, 2012; Nevis, 2011; Packham, 1989; Piccoli, 2010a, 2011; Stettler, 1992; Surian, 1984; Trevisan, 2004.

Chronic Renal Insufficiency

In women with chronic kidney disease who also have renal insufficiency, adverse outcomes are generally directly related to the degree of renal impairment. Outcomes of women with moderate versus severe renal insufficiency are usually not separated (Table 53-5). That said, Piccoli and associates (2010a) described 91 pregnancies complicated by stage 1 chronic kidney disease. Primarily because of hypertension, 33 percent were delivered preterm, and 13 percent had fetal-growth restriction. Alsuwaida and colleagues (2011) reported similar observations. Other investigators have described pregnancies complicated by moderate or severe renal insufficiency (Cunningham, 1990; Imbasciati, 2007; Zhang, 2015). Despite a high incidence of chronic hypertension, anemia, preeclampsia, preterm delivery, and fetal-growth restriction, perinatal outcomes were generally acceptable. As shown in Figure 53-5, fetal growth is frequently impaired and related to renal dysfunction severity.

TABLE 53-5

Outcomes in 179 Pregnancies in Women Undergoing Dialysis

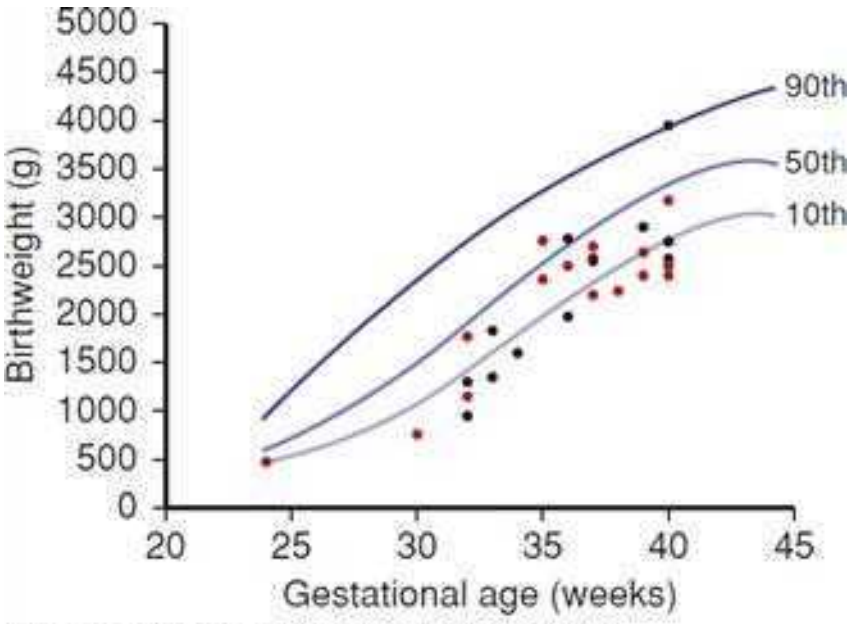
	Pregnancies			Pregnancy Outcomes (%)			
Study	**N**	**Delivery (wk)**	**Birthweight (g)**	**Hypertension**	**Hydramnios**	**Perinatal Mortality**	**Surviving Infants**
Chao (2002)	13	32	1540	72	46	31	69
Tan (2006)	11	31	1390	36	18	18	82
Chou (2008)	13	31	1510	57	71	50	50
Luders (2010)	52	33	1555	67	40	13	87
Shahir (2013)	13	NS	2130	19[a]	14	22	78
Jesudason (2014)	77	34	1750	NS	NS	20	80
Approximate averages	179	~32	~1600	~50	~44	~25	~80

[a]Preeclampsia only.

NS = not stated.

FIGURE 53-5

Birthweight percentiles of infants born to 29 women at Parkland Hospital with mild to moderate renal insufficiency—serum creatinine 1.4 to 2.4 mg/dL (*black points*) and severe renal insufficiency—serum creatinine ≥2.5 mg/dL (*red points*). (Data from Cunningham, 1990; Stettler, 1992. Growth curves are those reported by Alexander, 1996.)



Management

Prenatal care is tailored for women with chronic renal disease. Frequent monitoring of blood pressure is paramount, and serum creatinine levels, protein/creatinine ratio, and 24-hour protein excretion are quantified as indicated. Bacteriuria is treated to decrease the risk of pyelonephritis and further nephron loss. Protein-rich diets are recommended (Jim, 2016; Lindheimer, 2000). In some women with anemia from chronic renal insufficiency, a response is seen with recombinant erythropoietin, however, hypertension is a common side effect. Serial sonography is performed to follow fetal growth. The differentiation between worsening hypertension and superimposed preeclampsia is problematic. Preliminary data indicate that the angiogenic biomarkers placental growth factor (PlGF) and its soluble antiangiogenic receptor (sFlt-1) may be useful to separate chronic from gestational hypertension. This is described in Chapter 40 (Endothelial Cell Injury).

Long-Term Effects

In some women, pregnancy may accelerate chronic renal disease progression by increasing hyperfiltration and glomerular pressure to worsen nephrosclerosis (Baylis, 2003; Helal, 2012). This is more likely in women with severe chronic renal insufficiency (Abe, 1991; Jones, 1996). For example, Jungers and associates (1995) reported few long-term pregnancy-related adverse effects in 360 women with chronic glomerulonephritis and antecedent normal renal function. However, at 1 year after pregnancy, Jones and Hayslett (1996) reported that 10 percent of such women with moderate or severe renal insufficiency had developed end-stage renal failure—stage 5 chronic kidney disease. In a study from Parkland Hospital, we found that 20 percent of pregnant women with similar insufficiency had developed end-stage renal failure by a mean of 4 years (Cunningham, 1990). Similar findings in women with a median follow-up of 3 years were described by Imbasciati and coworkers (2007). By this time, end-stage disease was apparent in 30 percent of women whose serum creatinine was ≥1.4 mg/dL and who had proteinuria >1 g/d. Chronic proteinuria is also a marker for subsequent development of renal failure. In another report from Parkland Hospital, 20 percent of women with chronic proteinuria discovered during pregnancy progressed to end-stage renal failure within several years (Stettler, 1992).

Dialysis During Pregnancy

Significantly impaired renal function is accompanied by subfertility that may be corrected with chronic renal replacement therapy—either hemodialysis or peritoneal dialysis (Hladunewich, 2016b; Shahir, 2013). Not unexpectedly, these pregnancies can be complicated. In one review of 131 cases, mean fetal birthweights were higher in women who conceived while undergoing dialysis—1530 g versus 1245 g—than in women who conceived before starting dialysis (Chou, 2008). This was also true for 77 pregnancies described by Jesudason and coworkers (2014). Similar outcomes from several reports are shown in Table 53-5.

Outcomes are similar with either hemodialysis or peritoneal dialysis. Thus, for the woman already undergoing either method, it seems reasonable to continue that method with consideration for its increasing frequency. In the woman who has never been dialyzed, the threshold for initiation during pregnancy is unclear. Lindheimer and colleagues (2007a) recommend dialysis when serum creatinine levels are between 5 and 7 mg/dL. Because it is imperative to avoid abrupt volume changes that cause hypotension, dialysis frequency may be extended to five to six times weekly (Reddy, 2007).

Certain protocols emphasize attention to replacement of substances lost through dialysis (Jim, 2016). Multivitamin doses are doubled, and calcium and iron salts are provided along with sufficient dietary protein and calories. Chronic anemia is treated with erythropoietin. To meet pregnancy changes, extra calcium is added to the dialysate along with less bicarbonate.*Maternal complications are common and include severe hypertension, placental abruption, heart failure, and sepsis.* In a

review of 90 pregnancies in 78 women, as well as those shown in Table 53-5, high incidences of maternal hypertension and anemia, preterm and growth-restricted infants, stillbirths, and hydramnios were reported (Piccoli, 2010b).

ACUTE KIDNEY INJURY

Previously termed *acute renal failure,* acute kidney injury (AKI) is now used to describe suddenly impaired kidney function with retention of nitrogenous and other waste products normally excreted by the kidneys (Waikar, 2015). Severe AKI associated with pregnancy is less frequent today. For example, in a 6-year period, the overall incidence at the Mayo Clinic was 0.4 percent (Gurrieri, 2012). It is even less common for women who require dialysis—1 case per 10,000 births (Hildebrand, 2015). But, it still occasionally causes significant obstetrical morbidity, and women who require acute dialysis have increased maternal mortality rates (Kuklina, 2009; Van Hook, 2014). Outcomes are available from four older studies comprising a total of 266 women with renal failure (Drakeley, 2002; Nzerue, 1998; Sibai, 1990; Turney, 1989). Nearly 70 percent had preeclampsia, 50 percent had obstetrical hemorrhage, and 30 percent had a placental abruption. Almost 20 percent required dialysis, and the maternal mortality rate was 15 percent.

Although obstetrical cases of AKI that require dialysis have become less prevalent, acute renal ischemia is still often associated with severe preeclampsia and hemorrhage (Gurrieri, 2012; Jim, 2017). Particularly contributory are HELLP (hemolysis, elevated liver enzymes, low platelet levels) syndrome and placental abruption (Audibert, 1996; Drakely, 2002). Septicemia is another frequent comorbidity, especially in resource-poor countries (Acharya, 2013; Srinil, 2011; Zeeman, 2003). AKI is also common in women with acute fatty liver of pregnancy (Sibai, 2007). Some degree of renal insufficiency was found in virtually all of 52 such women cared for at Parkland Hospital (Nelson, 2013). Another woman from Parkland Hospital developed AKI from dehydration caused by severe hyperemesis gravidarum at 15 weeks (Hill, 2002). Other causes include thrombotic microangiopathies (Balofsky, 2016; Ganesan, 2011) (Chap. 56, Thrombotic Microangiopathies).

Diagnosis and Management

In most women, AKI develops postpartum, thus management is usually not complicated by fetal considerations. An abrupt rise in serum creatinine level is most often due to renal ischemia. Oliguria is an important sign. In obstetrical cases, both prerenal and intrarenal factors are often contributory. For example, with total placental abruption, severe hypovolemia from massive hemorrhage is common, and preexistent renal ischemia from preeclampsia is often comorbid. In addition, disseminated intravascular coagulopathy may be contributory.

When azotemia is evident and severe oliguria persists, some form of renal replacement treatment is indicated. Hemofiltration or dialysis is initiated before marked deterioration occurs. Hemodynamic measurements are normalized. Importantly, medication doses are adjusted, and magnesium sulfate, iodinated contrast agents, aminoglycosides, and nonsteroidal antiinflammatory drugs (NSAIDs) are prominent examples (Waikar, 2015). Early dialysis appears to reduce the maternal mortality rate appreciably and may enhance the extent of renal function recovery. With time, renal function usually returns to normal or near normal.

Prevention

AKI in obstetrics is most often due to acute blood loss, especially that associated with preeclampsia. Thus, it may often be prevented by the following means:

1. Prompt and vigorous volume replacement with crystalloid solutions and blood in instances of massive hemorrhage, such as in placental abruption, placenta previa, uterine rupture, and postpartum uterine atony (Chap. 41, Hypovolemic Shock).
2. Delivery or termination of pregnancies complicated by severe preeclampsia or eclampsia, and careful blood transfusion if loss is more than average (Chap. 40, Blood Volume).
3. Close observation for early signs of sepsis syndrome and shock in women with pyelonephritis, septic abortion, chorioamnionitis, or sepsis from other pelvic infections (Chap. 47, Sepsis Syndrome).
4. Avoidance of loop diuretics to treat oliguria before ensuring that blood volume and cardiac output are adequate for renal perfusion.
5. Judicious use of vasoconstrictor drugs to treat hypotension, and only after it has been determined that pathological vasodilatation is the cause.

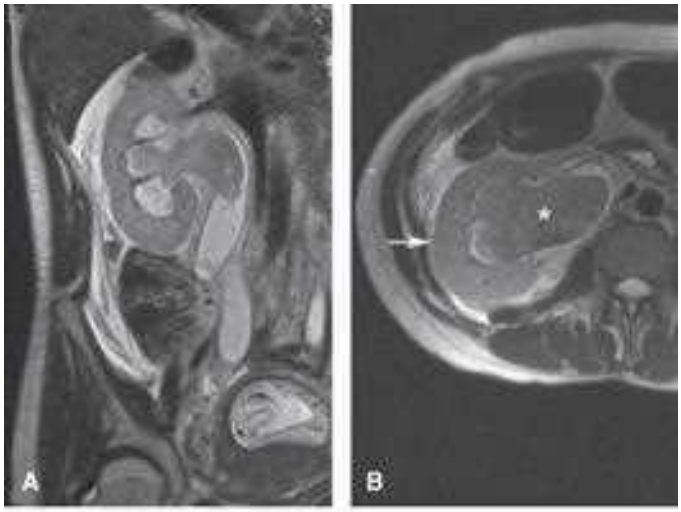
Irreversible ischemic renal failure caused by *acute cortical necrosis* is rare now in obstetrics (Frimat, 2016). Before widespread availability of dialysis, it complicated a fourth of obstetrical renal failure cases (Grünfeld, 1987; Turney, 1989). Most cases followed placental abruption, preeclampsia-eclampsia, and endotoxin-induced shock. Once common with septic abortion, this is a rare cause in this country today (Lim, 2011; Srinil, 2011). Histologically, the lesion appears to result from thrombosis of segments of the renal vascular system. The lesions may be focal, patchy, confluent, or gross. Clinically, renal cortical necrosis follows the course of AKI, and its differentiation from acute tubular necrosis is not possible during the early phase. The prognosis depends on the extent of the necrosis. Recovery of function is variable, and stable renal insufficiency may result (Lindheimer, 2007a).

Obstructive Renal Failure

Rarely, bilateral ureteral compression by a very large pregnant uterus is greatly exaggerated. Resultant ureteral obstruction in turn may cause severe oliguria and azotemia. An extreme example is shown in Figure 53-6. In their series of 13 obstruction cases, Brandes and Fritsche (1991) described one woman with twins who developed anuria and a serum creatinine level of 12.2 mg/dL at 34 weeks' gestation. After amniotomy, urine flow resumed at 500 mL/hr, and her serum creatinine levels rapidly dropped to normal range. Eckford and Gingell (1991) described 10 women in whom ureteral obstruction was relieved by stenting. The stents were left in place for a mean of 15.5 weeks and removed 4 to 6 weeks postpartum. Others have reported similar experiences (Sadan, 1994; Satin, 1993). Partial ureteral obstruction may be accompanied by fluid retention and significant hypertension. When the obstructive uropathy is relieved, diuresis ensues and hypertension dissipates. In our experience, women with previous urinary tract surgery for reflux are more likely to have such obstructions.

FIGURE 53-6

A. Magnetic resonance image in a coronal plane of a pregnant woman with unilateral hydronephrosis caused by ureteral obstruction. The serum creatinine level was 8 mg/dL and decreased to 0.8 mg/dL after a percutaneous nephrostomy tube was placed. **B.** Left kidney (*arrow*) and associated hydronephrosis (*asterisk*) are again noted in this axial plane image from the same patient.



LOWER GENITAL TRACT LESIONS

Urethral Diverticulum

Although infrequently complicating pregnancy, this type of diverticulum originates from an enlarging paraurethral gland abscess that ruptures into the urethral lumen. As infection clears, the remaining dilated diverticular sac and its ostium into the urethra persist. Urine collecting within and dribbling from the sac, pain, a palpable mass, and recurrent urinary infections may be associated findings. In general, a diverticulum is managed expectantly during pregnancy. Rarely, drainage may be necessary, or surgery required (Iyer, 2013). If additional antepartum evaluation is needed, MR imaging is preferred for its superior soft tissue resolution and ability to define complex diverticula (Dwarkasing, 2011; Pathi, 2013).

Urogenital Tract Fistulas

Fistulas found during pregnancy likely existed previously, but in rare cases, they form during pregnancy. In developed countries, *vesicovaginal or cervicovaginal fistula* following a McDonald cerclage has been reported (Massengill, 2012; Zanconato, 2015). These fistulas may also form with prolonged obstructed labor that is more often seen in resource-poor countries (Cowgill, 2015). In these cases, the genital tract is compressed between the fetal head and bony pelvis. Brief pressure is not significant, but prolonged pressure leads to tissue necrosis with subsequent fistula formation (Wall, 2012). *Vesicouterine fistulas* can develop after prior vaginal or cesarean delivery (DiMarco, 2006; Harfouche, 2014; Manjunatha, 2012). Rarely, *vesicocervical fistula* can follow cesarean delivery or may form if the anterior cervical lip is compressed against the symphysis pubis (Dudderidge, 2005). Finally, an *ileouterine fistula* from a degenerating posterior wall fibroid tumor has been described (Shehata, 2016).

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CHAPTER 54: Gastrointestinal Disorders

The diagnosis of acute appendicitis is more difficult than at other times, as the enlarged uterus renders it almost impossible to explore the right iliac region satisfactorily.

—J. Whitridge Williams (1903)

INTRODUCTION

These words summarize that during normal pregnancy, the gastrointestinal tract and its appendages undergo remarkable anatomical, physiological, and functional alterations. These changes, which are discussed in detail in Chapter 4 (Gastrointestinal Tract), can appreciably alter clinical findings normally relied on for diagnosis and treatment of gastrointestinal disorders such as appendicitis. Moreover, as pregnancy progresses, gastrointestinal symptoms become more difficult to assess. Physical findings are often obscured by a large uterus that displaces abdominal organs and can alter the location and intensity of pain and tenderness.

GENERAL CONSIDERATIONS

Diagnostic Techniques

Endoscopy

Fiberoptic endoscopic instruments have revolutionized diagnosis and management of most gastrointestinal conditions, and these are particularly well suited for pregnancy. Endoscopy in pregnancy is associated with a slightly increased risk for preterm birth, but this is likely due to the disease itself (Ludvigsson, 2017). With endoscopy, the esophagus, stomach, duodenum, and colon can be inspected (Cappell, 2011; Savas, 2014). The proximal jejunum can also be studied, and the ampulla of Vater cannulated to perform *endoscopic retrograde cholangiopancreatography—ERCP* (Akcakaya, 2014; Fogel, 2014). Preliminary data suggest that postendoscopic pancreatitis following gallstone removal may have a higher incidence in pregnant women (Inamdar, 2016). Experience in pregnancy with *videocapsule endoscopy* for small-bowel evaluation remains limited (Storch, 2006).

Upper gastrointestinal endoscopy is used for management as well as diagnosis of several problems. Common bile duct exploration and drainage are used for choledocholithiasis as described in Chapter 55 (Pancreatic Disorders). It is also used for sclerotherapy and for placement of *percutaneous endoscopic gastrostomy (PEG)* tubes. Several concise reviews have been provided (Cappell, 2011; Fogel, 2014; Gilinsky, 2006).

For visualization of the large bowel, *flexible sigmoidoscopy* can be used safely in pregnant women (Siddiqui, 2006). *Colonoscopy* is indispensible for viewing the entire colon and distal ileum to aid diagnosis and management of several bowel disorders. Except for the midtrimester, reports of colonoscopy during pregnancy are limited, but most results indicate that it should be performed if indicated (Cappell, 2010, 2011; De Lima, 2015). Bowel preparation is completed using polyethylene glycol electrolyte or sodium phosphate solutions. With these, serious maternal dehydration that may cause diminished uteroplacental perfusion should be avoided.

Noninvasive Imaging Techniques

The obvious ideal technique for gastrointestinal evaluation during pregnancy is abdominal sonography. Because computed tomography (CT) use is limited in pregnancy due to radiation exposure, magnetic resonance (MR) imaging is now commonly used to evaluate the abdomen and retroperitoneal space (Khandelwal, 2013). One example is magnetic resonance cholangiopancreatography—MRCP (Oto, 2009). Another is magnetic resonance enterography—MRE (Stern, 2014). These and other imaging modalities, and their safe use in pregnancy, are considered in more detail in Chapter 46.

Laparotomy and Laparoscopy

Surgery is lifesaving for certain gastrointestinal conditions— perforative appendicitis being the most common example. Laparoscopic procedures have replaced traditional surgical techniques for many abdominal disorders during pregnancy. These are shown in detail with descriptions of surgical technique in Chapter 46 (Perinatal Outcomes) and in *Cunningham and Gilstrap's Operative Obstetrics, 3rd edition* (Kho, 2016). Guidelines for diagnosis, treatment, and use of laparoscopy for surgical problems during pregnancy have been provided by the Society of American Gastrointestinal and Endoscopic Surgeons—SAGES (Pearl, 2017).

Nutritional Support

Specialized nutritional support can be delivered *enterally,* usually via nasogastric tube feedings, or *parenterally* with nutrition given by venous catheter access, either peripherally or centrally.

When possible, enteral alimentation is preferable because it has fewer serious complications (Bistrian, 2012; Stokke, 2015). In obstetrical patients, very few conditions prohibit enteral nutrition as a first effort to prevent catabolism. For extreme cases, such as recalcitrant hyperemesis gravidarum, percutaneous endoscopic gastrostomy with a jejunal port (PEG-J tube) has been described (Saha, 2009).

The purpose of *parenteral feeding*, or *hyperalimentation*, is to provide nutrition when the intestinal tract must be quiescent. Central venous access is necessary for total parenteral nutrition because its hyperosmolarity requires rapid dilution in a high-flow vascular system. These solutions provide 24 to 40 kcal/kg/d, principally as a hypertonic glucose solution.

Various conditions may prompt total parenteral nutrition during pregnancy (Table 54-1). Not surprisingly, gastrointestinal disorders are the most common indication, and in the many studies cited, feeding duration averaged approximately 33 days.

TABLE 54-1

Some Conditions Treated with Enteral or Parenteral Nutrition During Pregnancy[a]

Achalasia
Anorexia nervosa
Appendiceal rupture
Bowel obstruction
Burns
Cholecystitis
Crohn disease
Diabetic gastropathy
Esophageal injury
Hyperemesis gravidarum
Jejunoileal bypass
Malignancies
Ostomy obstruction
Pancreatitis
Preeclampsia syndrome
Short gut syndrome
Stroke
Ulcerative colitis

[a]Disorders are listed alphabetically.

Data from Folk, 2004; Guglielmi, 2006; Manhadevan, 2015; Ogura, 2003; Porter, 2014; Russo-Stieglitz, 1999; Saha, 2009; Spiliopoulos, 2013.

Importantly, complications of parenteral nutrition are frequent, and they may be severe (Guglielmi, 2006). An early report of 26 pregnancies described a 50-percent rate of complications, which included pneumothorax, hemothorax, and brachial plexus injury (Russo-Stieglitz, 1999). The most frequent serious complication is catheter sepsis, and Folk (2004) reported a 25-percent incidence in 27 women with hyperemesis gravidarum. Although bacterial sepsis is most common, *Candida* septicemia has been described (Paranyuk, 2006). The Centers for Disease Control and Prevention has updated its detailed guidelines to prevent catheter-related sepsis, and these serve to lessen the dangers of serious infections (O'Grady, 2011). Perinatal complications are uncommon, however, fetal subdural hematoma caused by maternal vitamin K deficiency has been described (Sakai, 2003).

Appreciable morbidity is also associated with long-term use of a *peripherally inserted central catheter (PICC)*. Infection is the most common serious long-term complication (Holmgren, 2008; Ogura, 2003). In a series of 84 such catheters inserted in 66 pregnant women, Cape and coworkers (2014) reported a 56-percent complication rate, of which bacteremia was the most frequent. From a review of 48 reports of nonpregnant adults, Turcotte and associates (2006) concluded that peripherally placed catheters provided no advantages compared with centrally placed ones. Still, for short-term nutrition lasting a few weeks, it seems reasonable that PICC placement has a greater benefit-versus-risk ratio (Bistrian, 2012).

UPPER GASTROINTESTINAL TRACT DISORDERS

Hyperemesis Gravidarum

Mild to moderate nausea and vomiting are especially common in pregnant women until approximately 16 weeks' gestation (Chap. 9, Caffeine). In a small but significant proportion of these, however, it is severe and unresponsive to simple dietary modification and antiemetics. Severe unrelenting nausea and

vomiting—*hyperemesis gravidarum*—is defined variably as being sufficiently severe to produce weight loss, dehydration, ketosis, alkalosis from loss of hydrochloric acid, and hypokalemia. Acidosis develops from partial starvation. In some women, transient hepatic dysfunction develops, and biliary sludge accumulates (Matsubara, 2012). Other causes should be considered because ultimately hyperemesis gravidarum is a diagnosis of exclusion (Benson, 2013).

Study criteria have not been homogeneous, thus reports of population incidences vary. There does, however, appear to be an ethnic or familial predilection (Grjibovski, 2008). In population-based studies from California, Nova Scotia, and Norway, the hospitalization rate for hyperemesis gravidarum was 0.5 to 1 percent (Bailit, 2005; Fell, 2006; Vikanes, 2013). Up to 20 percent of those hospitalized in a previous pregnancy for hyperemesis will again require hospitalization (Dodds, 2006; Trogstad, 2005). In general, obese women are less likely to be hospitalized for this (Cedergren, 2008).

The etiopathogenesis of hyperemesis gravidarum is unknown and is likely multifactorial. It apparently is related to high or rapidly rising serum levels of pregnancy-related hormones. Putative culprits include human chorionic gonadotropin (hCG), estrogen, progesterone, leptin, placental growth hormone, prolactin, thyroxine, and adrenocortical hormones (Verberg, 2005). More recently implicated are other hormones that include ghrelins, leptin, nesfatin-1, and peptide YY (3–36) (Albayrak, 2013; Gungor, 2013).

Superimposed on this hormonal cornucopia are an imposing number of biological and environmental factors. Moreover, in some but not all severe cases, interrelated psychological components play a major role (Christodoulou-Smith, 2011; McCarthy, 2011). Other factors that increase the risk for admission include hyperthyroidism, previous molar pregnancy, diabetes, gastrointestinal illnesses, some restrictive diets, and asthma and other allergic disorders (Fell, 2006; Mullin, 2012). An association of *Helicobacter pylori* infection has been proposed, but evidence is not conclusive (Goldberg, 2007). Chronic marijuana use may cause the similar *cannabinoid hyperemesis syndrome* (Alaniz, 2015; Andrews, 2015). And for unknown reasons—perhaps estrogen-related—a female fetus increases the risk by 1.5-fold (Schiff, 2004; Tan, 2006; Veenendaal, 2011). Finally, some but not all studies have reported an association between hyperemesis gravidarum and preterm labor, placental abruption, and preeclampsia (Bolin, 2013; Vandraas, 2013; Vikanes, 2013).

Complications

Vomiting may be prolonged, frequent, and severe, and a list of potentially fatal complications is given in Table 54-2. Various degrees of acute kidney injury from dehydration are encountered (Nwoko, 2012). An extreme example was a woman we cared for who required 5 days of dialysis when her serum creatinine level rose to 10.7 mg/dL (Hill, 2002). One complication from continuous retching is a Mallory-Weiss tear. Others are pneumothorax, pneumomediastinum, diaphragmatic rupture, and gastroesophageal rupture—*Boerhaave syndrome* (American College of Obstetricians and Gynecologists, 2015; Chen, 2012).

TABLE 54-2

Some Serious and Life-Threatening Complications of Recalcitrant Hyperemesis Gravidarum

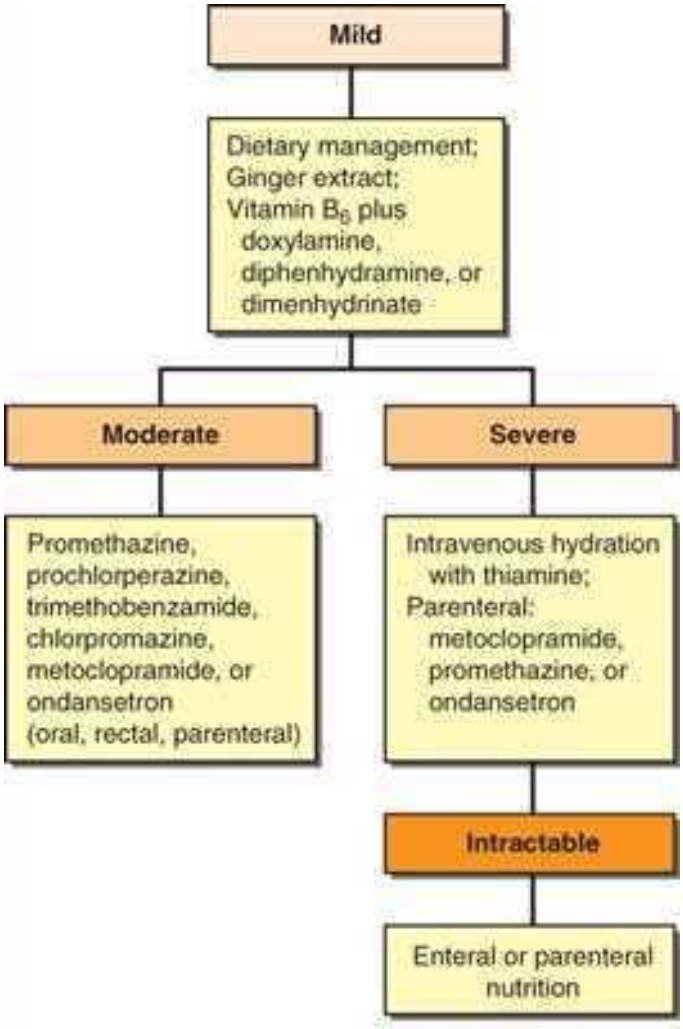
Acute kidney injury—may require dialysis Depression—cause versus effect? Diaphragmatic rupture
Esophageal rupture—Boerhaave syndrome
Hypoprothrombinemia—vitamin K deficiency
Hyperalimentation complications
Mallory-Weiss tears—bleeding, pneumothorax, pneumomediastinum, pneumopericardium
Rhabdomyolysis
Wernicke encephalopathy—thiamine deficiency

At least two serious vitamin deficiencies have been reported with hyperemesis in pregnancy. One is *Wernicke encephalopathy* from thiamine deficiency that has been recognized with increasing frequency (Di Gangi, 2012; Palacios-Marqués, 2012). In two reviews, ocular signs, confusion, and ataxia were common, but only half had this triad (Chiossi, 2006; Selitsky, 2006). With this encephalopathy, an abnormal electroencephalogram (EEG) may be seen, and usually MR imaging shows findings (Vaknin, 2006; Zara, 2012). At least three maternal deaths have been described, and long-term sequelae include blindness, convulsions, and coma (Selitsky, 2006). The second is *vitamin K deficiency* that has been reported to cause maternal coagulopathy and fetal intracranial hemorrhage, as well as vitamin K embryopathy (Kawamura, 2008; Lane, 2015; Sakai, 2003).

Management

One algorithm for management of nausea and vomiting of pregnancy is shown in Figure 54-1. Most women with mild to moderate symptoms respond as outpatients to any of several first-line antiemetic agents (Clark, 2014; Matthews, 2014). One that is becoming a mainstay is *Diclegis*—a combination of doxylamine (10 mg) plus pyridoxine (10 mg). It has been proven safe and effective (Briggs, 2015; Koren, 2014). The usual dose is two tablets orally at bedtime. If relief is insufficient, then additional doses, first in the morning, and then in the morning and midafternoon can be added each day to the bedtime dose. At our institution, for cost savings, we prescribe these two agents individually: Unisom (doxylamine) ½ of a 50-mg tablet plus a 25-mg vitamin B_6 tablet. The same graduated dosing is used but does not exceed three total daily doses.

FIGURE 54-1
Algorithm for outpatient and inpatient management of hyperemesis gravidarum.



Ondansetron (Zofran) also does not appear to be teratogenic. It was slightly more efficacious than a combination of doxylamine and pyridoxine in a randomized trial (Oliveira, 2014; Pasternak, 2013). Its drawbacks include potential maternal effects from prolonged QT-interval and serotonin syndrome (Koren, 2014).

When simple measures fail, intravenous crystalloid solutions are given to correct dehydration, ketonemia, electrolyte deficits, acid-base imbalances, and hypokalemia. No benefits are gained by infusing 5-percent dextrose along with crystalloids (Tan, 2013). Thiamine, 100 mg, is given to prevent Wernicke encephalopathy (Giugale, 2015; Niebyl, 2010). This is usually diluted in 1 L of the selected crystalloid and infused at the maintenance rate desired for patient hydration.

If vomiting persists after rehydration and failed outpatient management, hospitalization is recommended (American College of Obstetricians and Gynecologists, 2015). Day care has also been shown to be effective in one randomized study (McCarthy, 2014). Intravenous hydration is continued and antiemetics such as promethazine, prochlorperazine, chlorpromazine, or metoclopramide are given parenterally (Table 54-3). The bulk of evidence is that treatment with *glucocorticosteroids* is not effective (Yost, 2003). Because of their putative teratogenicity, they are not routinely recommended (American College of Obstetricians and Gynecologists, 2015).

TABLE 54-3

Medications for Gastric Disorders in Pregnancy

Medication (Brand Name)	Usual Dosing	Route(s)
Options for Nausea and Vomiting		
Antihistamine Doxylamine + pyridoxine (Diclegis)[a]	At bedtime; up to 4 times daily	PO
Phenothiazines	**Every 6 hr**	
Promethazine (Phenergan)[c]	12.5–25 mg	IM, IV, PO, PR
Prochlorperazine (Compazine)[c]	5–10 (25 PR) mg	IM, IV, PO, PR
Serotonin antagonist	**Every 8 hr**	
Ondansetron (Zofran)[b]	8 mg	IV, PO
Benzamides	**Every 6 hr**	
Metoclopramide (Reglan)[b]	5–15 mg	IM, IV, PO
Oral Options for Gastroesophageal Reflux (GERD)		
H2 receptor antagonists		
Ranitidine (Zantac)[b]	150 mg twice daily	
Cimetidine (Tagamet)[b]	400 mg 4 times daily for up to 12 wks 800 mg twice daily for up to 12 wks	
Nizatidine (Axid)[b]	150 mg twice daily	
Famotidine (Pepcid)[b]	20 mg twice daily up to 6 wks	
Proton-pump inhibitors		
Pantoprazole (Protonix)[b]	40 mg daily for up to 8 wks	
Lansoprazole (Prevacid)[b]	15 mg daily for up to 8 wks	
Omeprazole (Prilosec, Zegerid)[c]	20 mg daily for 4–8 wks	
Dexlansoprazole (Dexilant)[c]	30 mg daily for up to 4 wks	

[a]Food and Drug Administration category A.

[b]Food and Drug Administration category B.

[c]Food and Drug Administration category C.

With persistent vomiting after hospitalization, appropriate steps should be taken to exclude possible underlying diseases as a cause of hyperemesis. That said, in one study, endoscopy did not change management in 49 women (Debby, 2008). Other potential causes of vomiting include gastroenteritis, cholecystitis, pancreatitis, hepatitis, peptic ulcer, and pyelonephritis. In addition, severe preeclampsia and fatty liver are more likely after midpregnancy.

And although clinical thyrotoxicosis has been implicated as a cause of hyperemesis, it is more likely that abnormally elevated serum thyroxine levels are a surrogate for higher-than-average serum hCG levels (Sun, 2014). This is discussed further in Chapter 5 (Human Placental Lactogen). In our experiences, serum free thyroxine levels normalize quickly with hydration and emesis treatment.

With treatment, most women will have a salutary response and may be sent home with antiemetic therapy. Their readmission rate is 25 to 35 percent in most prospective studies. If associated psychiatric and social factors contribute to the illness, the woman usually improves remarkably while hospitalized (Swallow, 2004). That said, symptoms may relapse in these women, and some go on to develop *posttraumatic stress syndrome* (Christodoulou-Smith, 2011; McCarthy, 2011). For some women, hyperemesis can be an indication for elective termination (Poursharif, 2007).

In the small percentage of women who continue to have recalcitrant vomiting after intensive therapy, consideration is given for *enteral nutrition* (Upper Gastrointestinal Tract Disorders). Stokke and associates (2015) described successful use of nasojejunal feeding for up to 41 days in 107 such women. Use of sonography to confirm correct placement of the tube has been described (Swartzlander, 2013). Percutaneous endoscopic gastrostomy with a jejunal port has also been reported (Saha, 2009; Schrag, 2007). A randomized trial failed to show any advantages from early enteral feeding (Grooten, 2017).

In our experiences, only a very few women will require *parenteral nutrition* (Yost, 2003). In a study of 599 women, however, Peled and coworkers (2014) reported that 20 percent required central venous access to be established for nutrition.

Gastroesophageal Reflux Disease

Symptomatic reflux is seen in up to 15 percent of nonpregnant individuals (Kahrilas, 2015). The spectrum of sequelae includes esophagitis, stricture, Barrett esophagus, and adenocarcinoma. The main symptom of reflux is heartburn, or *pyrosis*, which is especially common in pregnancy. Its prevalence rose from 26 percent in the first trimester to 36 percent in the second and 51 percent in the third trimesters (Malfertheiner, 2012). The retrosternal burning sensation stems from esophagitis caused by gastroesophageal reflux related to relaxation of the lower esophageal sphincter.

Reflux symptoms usually respond to tobacco and alcohol abstinence, small meals, head of the bed elevation, and avoidance of postprandial recumbency. So-called “trigger” foods are also avoided and usually include fatty foods, tomato-based foods, and coffee. Oral antacids are first-line therapy. If severe symptoms persist, sucralfate (Carafate) is given along with a proton-pump inhibitor or an H_2-receptor antagonist (see Table 54-3). Both classes are generally safe for use in pregnancy (Briggs, 2015; Mahadevan, 2006b). Of these, a 1-g sucralfate tablet is taken orally 1 hour before each of the three meals and at bedtime for up to 8 weeks. Antacids are not used within ½ hour before or after sucralfate doses. If relief is not attained, then endoscopy should be considered. *Misoprostol* is contraindicated because it stimulates labor (Chap. 26, Methods of Induction and Augmentation).

In nonpregnant patients, surgical fundoplication is performed (Kahrilas, 2015). Although the procedure is not done during pregnancy, Biertho and colleagues (2006) described 25 women who had undergone laparoscopic Nissen fundoplication before pregnancy. Only 20 percent had reflux symptoms during pregnancy.

Hiatal Hernia

The older literature is informative regarding hiatal hernias in pregnancy. Upper gastrointestinal radiographs performed in 195 women in late pregnancy showed that 20 percent of 116 multiparas and 5 percent of 79 nulliparas had a hiatal hernia (Rigler, 1935). Of 10 women studied postpartum, hernia persisted in three at 1 to 18 months.

The relationship of hiatal hernia with reflux esophagitis, and thus symptoms, is not clear. One study demonstrated no relationship between reflux and hernia and showed that the lower esophageal sphincter functioned effectively even when displaced intrathoracically (Cohen, 1971). Nevertheless, during pregnancy, these hiatal hernias may cause vomiting, epigastric pain, and bleeding from ulceration. Schwentner (2011) reported severe herniation requiring surgical repair in a woman with a 12-week gestation. Curran and coworkers (1999) described a 30-week pregnancy complicated by gastric outlet obstruction from a paraesophageal hernia.

Diaphragmatic Hernia

These are caused by herniations of abdominal contents through either the foramen of Bochdalek or Morgagni. Fortunately, they rarely complicate pregnancy. Kurzel and associates (1988) reviewed the outcomes of 18 pregnant women with such a hernia and who developed acute obstruction. Because the maternal mortality rate was 45 percent, they recommend repair during pregnancy even if a woman is asymptomatic. Herniation has been reported in one pregnant woman from a previous traumatic diaphragmatic defect and in another who had antireflux surgery in early pregnancy (Brygger, 2013; Flick, 1999). Several case reports also describe spontaneous diaphragmatic rupture from increased intraabdominal pressure during delivery (Chen, 2012; Sharifah, 2003).

Achalasia

This is a rare motility disorder in which the lower esophageal sphincter does not relax properly with swallowing. There is also nonperistaltic contraction activity of the esophageal muscularis to cause symptoms (Kahrilas, 2015; Khudyak, 2006). The defect is caused by inflammatory destruction of the myenteric (Auerbach) plexus within smooth muscle of the lower esophagus and its sphincter. Postganglionic cholinergic neurons are unaffected, thus,

sphincter stimulation is unopposed. Symptoms are dysphagia, chest pain, and regurgitation. Barium swallow radiography demonstrates *bird beak* or *ace of spades* narrowing at the distal esophagus. Endoscopy is performed to exclude gastric carcinoma, and manometry is confirmatory. If dilatation of the esophagus and medical therapy does not provide relief, myotomy is considered (Torquati, 2006).

During pregnancy, normal relaxation of the lower esophageal sphincter in women with achalasia theoretically should not occur. Even so, in most women, pregnancy does not seem to worsen achalasia. One report of 20 affected pregnant women found no excessive reflux esophagitis (Mayberry, 1987). Khudyak and coworkers (2006) reviewed 35 cases and described most women as symptom free, although esophageal dilatation was needed in a few. A maternal death was reported at 24 weeks' gestation associated with perforation of a 14-cm diameter megaesophagus (Fassina, 1995).

Management of achalasia includes soft diet and anticholinergic drugs. With persistent symptoms, other options include nitrates, calcium-channel antagonists, and botulinum toxin A injected locally (Hooft, 2015; Kahrilas, 2015). Balloon dilatation of the sphincter may be necessary, and 85 percent of nonpregnant patients respond to this. Satin (1992) and Fiest (1993) and their associates reported successful use of pneumatic dilatation in pregnancy. *One caveat is that esophageal perforation is a serious complication of dilatation.* Spiliopoulos and colleagues (2013) described a 29-week pregnant woman with achalasia treated for 10 weeks with parenteral nutrition. Surgical correction was performed postpartum.

Peptic Ulcer Disease

The lifetime prevalence of acid peptic disorders in women is 10 percent (Del Valle, 2015). Erosive ulcer disease involves the stomach and duodenum. Gastroduodenal ulcers may be caused by chronic gastritis from *H pylori,* or they develop from nonsteroidal antiinflammatory drug (NSAID) use. Neither is common in pregnancy (McKenna, 2003; Weyermann, 2003). Acid secretion is also important, and thus underlies the efficacy of antisecretory agents (Suerbaum, 2002). Gastroprotection during pregnancy probably originates from physiological changes that include reduced gastric acid secretion, decreased motility, and considerably increased mucus secretion (Hytten, 1991). Despite this, ulcer disease may be underdiagnosed because of frequent treatment for reflux esophagitis (Mehta, 2010). In the past 50 years at Parkland Hospital, during which time we have cared for more than 500,000 pregnant women, we have encountered very few who had proven ulcer disease. Perforation is rare (Goel, 2014). Before appropriate therapy was commonplace, Clark (1953) studied 313 pregnancies in 118 women with ulcer disease and noted a clear remission during pregnancy in almost 90 percent. However, benefits were short lived. Symptoms recurred in more than half by 3 months postpartum and in almost all by 2 years.

The mainstay of management is eradication of *H pylori* and prevention of NSAID-induced disease. Antacids are usually self-prescribed, but first-line therapy is with H_2-receptor blockers or proton-pump inhibitors (Del Valle, 2015). *Sucralfate* is the aluminum salt of sulfated sucrose that inhibits pepsin. It provides a protective coating at the ulcer base. Approximately 10 percent of the aluminum salt is absorbed, and it is considered safe for pregnant women (Briggs, 2015).

With active ulcers, a search for *H pylori* is undertaken. Diagnostic aids include the urea breath test, serological testing, or endoscopic biopsy. If any of these yield positive results, combination antimicrobial and proton-pump inhibitor therapy is indicated. Several effective oral treatment regimens do not include tetracycline and can be used during pregnancy. These 14-day regimens include amoxicillin, 1000 mg twice daily plus clarithromycin, 250 to 500 mg twice daily, plus metronidazole, 500 mg twice daily given along with the proton-pump inhibitor omeprazole (Del Valle, 2015).

Upper Gastrointestinal Bleeding

In some women, persistent vomiting is accompanied by worrisome upper gastrointestinal bleeding. Occasionally, a peptic ulceration is the source. However, most of these women have small linear mucosal tears near the gastroesophageal junction—*Mallory-Weiss tears*, described earlier. Bleeding usually responds promptly to conservative measures, including iced-saline irrigations, topical antacids, and intravenously administered H_2-blockers or proton-pump inhibitors. Transfusions may be needed, and if bleeding persists, then endoscopy is usually indicated (O'Mahony, 2007). With sustained retching, the less common, but more serious, esophageal rupture—*Boerhaave syndrome*—may develop from greatly increased esophageal pressure.

SMALL BOWEL AND COLON DISORDERS

The small bowel has diminished motility during pregnancy. Using a nonabsorbable carbohydrate, Lawson (1985) showed that small bowel mean transit times were 99, 125, and 137 minutes in each trimester, compared with 75 minutes when nonpregnant. In a study cited by Everson (1992), mean transit time for a mercury-filled balloon from the stomach to the cecum was 58 hours in term pregnant women compared with 52 hours in nonpregnant women.

Muscular relaxation of the colon is accompanied by increased absorption of water and sodium that predisposes to constipation. This complaint is reported by almost 40 percent of women at some time during pregnancy (Everson, 1992). Such symptoms are usually only mildly bothersome, and preventive measures include a high-fiber diet and bulk-forming laxatives. Wald (2003) has reviewed treatment options. We have encountered several pregnant women who developed megacolon from impacted stool. These women almost invariably had chronically abused stimulatory laxatives.

Acute Diarrhea

The estimated monthly prevalence of diarrhea among adults is 3 to 7 percent (DuPont, 2014). Diarrhea can be classified as acute (<2 weeks), persistent (2 to 4 weeks), and chronic (>4 weeks). Most cases of acute diarrhea are caused by infectious agents, and a third result from foodborne pathogens. The large variety of viruses, bacteria, helminths, and protozoa that cause diarrhea in adults inevitably also afflict pregnant women. Some of these are discussed in

Chapter 64. Evaluation of acute diarrhea depends on its severity and duration. Some indications for evaluation include profuse watery diarrhea with dehydration, grossly bloody stools, fever >38°C, duration >48 hours without improvement, recent antimicrobial use, and diarrhea in the immunocompromised patient (Camilleri, 2015; DuPont, 2014). Cases of moderately severe diarrhea with fecal leukocytes or gross blood may best be treated with empirical antibiotics rather than evaluation. Some features of the more common acute diarrheal syndromes and their treatment are shown in Table 54-4.

TABLE 54-4

Etiology, Clinical Features, and Treatment of Common Acute Diarrheal Syndromes

Agents	Incubation	Emesis	Pain	Fever	Diarrhea	Treatment
Toxin producers 1. *Staphylococcus* 2. *C perfringens* 3. *E coli* (*enterotoxin)* 4. *B cereus*	1–72 hr	3–4+	1–2+	0–1+	3–4+, watery	 1. None 2. None 3. Ciprofloxacin 4. None
Enteroadherent 1. *E coli* 2. *Giardia* 3. Helminths	1–8 days	0–1+	1–3+	0–2+	1–2+, watery, mushy	 1. Ciprofloxacin 2. Tinidazole 3. As detected
Cytotoxin producers 1. *C difficile* 2. *E coli* (hemorrhagic)	1–3 days	0–1+	3–4+	1–2+	1–3+, watery, then bloody	 1. Metronidazole 2. None
Inflammatory ***Minimal*** 1. *Rotavirus* 2. *Norovirus*	1–3 days	1–3+	2–3+	3–4+	1–3+, watery	 1. None 2. None
Variable 3. *Salmonella* 4. *Campylobacter* 5. *Vibrio*	1–11 days	0–3+	2–4+	3–4+	1–4+ watery or bloody	 3. Ciprofloxacin 4. Azithromycin 5. Doxycycline
Severe 6. *Shigella* 7. *E coli* 8. *Entamoeba histolytica*	1–8 days	0–1+	3–4+	3–4+	1–2+, bloody	 6. Ciprofloxacin 7. Ciprofloxacin 8. Metronidazole

B cereus = Bacillus cereus; C difficile = Clostridium difficile; C perfringens = Clostridium perfringens; E coli = Escherichia coli.

Data from Camilleri, 2015; DuPont, 2014.

The mainstay of treatment is intravenous hydration using normal saline or Ringer lactate with potassium supplementation in amounts to restore maternal blood volume and to ensure uteroplacental perfusion. Vital signs and urine output are monitored for signs of sepsis syndrome. For moderately severe nonfebrile illness without bloody diarrhea, antimobility agents such as loperamide (Imodium) may be useful. Bismuth subsalicylate (Pepto-Bismol) may also alleviate symptoms.

Judicious use of antimicrobial agents is warranted. For moderate to severely ill women, some recommend empirical treatment with ciprofloxacin, 500 mg twice daily for 3 to 5 days. Specific pathogens are treated as needed when identified (see Table 54-4). Syndromes for which treatment is usually unnecessary include those caused by *Escherichia coli*, staphylococcal species, *Bacillus cereus*, and Norwalk-like virus. Severe illness caused by *Salmonella* spp is treated with ciprofloxacin or trimethoprim-sulfamethoxazole; by *Campylobacter* spp with azithromycin; by *Clostridium difficile* with oral metronidazole or vancomycin; and by *Giardia* spp and *Entamoeba histolytica* with metronidazole (DuPont, 2014; Rocha-Castro, 2016).

***Clostridium Difficile* Infection**

This anaerobic gram-positive bacillus is transmitted by the fecal-oral route. It is the most frequent nosocomial infection in the United States. In 2011, 453,000 cases of *C difficile* and 29,000 associated deaths were reported by the Centers for Disease Control and Prevention (CDC) (Lessa, 2015). The most important risk factor is antibiotic use, and the highest risk is with aminopenicillins, clindamycin, cephalosporins, and fluoroquinolones. Other risk factors include inflammatory bowel disease, immunosuppression, advanced age, and gastrointestinal surgery. Most cases are hospital-acquired, however, community-acquired cases are becoming common (Leffler, 2015). With severe colitis, the infection-related mortality rate is 5 percent.

Diagnosis is by enzyme immunoassay for toxins in the stool, or by DNA-based tests that identify toxin genes. Only patients with diarrhea should be tested, and posttreatment testing is not recommended. Prevention is by soap-and-water hand washing, and infected individuals are isolated. Treatment is oral vancomycin or metronidazole. The risk of recurrence after an initial episode is 20 percent. Fecal microbial transplantation may become standard for recurrent clostridial colitis.

Inflammatory Bowel Disease

Two presumably noninfectious forms of intestinal inflammation are ulcerative colitis and Crohn disease. Differentiation between these is important because treatment differs. That said, they both share common features, and sometimes are indistinguishable if Crohn disease involves the colon. The salient clinical and laboratory features shown in Table 54-5 permit a reasonably confident diagnostic differentiation in most cases. The etiopathogenesis is enigmatic in both, but a genetic predisposition is suspected. Inflammation is thought to result from dysregulated mucosal immune function in response to commensal microbiota, with or without an autoimmune component (Friedman, 2015).

TABLE 54-5

Some Shared and Differentiating Characteristics of Inflammatory Bowel Disease

	Ulcerative Colitis	Crohn Disease
Shared Characteristics		
Hereditary	More than 100 disease-associated genetic loci–a third shared; Jewish predominance; familial in 5–10% of cases; Turner syndrome; immune dysregulation	
Other	Chronic and intermittent with exacerbations and remissions; extraintestinal manifestations: arthritis, erythema nodosum, uveitis	
Differentiating Characteristics		
Major symptoms	Diarrhea, tenesmus, rectal bleeding, cramping pain; chronic, intermittent	Fibrostenotic–recurrent RLQ colicky pain; fever Fistulizing–cutaneous, bladder, interenteric
Bowel involvement	Mucosa and submucosa of large bowel; usually begins at rectum (40% proctitis only); continuous disease	Deep layers small and large bowel; commonly transmural; discontinuous involvement; strictures and fistulas
Endoscopy	Granular and friable erythematous mucosa; rectal involvement	Patchy; rectum spared; perianal involvement
Serum antibodies	Antineutrophil cytoplasmic (pANCA) ~70%	Anti-*S cerevisiae* ~50%
Complications	Toxic megacolon; strictures; arthritis; cancer (3–5%)	Fistulas; arthritis; toxic megacolon
Management	Medical; proctocolectomy curative	Medical; segmental and fistula resection

RLQ = right lower quadrant; *S cerevisiae* = Saccharomyces cerevisiae.

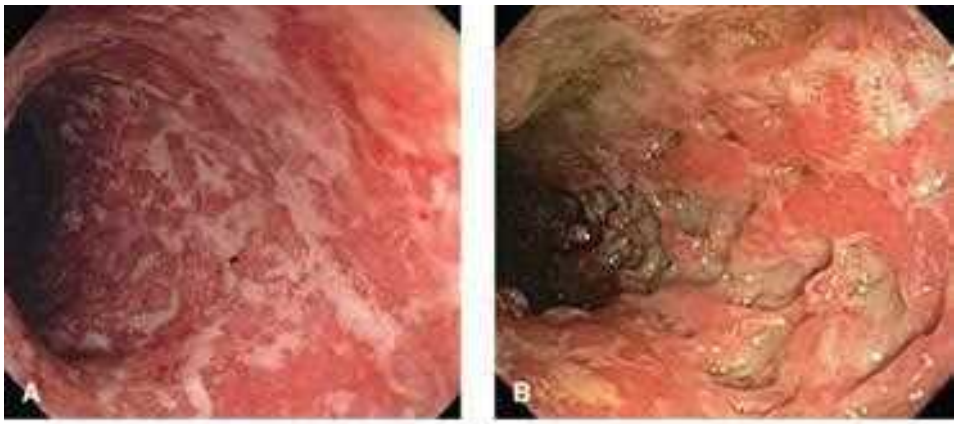
Data from Friedman, 2015; Lichtenstein, 2009; Podolsky, 2002.

Ulcerative Colitis

This is a mucosal disorder with inflammation confined to the superficial luminal layers of the colon. It typically begins at the rectum and extends proximally for a variable distance. In approximately 40 percent of cases, disease is confined to the rectum and rectosigmoid, but 20 percent have pancolitis. For unknown reasons, prior appendectomy protects against development of ulcerative colitis (Friedman, 2015). Endoscopic findings include mucosal granularity and friability that is interspersed with mucosal ulcerations and a mucopurulent exudate (Fig. 54-2).

FIGURE 54-2

Causes of colitis. **A.** Chronic ulcerative colitis with diffuse ulcerations and exudates. **B.** Crohn colitis with deep ulcers. (Reproduced with permission from Song LM, Topazian M: Gastointestinal endoscopy. Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. New York: McGraw-Hill Education; 2015.)



Major symptoms of ulcerative colitis include diarrhea, rectal bleeding, tenesmus, and abdominal cramps. The disease can be acute or intermittent and is characterized by exacerbations and remissions. *Toxic megacolon* and catastrophic hemorrhage are particularly dangerous complications that may necessitate colectomy. *Extraintestinal manifestations* include arthritis, uveitis, and erythema nodosum. Another serious problem is that the risk of colon cancer approaches 1 percent per year. With either ulcerative colitis or Crohn disease, there is also concern for possible increased risks for venous thromboembolism (Kappelman, 2011; Novacek, 2010).

Crohn Disease

Also known as regional enteritis, Crohn ileitis, and granulomatous colitis, Crohn disease has more protean manifestations than ulcerative colitis. It involves not only the bowel mucosa but also the deeper layers, and sometimes involvement is transmural (see Fig. 54-2). Lesions can be seen throughout the entire gastrointestinal tract, from the mouth to the anus, but it typically is segmental (Friedman, 2015). Approximately 30 percent of patients have small-bowel involvement, 25 percent have isolated colonic involvement, and 40 percent have both, usually with the terminal ileum and colon involved. Perianal fistulas and abscesses develop in a third of those with colonic involvement.

Symptoms depend on which bowel segment(s) is involved. Thus, complaints may include lower-right-sided cramping abdominal pain, diarrhea, weight loss, low-grade fever, and obstructive symptoms. The disease is chronic with exacerbations and remissions, and importantly, it cannot be cured medically or surgically. Approximately a third of patients require surgery within the first year after diagnosis, and thereafter, 5 percent per year. Reactive arthritis is common, and the gastrointestinal cancer risk, although not as great as with ulcerative colitis, is increased substantially.

Inflammatory Bowel Disease and Fertility

Subfertility is commonly linked to chronic medical disease, but Mahadevan (2006a) cited a normal fertility rate for inflammatory bowel disease unless severe disease warranted surgery. Similarly, Alstead (2003) reported that decreased female fertility from active Crohn disease returned to normal with remission. For women requiring surgical resection, laparoscopic anastomosis has a higher subsequent fertility rate (Beyer-Berjot, 2013). With colectomy, however, even though fertility is improved, up to half of women will be persistently infertile (Bartels, 2012). Sexual function and fertility are only modestly affected by ileal pouch-anal anastomosis (Hor, 2016). Subfertility may also be partially due to sulfasalazine, which causes reversible sperm abnormalities (Feagins, 2009).

Inflammatory Bowel Disease and Pregnancy

Because ulcerative colitis and Crohn disease are relatively common in young women, they are encountered with some frequency in pregnancy. In this regard, a few generalizations can be made. First, consensus supports that pregnancy does not increase the likelihood of an inflammatory bowel disease flare (Mahadevan, 2015). Indeed, in a 10-year surveillance of women in the European Collaborative on Inflammatory Bowel Disease, the likelihood of a flare during pregnancy was decreased compared with the preconceptional rate (Riis, 2006). Although most women with quiescent disease in early pregnancy do not have relapses, when a flare develops, it may be severe. Also, active disease in early pregnancy increases the likelihood of poor pregnancy outcome, which is discussed subsequently. In general, most usual treatment regimens may be continued during pregnancy. Diagnostic evaluations should be undertaken if needed to direct management, and surgery should be performed if indicated. For women who successfully complete pregnancy, about half experience improvement in their health-related quality of life (Ananthakrishnan, 2012).

At first glance, it appears that adverse pregnancy outcomes are increased with inflammatory bowel disease (Boyd, 2015; Cornish, 2012; Getahun, 2014). Initially, this was attributed to the fact that most studies included women with either form of disease. Specifically, Crohn disease was noted to be linked to excessive morbidity (Dominitz, 2002; Stephansson, 2010). But, according to Reddy (2008) and others, these adverse outcomes were in women with severe disease and multiple recurrences. Indeed, in the prospective European case-control *ECCO-EpiCom study* of 332 pregnant women with inflammatory bowel

disease, Bortoli and coworkers (2011) found similar outcomes in women with ulcerative colitis or Crohn disease compared with normally pregnant women. Importantly, perinatal mortality rates are not appreciably increased.

Ulcerative Colitis and Pregnancy

Ulcerative colitis does not significantly alter the course of pregnancy in affected women. In one review of 755 pregnancies, colitis that was quiescent at conception worsened in approximately a third of pregnancies (Fonager, 1998). In women with active disease at the time of conception, approximately 45 percent worsened, 25 percent remained unchanged, and only 25 percent improved. These observations are similar to those previously described in an extensive review by Miller (1986) and a later report from Oron and colleagues (2012).

Osteoporosis is a significant complication in up to a third of these women, and thus vitamin D—800 IU daily—and calcium—1200 mg daily—are given. Folic acid, 4 mg orally daily, is recommended preconceptionally and during the first trimester for neural-tube defect prevention. This high dose counteracts the antifolate actions of sulfasalazine. Flares may be caused by psychogenic stress, and reassurance is important.

Management for colitis for the most part mirrors that outside of pregnancy. Treatment of active colitis and maintenance therapy incorporate drugs that deliver 5-aminosalicyclic acid (5-ASA) or mesalamine. *Sulfasalazine (Azulfidine*) is the prototype, and its 5-ASA moiety inhibits prostaglandin synthase in colonic mucosa. Others include *olsalazine (Dipentum), balsalazide (Colazal),* and delayed-release 5-ASA derivatives *(Apriso, Asacol, Pentasa, Lialda).* Glucocorticoids are given orally, parenterally, or by enema for moderate or severe disease that does not respond to 5-ASA. However, these latter drugs are not given for maintenance therapy. Recalcitrant disease is managed with immunomodulating drugs, including *azathioprine*, *6-mercaptopurine*, or *cyclosporine*, which appear relatively safe in pregnancy (Briggs, 2015; Mozaffari, 2015). Importantly, *methotrexate* is contraindicated in pregnancy.

In the past, biological therapy was reserved for recalcitrant moderate to severe disease. Because of their considerable efficacy, these medications are now frequently given *initially* for severe disease to prevent future complications. These agents are antibodies against tumor necrosis factor-alpha (TNF-alpha). Those approved for treatment of ulcerative colitis include *infliximab (Remicade)*, *adalimumab* (*Humira)*, and *golinumab (Simponi).* These drugs are administered intravenously or subcutaneously. Several studies indicate that they are safe for use in pregnancy, although there are concerns that their discontinuance may prompt a relapse (Torres, 2015). Another worry is that they may cause immunosuppression in the neonate (Bröms, 2016; Diav-Citrin, 2014; Gisbert, 2013).

Colorectal endoscopy is performed as indicated (Katz, 2002). During pregnancy, colectomy and ostomy creation for fulminant colitis may be needed as a lifesaving measure, and it has been described during each trimester. Dozois (2006) reviewed 42 such cases and found that, in general, outcomes have been good in recent reports. Most women underwent partial or complete colectomy, but Ooi and colleagues (2003) described decompression colostomy with ileostomy in a 10- and a 16-week pregnancy. Parenteral nutrition discussed in Upper Gastrointestinal Tract Disorders is occasionally necessary for women with prolonged exacerbations.

For women with an ileal pouch and an anal anastomosis performed before pregnancy, sexual function and fertility are improved (Cornish, 2007). Disadvantages that temporarily worsen in pregnancy include frequent bowel movements, fecal incontinence, and pouchitis. The last is an inflammatory condition of the ileoanal pouch probably due to bacterial proliferation and stasis. Pouchitis usually responds to cephalosporins or metronidazole. In one rare case, adhesions to the growing uterus led to ileal pouch perforation (Aouthmany, 2004).

Women who have had a prior proctocolectomy and ileal pouch–anal anastomosis can be safely delivered vaginally (Ravid, 2002). Hahnloser (2004) reviewed routes of delivery in women with 235 pregnancies before and 232 pregnancies after ileoanal pouch surgery. Functional outcomes were similar, and it was concluded that cesarean delivery should be reserved for obstetrical indications. Postcesarean delivery ileoanal pouch obstruction has been described (Malecki, 2010).

To reiterate, ulcerative colitis likely has minimal adverse effects on pregnancy outcome. Modigliani (2000) reviewed perinatal outcomes in 2398 pregnancies and reported them to be not substantively different from those in the general obstetrical population. Specifically, the incidences of spontaneous abortion, preterm delivery, and stillbirth were remarkably low. In a population-based cohort study of 107 women from Washington state, perinatal outcomes, with two exceptions, were similar to those of 1308 normal pregnancies (Dominitz, 2002). One exception was an inexplicably increased incidence of congenital malformations. These authors and others also describe a cesarean delivery rate that was substantially increased compared with that for normal controls (Mahadevan, 2015). The previously described ECCO-EpiCom study reported similar outcomes in 187 gravidas with ulcerative colitis compared with normal pregnant controls (Bortoli, 2011).

Crohn Disease and Pregnancy

In general, Crohn disease activity during pregnancy is related to its status around the time of conception. In a cohort study of 279 pregnancies in 186 women whose disease was inactive at conception, a fourth relapsed during pregnancy (Fonager, 1998). In 93 with active disease at conception, however, two thirds either remained active or worsened. Miller (1986) had described similar findings from his earlier review, as did Oron and associates (2012).

Calcium, vitamin D, and folic acid supplementation mirror that for ulcerative colitis. For maintenance during asymptomatic periods, no regimen is universally effective. *Sulfasalazine* is effective for some, but the newer 5-ASA formulations are better tolerated. *Prednisone* therapy may control moderate to severe flares but is less effective for small-bowel involvement. Immunomodulators such as *azathioprine*, *6-mercaptopurine*, and *cyclosporine* are used for active disease and for maintenance. These appear relatively safe during pregnancy (Briggs, 2015; Chande, 2015). As discussed in Chapter 12 (Antimicrobial Drugs and Immunosuppressant Medications), methotrexate, mycophenolate mofetil, and mycophenolic acid are contraindicated in pregnancy (Briggs, 2015; Food and Drug Administration, 2008).

As with ulcerative colitis, treatment with antitumor necrosis factor monoclonal antibodies is often used initially for active Crohn disease and maintenance (Casanova, 2013; Cominelli, 2013; Friedman, 2015). These biological compounds include *infliximab*, *adalimumab*, *certolizumab (Cimzia)*, *natalizumab (Tysabri),* and *vedolizumab (Entyvio).* As discussed in Inflammatory Bowel Disease and Fertility, this class of immunomodulators is considered safe in pregnancy (Briggs, 2015; Clowse, 2015). Their discontinuance may be followed by a relapse (Torres, 2015).

Endoscopy or conservative surgery is indicated for complications. Patients with small-bowel involvement are more likely to require surgery for complications that include fistulas, strictures, abscesses, and intractable disease. An abdominal surgical procedure was required during 5 percent of pregnancies described by Woolfson (1990). Parenteral hyperalimentation has been used successfully during severe recurrences (Russo-Stieglitz, 1999). Those with an ileal loop colostomy may have significant problems. Women with a perianal fistula—unless these are rectovaginal—usually can undergo vaginal delivery without complications (Forsnes, 1999; Takahashi, 2007).

As discussed, the likelihood is greater that Crohn disease is associated with adverse pregnancy outcomes compared with ulcerative colitis (Stephansson, 2010). Outcomes are probably related to disease activities. In a case-control Danish study, Norgård (2007) reported a twofold risk of preterm births. Dominitz (2002) reported a two- to threefold increased risk for preterm delivery, low birthweight, fetal growth restriction, and cesarean delivery in 149 women with Crohn disease. Recall, however, that the prospective ECCO-EpiCom study found outcomes to be similar to those for normal pregnancies.

Ostomy and Pregnancy

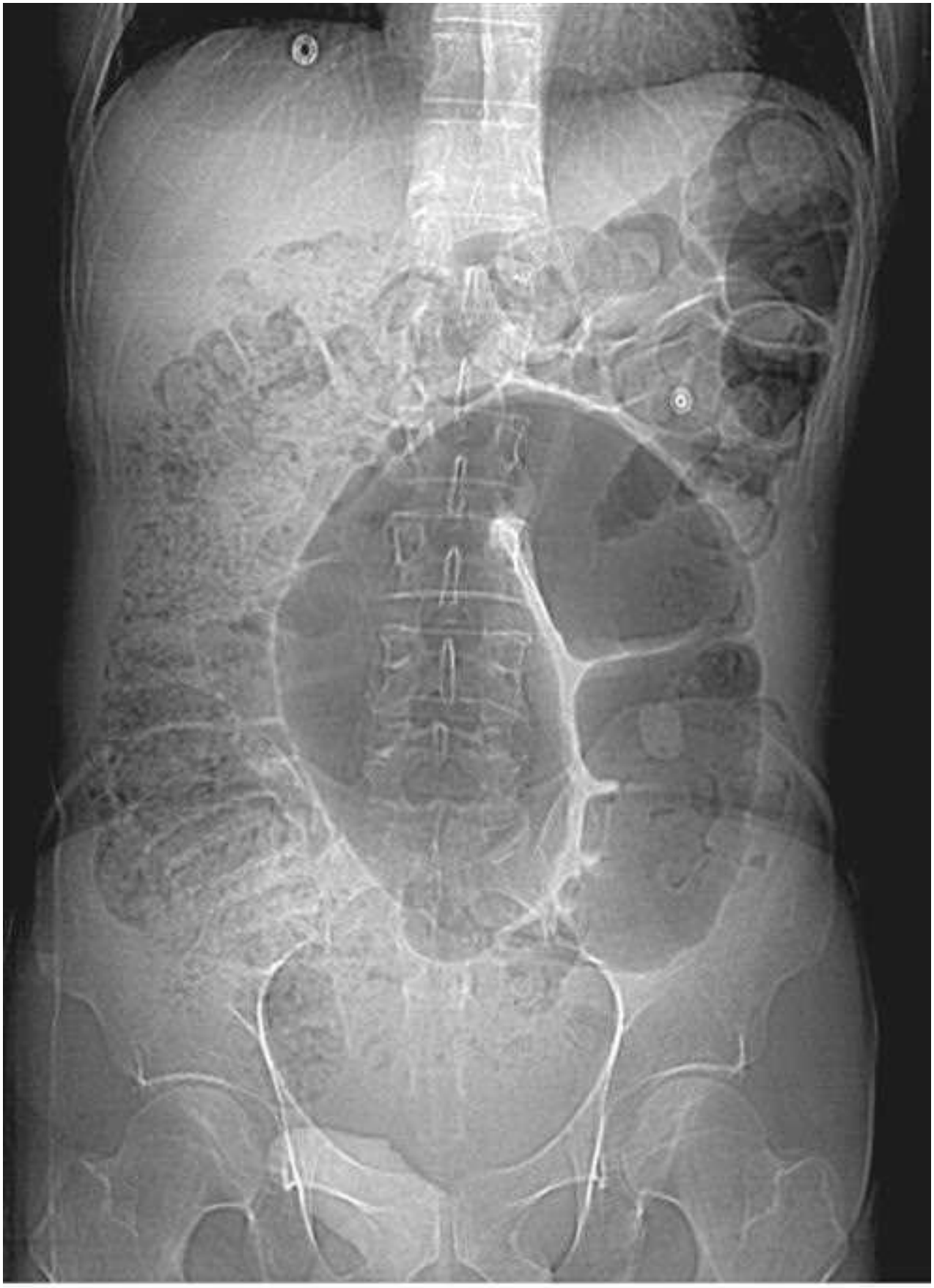
A colostomy or an ileostomy can be problematic during pregnancy because of its location (Hux, 2010). In a report of 82 pregnancies in 66 women with an ostomy, *stomal dysfunction* was common, but it responded to conservative management in most cases (Gopal, 1985). Surgical intervention was necessary, however, in three of six women who developed *bowel obstruction* and in another four with *ileostomy prolapse*—almost 10 percent overall. In this older study, only a third of 82 women underwent cesarean delivery, but Takahashi (2007) described six of seven cesarean deliveries in women with Crohn disease and a stoma. Although adhesions usually are involved with an obstructed ileostomy, the enlarging uterus may act to obstruct (Porter, 2014). Finally, Farouk and coworkers (2000) reported that pregnancy did not worsen long-term ostomy function.

Intestinal Obstruction

The incidence of bowel obstruction is not increased during pregnancy, although it generally is more difficult to diagnose. Meyerson (1995) reported a 20-year incidence of 1 in 17,000 deliveries at two Detroit hospitals. In one study, adhesive disease leading to small-bowel obstruction was the second most common cause of an acute abdomen in pregnancy following appendicitis—15 versus 30 percent, respectively (Unal, 2011). Approximately half of cases are due to adhesions from previous pelvic surgery that includes cesarean delivery (Al-Sunaidi, 2006; Andolf, 2010; Lyell, 2011). Another 25 percent of bowel obstruction cases are caused by volvulus—sigmoid, cecal, or small bowel. These have been reported in late pregnancy or early puerperium (Bade, 2014; Biswas, 2006; Al Maksoud, 2015). Small-bowel obstruction has been reported in pregnancy following the currently popular Roux-en-Y gastric bypass for weight loss (Bokslag, 2014; Wax, 2013). Intussusception is occasionally encountered (Bosman, 2014; Harma, 2011). Bowel obstruction subsequent to colorectal surgery for cancer was increased threefold in women who had open versus laparoscopic surgery (Haggar, 2013). Finally, Serra and colleagues (2014) described a massive ventral hernia with intestinal obstruction.

Most cases of intestinal obstruction during pregnancy result from pressure of the growing uterus on intestinal adhesions. According to Davis and Bohon (1983), this more likely occurs around midpregnancy when the uterus becomes an abdominal organ; in the third trimester when the fetal head descends; or immediately postpartum when uterine size acutely shrinks. Perdue (1992) reported that 98 percent of affected pregnant women had either continuous or colicky abdominal pain, and 80 percent had nausea and vomiting. Abdominal tenderness was found in 70 percent, and abnormal bowel sounds noted in only 55 percent. Plain abdominal radiographs following soluble contrast showed evidence of obstruction in 90 percent of women (Fig. 54-3). Plain radiographs, however, are less accurate for diagnosing small-bowel obstruction, and we and others have found that CT and MR imaging can be diagnostic (Biswas, 2006; Essilfie, 2007; McKenna, 2007). Colonoscopy can be both diagnostic and therapeutic for colonic volvulus (Dray, 2012; Khan, 2012).

FIGURE 54-3
Characteristic “bent inner tube” seen with sigmoid volvulus on abdominal radiograph. (Reproduced with permission from Song LM, Topazian M: Gastointestinal endoscopy. Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison’s Principles of Internal Medicine, 19th ed. New York: McGraw-Hill Education; 2015.)



During pregnancy, mortality rates with obstruction can be excessive because of difficult and thus delayed diagnosis, reluctance to operate during pregnancy, and the need for emergency surgery (Firstenberg, 1998; Shui, 2011). In an older report of 66 pregnancies, Perdue and associates (1992) described a 6-percent maternal mortality rate and 26-percent fetal mortality rate. Two of the four women who died were in late pregnancy, and they had bowel perforation from sigmoid or cecal volvulus caused by adhesions.

Colonic Pseudo-obstruction

Also known as *Ogilvie syndrome,* pseudo-obstruction is caused by adynamic colonic ileus. It is characterized by massive abdominal distention with cecal and right-hemicolon dilatation. Approximately 10 percent of all cases are associated with pregnancy, and its frequency has been reported as high as 1 in 1500 deliveries (Reeves, 2015). The syndrome usually develops postpartum—most commonly after cesarean delivery—but it has been reported antepartum (Tung, 2008). Rarely, the large bowel may rupture (Singh, 2005). Treatment with an intravenous infusion of neostigmine, 2 mg, usually results in prompt decompression (Song, 2015). In some cases, colonoscopic decompression is performed, and laparotomy is needed for perforation (De Giorgio, 2009; Rawlings, 2010).

Appendicitis

The lifetime incidence for appendicitis ranges from 7 to 10 percent (Flum, 2015). Thus, it is not surprising that an evaluation for possible appendicitis is relatively common during pregnancy. Theilen and colleagues (2015) studied 171 such women during a 5-year period, but only 12 women ultimately were found to have pathologically confirmed appendicitis. After clinical and imaging evaluation, the frequency of suspected appendicitis is much lower and that of confirmed appendicitis in more than 8 million women ranged from 1 in 1000 to 1 in 5500 births (Abbasi, 2014; Hée, 1999; Mazze, 1991).

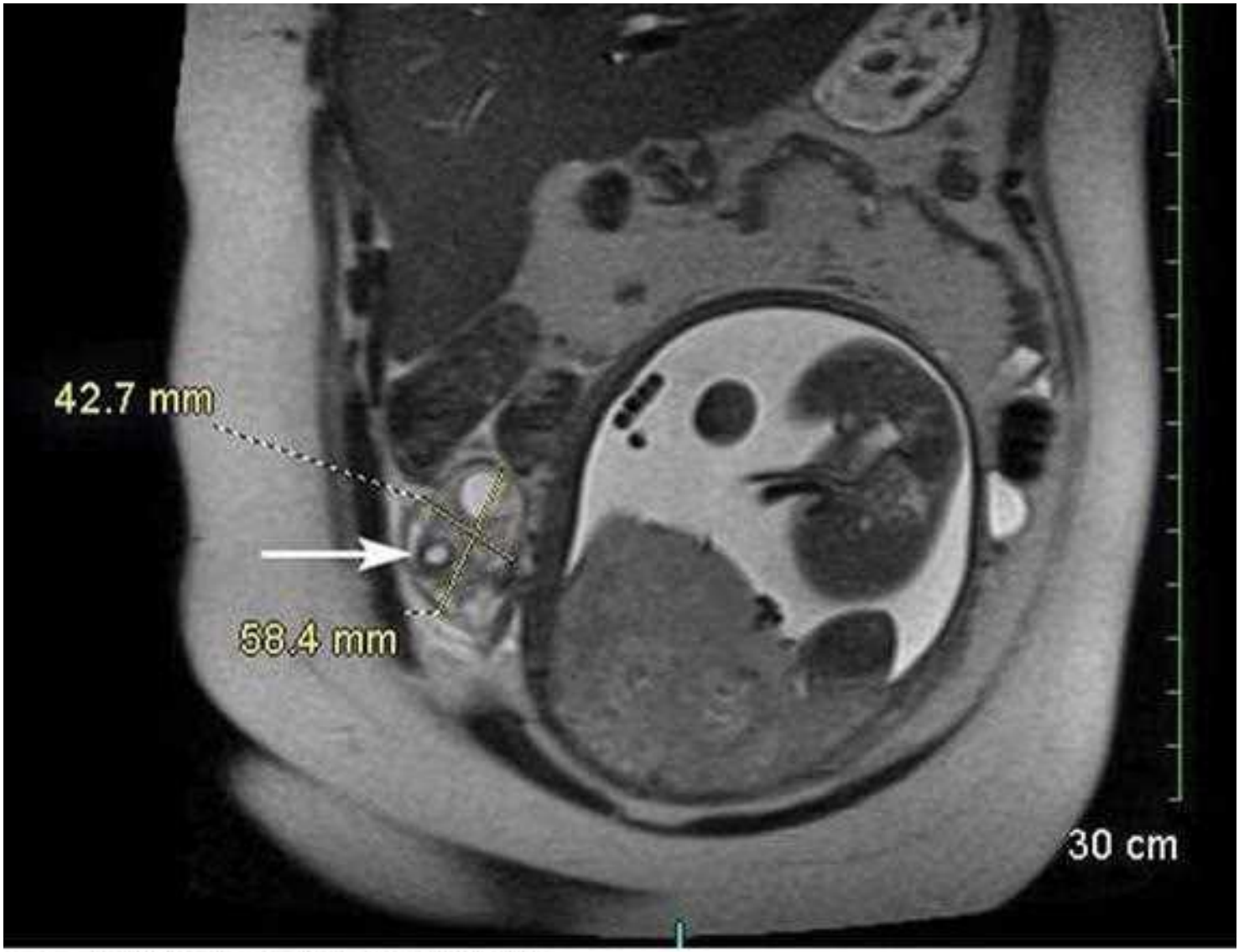
It is repeatedly—and appropriately—emphasized that pregnancy makes the diagnosis of appendicitis more difficult. Nausea and vomiting accompany normal pregnancy, but also, as the uterus enlarges, the appendix commonly moves upward and outward from the right lower quadrant (Baer, 1932; Erkek, 2015; Pates, 2009). Another often-stated reason for late diagnosis is that some degree of leukocytosis accompanies normal pregnancy. For these and other reasons, pregnant women—especially those late in gestation—frequently do not have clinical findings “typical” for appendicitis. Thus, it commonly is confused with cholecystitis, labor, pyelonephritis, renal colic, placental abruption, or uterine leiomyoma degeneration.

Most reports indicate increasing morbidity and mortality rates with advancing gestational age. And as the appendix is progressively deflected upward by the growing uterus, omental containment of infection becomes increasingly unlikely. It is indisputable that appendiceal perforation is more common during later pregnancy (Abbasi, 2014). In the studies by Andersson (2001) and Ueberrueck (2004), the incidence of perforation was approximately 8, 12, and 20 percent in successive trimesters.

Diagnosis

Persistent abdominal pain and tenderness are the most reproducible findings. Right-lower quadrant pain is the most frequent, although pain migrates upward with appendiceal displacement (Mourad, 2000). For initial evaluation, sonographic abdominal imaging is reasonable in suspected appendicitis, even if to exclude an obstetrical cause of pain (Butala, 2010). That said, *graded compression sonography* is difficult because of cecal displacement and uterine imposition (Pedrosa, 2009). *Appendiceal computed tomography* is more sensitive and accurate than sonography to confirm suspected appendicitis (Katz, 2012; Raman, 2008). Specific views can be designed to diminish fetal radiation exposure (Chap. 46, Computed Tomography). It is generally accepted that when available, MR imaging is the preferred modality for evaluation of suspected appendicitis in pregnancy (Fig. 54-4). MR imaging has high diagnostic yield and accuracy, and it also provides alternative diagnoses (Fonseca, 2014; Theilen, 2015). One metaanalysis cited positive- and negative-predictive values for MR imaging of 90 and 99.5 percent, respectively (Blumenfeld, 2011). Burke and associates (2015) reported similar findings. Using a decision-analysis model, CT and MR imaging were found to be cost effective (Kastenberg, 2013). This was verified in the clinical study of more than 7000 cases reported by Fonseca and coworkers (2014).

FIGURE 54-4
Anterior-posterior magnetic resonance image of a periappendiceal abscess in a midtrimester pregnancy. The abscess is approximately 5 × 6 cm, and the appendiceal lumen (*arrow*) is visible within the right-lower quadrant mass. The gravid uterus is seen to the right of this mass.



Management

When appendicitis is suspected, treatment is prompt surgical exploration. Although diagnostic errors may lead to removal of a normal appendix, surgical evaluation is preferable to postponed intervention and generalized peritonitis (Abbasi, 2014). In earlier reports, the diagnosis was verified in only 60 to 70 percent of pregnant women. As indicated above, however, with CT and MR imaging, these figures have improved (Blumenfeld, 2011; Theilen, 2015). Still and importantly, the accuracy of diagnosis is inversely proportional to gestational age.

Currently, laparoscopy is almost always used to treat suspected appendicitis during the first two trimesters. In a report from a Swedish database of nearly 2000 laparoscopic appendectomies, perinatal outcomes were similar to those of more than 1500 open laparotomies done before 20 weeks' gestation (Reedy, 1997). Conversely, in their review, Wilasrusmee and coworkers (2012) reported a higher rate of fetal loss with laparoscopy. Authors of a more recent systematic review indicate that the level of evidence is not strong enough to demonstrate a preferred approach to appendectomy. They concede that laparoscopy may be associated with a higher risk of miscarriage (Walker, 2014). It has evolved that in many centers, laparoscopic appendectomy is also performed in most cases during the third trimester (Donkervoort, 2011). This is encouraged by the Society of American Gastrointestinal and Endoscopic Surgeons (Pearl, 2017; Soper, 2011). That said, most are of the opinion that laparoscopic surgery in pregnancy after 26 weeks' gestation should be performed only by the most experienced endoscopic surgeons (Parangi, 2007).

Before exploration, intravenous antimicrobial therapy is begun, usually with a second-generation cephalosporin or third-generation penicillin. Unless there is gangrene, perforation, or a periappendiceal phlegmon, antimicrobial therapy can usually be discontinued after surgery. Without generalized peritonitis, the prognosis is excellent. Seldom is cesarean delivery indicated at the time of appendectomy. Uterine contractions are common, and although some clinicians recommend tocolytic agents, we do not. De Veciana (1994) reported that tocolytic use substantially increased the risk for pulmonary-permeability edema caused by sepsis syndrome (Chap. 47, Acute Pulmonary Edema).

Antimicrobial versus Surgical Treatment

Because of European studies, some have advocated that many cases of appendicitis can be treated successfully with intravenous antimicrobials alone (Flum, 2015; Joo, 2017). At this time, we discourage this practice until appropriate studies have been done with pregnant women. In one study, 6 percent of pregnant women with appendicitis were treated medically, and these gravidas had "considerably" elevated risks for septic shock, peritonitis, and venous thromboembolism compared with surgically managed cases (Abbasi, 2014).

Pregnancy Outcomes

Appendicitis increases the likelihood of abortion or preterm labor, especially if peritonitis has developed. In two studies, spontaneous labor after 23 weeks ensued with greater frequency following surgery for appendicitis compared with surgery for other indications (Cohen-Kerem, 2005; Mazze, 1991). In one study, the fetal loss rate was 22 percent if surgery was performed after 23 weeks' gestation. Two large population-based studies attest to the adverse outcomes from appendicitis in pregnancy. From the California Inpatient File of 3133 pregnant women undergoing surgery for suspected appendicitis, the fetal loss rate was 23 percent, and it was doubled—6 versus 11 percent—with simple versus complicated disease (McGory, 2007). A nationwide study from Taiwan found that risks for low birthweight and preterm delivery rose 1.5- to 2-fold when outcomes in 908 women with acute appendicitis were compared with those of controls (Wei, 2012).

Long-term complications are not common. The possible link between sepsis and neonatal neurological injury has not been verified (Mays, 1995). Finally, appendicitis during pregnancy does not appear to be associated with subsequent infertility (Viktrup, 1998).

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CHAPTER 55: Hepatic, Biliary, and Pancreatic Disorders

Pregnancy is comparatively seldom complicated by jaundice. Notwithstanding the fact that in most cases the jaundice disappears without treatment, too favorable a prognosis should not be ventured, for the reason that now and again the condition may represent the initial symptom of acute yellow atrophy of the liver.

—J. Whitridge Williams (1903)

INTRODUCTION

Even though Williams only mentions acute hepatic fatty metamorphosis, in practice, disorders of the liver, gallbladder, and pancreas together comprise a formidable list of complications that may arise in pregnancy. Some stem from preexisting conditions and some are unique to gestation. The relationships of several of these with pregnancy can be fascinating, intriguing, and challenging.

HEPATIC DISORDERS

Customarily, liver diseases complicating pregnancy are placed into three general categories. The first includes those specifically related to pregnancy that resolve either spontaneously or following delivery. Examples are intrahepatic cholestasis and acute fatty liver, both discussed in the next sections. Also, hepatic dysfunction from hyperemesis gravidarum may involve the liver. Mild hyperbilirubinemia with elevated serum transaminase levels is seen in up to half of affected women requiring hospitalization. However, these levels seldom exceed 200 U/L (Table 55-1). Liver biopsy may show minimal fatty changes. Hyperemesis gravidarum is discussed in detail in Chapter 54 (Upper Gastrointestinal Tract Disorders). Another in this first category is hepatocellular damage with preeclampsia—the *HELLP syndrome*—which is characterized by hemolysis, elevated serum liver enzyme levels, and low platelet counts. These changes are discussed in detail in Chapter 40 (Liver).

TABLE 55-1

Clinical and Laboratory Findings with Acute Liver Diseases in Pregnancy

			Hepatic		Renal	Hematological and Coagulation					
Disorder	**Onset in Pregnancy**	**Clinical Findings**	**AST (U/L)**	**Bili (mg/dL)**	**Cr (mg/dL)**	**Hct**	**Plat**	**Fib**	**DD**	**PT**	**Hemolysis**
Hyperemesis	Early	Severe N&V	NL–300	NL–4	↑	↑↑	NL	NL	NL	NL	No
Cholestasis	Late	Pruritus, jaundice	NL–200	1–5	NL	NL	NL	NL	NL	NL	No
Fatty liver	Late	Moderate N&V, ± HTN, liver failure	200–800	4–10	↑↑↑	↑↑↑	↓↓	↓↓↓	↑	↑↑	↑↑↑
Preeclampsia	Mid to late	HA, HTN	NL–300	1–4	↑	↑	↓↓	NL	↑	NL	↑–↑↑
Hepatitis	Variable	Jaundice	2000+	5–20	NL	↑	↓	NL	NL	↑	No

↑ = increased levels; ↓ = decreased levels; AST = aspartate transaminase; Bili = bilirubin; Cr = creatinine; DD = d-dimers; Fib = fibrinogen; HA = headache; Hct = hematocrit; HTN = hypertension; N&V = nausea and vomiting; NL = normal; Plat = platelets; PT = prothrombin time.

The second category involves acute hepatic disorders that are coincidental to pregnancy, such as acute viral hepatitis. The third category includes chronic liver diseases that predate pregnancy, such as chronic hepatitis, cirrhosis, or esophageal varices.

Importantly, several normal pregnancy-induced physiological changes induce appreciable liver-related clinical and laboratory manifestations (Chap. 4, Gastrointestinal Tract, and Appendix, Serum and Blood Constituents). Findings such as elevated serum alkaline phosphatase levels, palmar erythema, and spider angiomas, which might suggest liver disease, are common during normal pregnancy. Metabolism is also affected, due to altered expression of the cytochrome P450 system. This alteration is mediated by higher levels of estrogen, progesterone, and other pregnancy hormones. For example, hepatic CYP1A2 expression declines, whereas that of CYP2D6 and CYP3A4 rises. Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta. The net effect is complex and likely influenced by gestational age and organ of expression (Isoherranen, 2013). Despite all of these functional changes, no major hepatic histological changes are induced by normal pregnancy.

Intrahepatic Cholestasis of Pregnancy

This condition has been called recurrent jaundice of pregnancy, cholestatic hepatosis, and icterus gravidarum and is characterized by pruritus, icterus, or both. It may be more common in multifetal pregnancy, and there is a significant genetic influence (Lausman, 2008; Webb, 2014). Because of this, its incidence varies by population. For example, cholestasis is infrequent in North America, with an overall incidence approximating 1 case in 500 to 1000 pregnancies. But, its rate nears 5.6 percent among Latina women in Los Angeles (Lee, 2006). Historically, indigenous women from Chile and Bolivia also have a relatively high incidence. For unknown reasons, this incidence has declined since the 1970s and is now less than 2 percent (Reyes, 2016). In other countries, for example Sweden, China, and Israel, the incidence varies from 0.25 to 1.5 percent (Glantz, 2004; Luo, 2015; Sheiner, 2006).

Pathogenesis

The cause of obstetrical cholestasis is unclear, but changes in various sex steroid levels are implicated. However, current research focuses on the numerous mutations in the many genes that control hepatocellular transport systems. Examples include mutations of the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3) associated with *progressive familial intrahepatic cholestasis,* and errors of the *ABCB11* gene, which encodes a bile-salt export pump (Anzivino, 2013; Dixon, 2014). Other potential gene products are the farnesoid X receptor and transporting ATPase encoded by *ATP8B1* (Abu-Hayyeh, 2016; Davit-Spraul, 2012). Some drugs that similarly decrease canalicular transport of bile acids aggravate the disorder. We have encountered impressive cholestatic jaundice in gravidas taking azathioprine following renal transplantation.

Whatever the inciting cause(s), bile acids are cleared incompletely and accumulate in plasma. Hyperbilirubinemia results from retention of conjugated pigment, but total plasma concentrations rarely exceed 4 to 5 mg/dL. Alkaline phosphatase levels are usually elevated even more than in normal pregnancy. Serum transaminase levels are normal to moderately elevated but seldom exceed 250 U/L (see Table 55-1). Liver biopsy shows mild cholestasis with bile plugs in the hepatocytes and canaliculi of the centrilobular regions, but without inflammation or necrosis. These changes disappear after delivery but often recur in subsequent pregnancies or with estrogen-containing contraceptives.

Clinical Presentation

Pruritus develops in late pregnancy, although it occasionally manifests earlier. Constitutional symptoms are absent, and generalized pruritus shows predilection for the soles. Skin changes are limited to excoriations from scratching. Biochemical tests may be abnormal at presentation, but pruritus may precede laboratory findings by several weeks. Approximately 10 percent of women have jaundice.

With normal liver enzymes, the differential diagnosis of pruritus includes other skin disorders (Table 62-1). Findings are unlikely to stem from preeclamptic liver disease if blood pressure elevation or proteinuria is absent. Sonography may be warranted to exclude cholelithiasis and biliary obstruction. Moreover, *acute viral hepatitis* is an unlikely diagnosis because of the usually low serum transaminase levels seen with cholestasis. Conversely, *chronic hepatitis C* is associated with a significantly increased risk of cholestasis, which may be as high as 20-fold among women who test positively for hepatitis C RNA (Marschall, 2013).

Management

Pruritus may be troublesome and is thought to result from elevated serum bile salt concentrations. *Antihistamines* and *topical emollients* may provide some relief. Although cholestyramine is reported to be effective, this compound also lowers absorption of fat-soluble vitamins, which may lead to vitamin K deficiency. Fetal coagulopathy with subsequent intracranial hemorrhage and stillbirth have been reported (Matos, 1997; Sadler, 1995).

A recent metaanalysis suggests that *ursodeoxycholic acid* relieves pruritus, lowers bile acid and serum enzyme levels, and may reduce certain neonatal complications. These include preterm birth, fetal distress, respiratory distress syndrome, and neonatal intensive care unit (NICU) admission (Bacq, 2012). Kondrackiene and associates (2005) randomly assigned 84 symptomatic women to receive either ursodeoxycholic acid (8 to 10 mg/kg/d) or cholestyramine. They reported superior relief with ursodeoxycholic acid—67 versus 19 percent, respectively. Similarly, Glantz and coworkers (2005) found superior benefits to women randomly assigned to ursodeoxycholic acid versus dexamethasone. The American College of Obstetricians and Gynecologists (2015) has concluded that ursodeoxycholic acid relieves pruritus and improves fetal outcomes, although evidence for the latter is not compelling.

Pregnancy Outcomes

Earlier reports describe excessive adverse pregnancy outcomes in women with cholestatic jaundice. That said, data accrued during the past two decades are ambiguous concerning increased perinatal mortality rates and whether close fetal surveillance is preventative. Several studies also illustrate this. In one

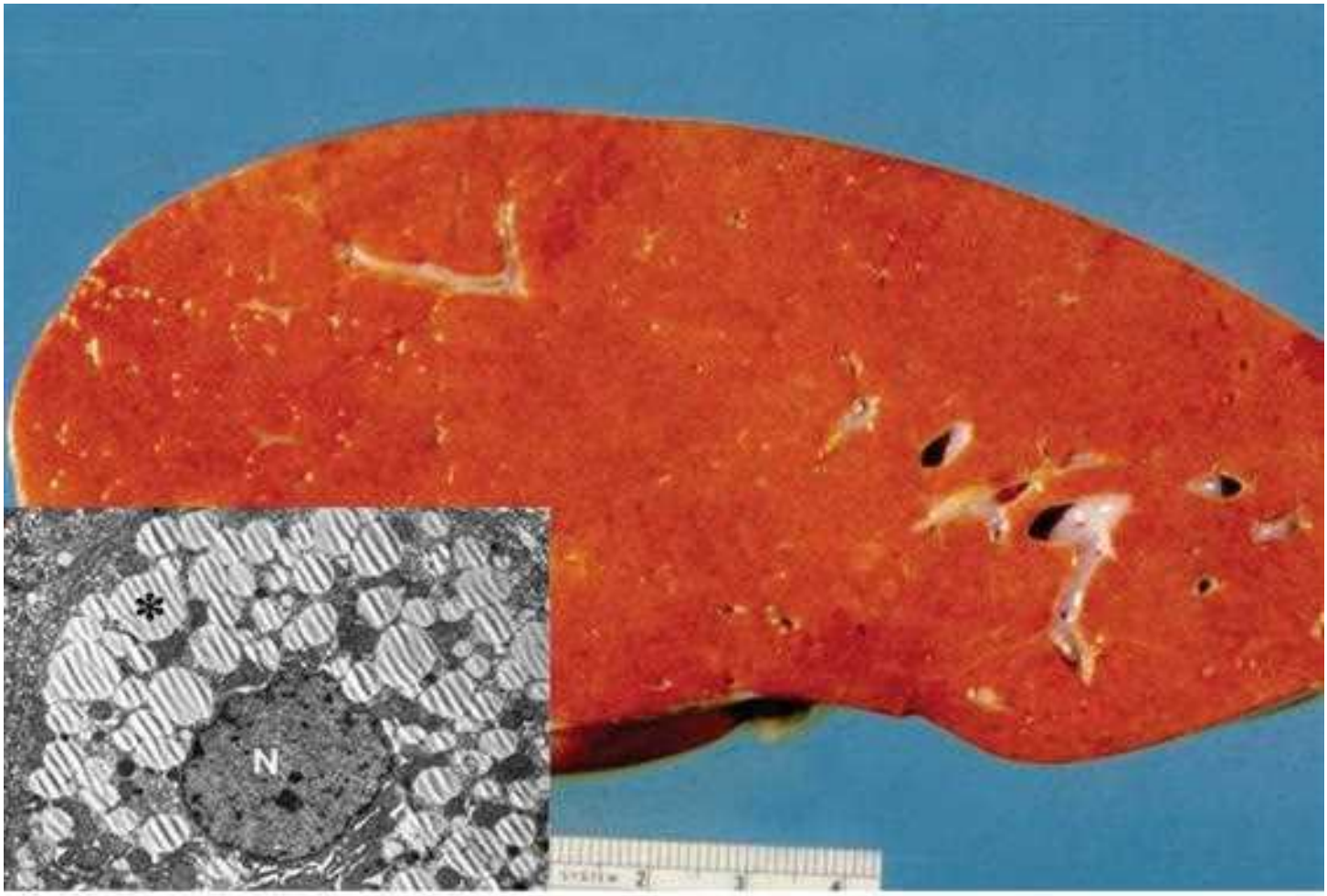
evaluation of 693 Swedish women, perinatal mortality rates were slightly increased, but only in mothers with severe disease (Glantz, 2004). Sheiner and coworkers (2006) described no differences in perinatal outcomes in 376 affected pregnancies compared with their overall obstetrical population. However, rates of labor induction and cesarean delivery in affected women significantly rose. Lee and associates (2009) described two cases of sudden fetal death not predicted by nonstress testing. In another study of 101 affected women, no term fetuses died, but 87 percent of women underwent labor induction, ostensibly to avoid adverse outcomes (Rook, 2012). Nonetheless, neonatal complications developed in a third of the pregnancies, particularly respiratory distress, fetal distress, and meconium-stained amnionic fluid. These problems were noted more frequently in those with higher total bile acid levels. Herrera and coworkers (2017) reported similar results. Finally, Wikström Shemer and colleagues (2013) reported outcomes in 5477 women with cholestasis from a database of 1,213,668 births. They described novel associations of cholestasis with preeclampsia and gestational diabetes. Although neonates were more likely to have a low 5-minute Apgar score and to be large for gestational age, the stillbirth rate was not increased. This was thought to reflect higher induction and preterm birth rates. Thus, by this time, many had now recommended early labor induction to avoid stillbirth. Reflecting this, at Parkland Hospital, some maternal-fetal specialists offer induction at 38 weeks, whereas others suggest 39 weeks.

As discussed, some evidence supports that high serum bile acid levels may contribute to fetal death. Bile acids typically remain <10 µmol/L throughout normal pregnancy (Egan, 2012). Elevated levels have been associated with meconium passage and stillbirth. For example, in the prior study of 693 Swedish women, stillbirths were limited to women with bile acid levels >40 µmol/L (Glantz, 2004). More recent data indicate that adverse outcomes are associated with even higher bile acid levels. For instance, Brouwers and coworkers (2015) reported high rates of spontaneous preterm birth (19 percent), meconium-stained amnionic fluid (48 percent), and perinatal death (10 percent) with bile acids levels >100 µmol/L despite active management leading to earlier delivery. Kawakita and colleagues (2015) found a similar stillbirth link. In particular, among 233 women followed with cholestasis of pregnancy, there were four stillbirths, all of which were among women with bile acid levels >100 µmol/L. Gao and associates (2014) implicated bile acids in cardiac dysfunction. Namely, in an ex-vivo preparation of cardiac myocytes, cholic acid lowered the beating rates in a dose-dependent manner, while increasing intracellular calcium levels. Intriguingly, studies have shown prolongations in the PR interval during fetal echocardiography among affected women (Rodríguez, 2016; Strehlow, 2010).

Acute Fatty Liver of Pregnancy

The most frequent cause of acute liver failure during pregnancy is acute fatty liver—also called *acute fatty metamorphosis* or *acute yellow atrophy.* It is characterized by accumulation of microvesicular fat that literally “crowds out” normal hepatocytic function (Fig. 55-1). Grossly, the liver is small, soft, yellow, and greasy. In its worst form, the incidence approximates 1 case in 10,000 pregnancies (Nelson, 2013). Fatty liver recurring in subsequent pregnancy is rare, but a few cases have been described (Usta, 1994).

FIGURE 55-1
Acute fatty liver of pregnancy. Cross section of the liver from a woman who died as the result of pulmonary aspiration and respiratory failure. The liver has a greasy yellow appearance, which was present throughout the entire specimen. Inset: Electron photomicrograph of one swollen hepatocyte containing numerous microvesicular fat droplets (*). The nuclei (*N*) remain centered within the cell, in contrast to the case with macrovesicular fat deposition. (Used with permission from Dr. Don Wheeler.)



Etiopathogenesis

Although much has been learned about this disorder, interpretation of conflicting data has led to incomplete but interesting observations. For example, some if not most cases of maternal fatty liver are associated with recessively inherited mitochondrial abnormalities of fatty acid oxidation. These are similar to those in children with Reye-like syndromes. Several mutations have been described for the mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway. The most common are the *G1528C* and *E474Q* mutations of the gene on chromosome 2 that codes for long-chain-3-hydroxyacyl-CoA-dehydrogenase—known as LCHAD. There are other mutations for medium-chain acyl-CoA dehydrogenase—MCAD, as well as for carnitine palmitoyltransferase 1 (CPT1) deficiency (Santos, 2007; Ylitalo, 2005).

Sims and coworkers (1995) observed that some *homozygous* LCHAD-deficient children with Reye-like syndromes had *heterozygous* mothers with fatty liver. This was also seen in women with a compound heterozygous fetus. Although some conclude that *only* heterozygous LCHAD-deficient mothers are at risk when their fetus is homozygous, this is not always true (Baskin, 2010).

There is a controversial association between fatty acid β-oxidation enzyme defects and severe preeclampsia—especially in women with HELLP syndrome (Chap. 40, Liver). Most of these observations derive from retrospective study of mothers delivered of a child who later developed Reye-like syndrome. For example, one case-control study compared 50 mothers of children with a fatty-acid oxidation defect and 1250 mothers of matched control infants (Browning, 2006). During their pregnancy, 16 percent of mothers with an affected child developed liver problems compared with only 0.9 percent of control women. Problems included HELLP syndrome in 12 percent and fatty liver in 4 percent. Despite these findings, the clinical, biochemical, and histopathological findings are sufficiently disparate to suggest that severe preeclampsia, with or without HELLP syndrome, and fatty liver are distinct syndromes (American College of Obstetricians and Gynecologists, 2015; Sibai, 2007).

Clinical Findings

Acute fatty liver almost always manifests late in pregnancy. Nelson and colleagues (2013) described 51 affected women at Parkland Hospital with a mean gestational age of 37 weeks (range 31.7 to 40.9). Almost 20 percent were delivered at 34 weeks' gestation or earlier. Of these 51 women, 41 percent were nulliparous, and two thirds carried a male fetus. From other data, 10 to 20 percent of cases are in women with a multifetal gestation (Fesenmeier, 2005; Vigil-De Gracia, 2011).

Fatty liver has a clinical spectrum of severity. In the worst cases, symptoms usually develop over several days. Persistent nausea and vomiting are major complaints, and degrees of malaise, anorexia, epigastric pain, and progressive jaundice vary. Perhaps half of affected women have hypertension, proteinuria, and edema, alone or in combination—signs suggestive of preeclampsia. As shown in Tables 55-1 and 55-2, degrees of moderate to severe liver dysfunction are manifest by hypofibrinogenemia, hypoalbuminemia, hypocholesterolemia, and prolonged clotting times. Serum bilirubin levels usually are <10 mg/dL, and serum transaminase levels are modestly elevated and usually <1000 U/L.

TABLE 55-2

Laboratory Findings in 215 Women with Acute Fatty Liver of Pregnancy

	Most Abnormal Laboratory Values Mean ± 1 SD (range)[a]				
Series	**No.**	**Fibrinogen (mg/dL)**	**Platelets (10^3/μL)**	**Creatinine (mg/dL)**	**AST (U/L)**
Pereira (1997)	32	ND	123 (26–262)	2.7 (1.1–8.4)	99 (25–911)
Fesenmeier (2005)	16	ND	88 (22–226)	3.3 (0.5–8.6)	692 (122–3195)
Vigil-De Gracia (2011)	35	136 ± 80	86	—	280 ± 236
Nelson (2013)	51	147 ± 96 (27–400)	99 ± 68 (9–385)	2.0 ± 0.8 (0.7–5.0)	449 ± 375 (53–2245)
Xiong (2015)	25	ND	82 (16–242)	2.4 (0.8–5.9)	385 (10–2144)
Zhang (2016)	56	246 ± 186	145 ± 75	1.4 ± 0.9	260 ± 237
Estimated average	215	140	102	2.5	330

[a]Fibrinogen and platelet values listed reflect the nadir for each patient, whereas creatinine and AST values reflect peak values for each patient.

AST = aspartate transaminase; ND = not done.

In almost all severe cases, profound endothelial cell activation with capillary leakage causes hemoconcentration, acute kidney injury, ascites, and sometimes pulmonary permeability edema (Bernal, 2013). With severe hemoconcentration, uteroplacental perfusion is reduced and this, along with maternal acidosis, can cause fetal death even before presentation for care. Both maternal and fetal acidemia are associated with a high incidence of fetal jeopardy and a concordantly high cesarean delivery rate.

Hemolysis can be severe and evidenced by leukocytosis, nucleated red cells, mild to moderate thrombocytopenia, and elevated serum levels of lactic acid dehydrogenase (LDH). Because of hemoconcentration, however, the hematocrit is often within the normal range. The peripheral blood smear demonstrates echinocytosis, and hemolysis is thought to stem from effects of hypocholesterolemia on erythrocyte membranes (Cunningham, 1985).

The degree of clotting dysfunction also varies and can be serious and life threatening, especially if operative delivery is undertaken. Coagulopathy is caused by diminished hepatic procoagulant synthesis, although some evidence supports increased consumption from disseminated intravascular coagulopathy. As shown in Table 55-2, hypofibrinogenemia sometimes is profound. Of 51 women with fatty liver cared for at Parkland Hospital, almost a third had a plasma fibrinogen level nadir to <100 mg/dL (Nelson, 2014). Modest level elevations of serum d-dimers or fibrin-split products indicate an element of consumptive coagulopathy. Although usually modest, occasionally thrombocytopenia is marked (see Table 55-2). Again, among the group from Parkland Hospital, 20 percent had platelet counts <100,000/μL and 10 percent had platelet counts <50,000/μL (Nelson, 2014).

Various liver imaging techniques have been used to confirm the diagnosis, however, none are particularly reliable. Specifically, Castro and associates (1996) reported poor sensitivity for confirmation by sonography—three of 11 patients, computed tomography (CT)—five of 10, and magnetic resonance (MR) imaging—none of five. Similarly, in a prospective evaluation of the Swansea criteria proposed by Ch'ng and coworkers (2002), only a quarter of women had classic sonographic findings that include maternal ascites or an echogenic hepatic appearance (Knight, 2008). Our experiences are similar (Nelson, 2013).

The syndrome typically continues to worsen after diagnosis. Hypoglycemia is common, and obvious hepatic encephalopathy, severe coagulopathy, and some degree of renal failure each develop in approximately half of women. Fortunately, delivery arrests liver function deterioration.

We have encountered several women with a *forme fruste* of this disorder. Clinical involvement is relatively minor and laboratory aberrations—usually only hemolysis and a decreased plasma fibrinogen level—herald the syndrome. Thus, the spectrum of liver involvement varies from milder cases that go unnoticed or are attributed to preeclampsia, to overt hepatic failure with encephalopathy.

Management

Intensive supportive measures and good obstetrical care are essential. In some cases, the fetus may already be dead when the diagnosis is made, and the route of delivery is less problematic. Often, living fetuses tolerate labor poorly. Because significant procrastination in effecting delivery may increase maternal and fetal risks, we prefer a trial of labor induction with close fetal surveillance. Although some recommend cesarean delivery to hasten hepatic healing, this increases maternal risk when coagulopathy is severe. Nonetheless, cesarean delivery is common, and rates approach 90 percent. Transfusions with whole blood or packed red cells, along with fresh-frozen plasma, cryoprecipitate, and platelets, are usually necessary if surgery is performed or if obstetrical lacerations complicate vaginal delivery (Chap. 41, Hypovolemic Shock).

Hepatic dysfunction resolves postpartum. It usually normalizes within a week, and in the interim, intensive medical support may be required. Two associated conditions can be seen around this time. Perhaps a fourth of women have evidence for *transient diabetes insipidus.* This presumably stems from elevated vasopressinase concentrations caused by diminished hepatic production of its inactivating enzyme. Finally, *acute pancreatitis* develops in approximately 20 percent.

With supportive care, recovery usually is complete. Maternal deaths are caused by sepsis, hemorrhage, aspiration, renal failure, pancreatitis, and gastrointestinal bleeding. Two women died in the series from Parkland Hospital. One was an encephalopathic woman who aspirated before intubation during transfer to our care. The other was in a woman with massive liver failure and nonresponsive hypotension (Nelson, 2013). In some centers, other measures have included plasma exchange and even liver transplantation (Fesenmeier, 2005; Franco, 2000; Martin, 2008).

Maternal and Perinatal Outcomes

Although maternal mortality rates with acute fatty liver of pregnancy have approached 75 percent in the past, the contemporaneous outlook is much better. From his review, Sibai (2007) cites an average mortality rate of 7 percent. He also cited a 70-percent preterm delivery rate and a perinatal mortality rate of 15 percent, which in the past was nearly 90 percent. At Parkland Hospital, the maternal and perinatal mortality rates during the past four decades have been 4 percent and 12 percent, respectively (Nelson, 2013).

Acute Viral Hepatitis

Although most viral hepatitis syndromes are asymptomatic, during the past 30 years, acute symptomatic infections have become even less common in the United States (Daniels, 2009). There are at least five distinct types of viral hepatitis: A (HAV), B (HBV), D (HDV) caused by the hepatitis B-associated delta agent, C (HCV), and E (HEV). The clinical presentation is similar in all, and although the viruses themselves probably are not hepatotoxic, the immunological response to them causes hepatocellular necrosis (Dienstag, 2015a,b).

Acute infections are most often subclinical and *anicteric*. When they are clinically apparent, nausea and vomiting, headache, and malaise may precede jaundice by 1 to 2 weeks. Low-grade fever is more common with hepatitis A. By the time jaundice develops, symptoms are usually improving. Serum transaminase levels vary, and their peaks do not correspond with disease severity (see Table 55-1). Peak levels that range from 400 to 4000 U/L are usually reached by the time jaundice develops. Serum bilirubin values typically continue to rise, despite falling serum transaminase levels, and peak at 5 to 20 mg/dL.

Any evidence for severe disease should prompt hospitalization. These include persistent nausea and vomiting, prolonged prothrombin time, low serum albumin level, hypoglycemia, high serum bilirubin level, or central nervous system symptoms. In most cases, however, clinical and biochemical recovery is complete within 1 to 2 months in all cases of hepatitis A, in most cases of hepatitis B, but in only a small proportion of cases of hepatitis C.

When patients are hospitalized, their feces, secretions, bedpans, and other articles in contact with the intestinal tract should be handled with glove-protected hands. Extra precautions, such as double gloving during delivery and surgical procedures, are recommended. Due to significant exposure of health-care personnel to hepatitis B, the Centers for Disease Control and Prevention (CDC) (2016a) recommend active and passive vaccination, described later. There is no vaccine for hepatitis C, so recommendations are for postexposure serosurveillance only.

Acute hepatitis has a case-fatality rate of 0.1 percent. For patients ill enough to be hospitalized, it may reach 1 percent. Most fatalities are due to *fulminant hepatic necrosis,* which in later pregnancy may resemble acute fatty liver. In these cases, hepatic encephalopathy is the usual presentation, and the mortality rate is 80 percent. Approximately half of patients with fulminant disease have hepatitis B infection, and co-infection with the delta agent is common.

Chronic Viral Hepatitis

The CDC (2016b) estimated that more than 4 million Americans were living with chronic viral hepatitis. Although most chronically infected persons are asymptomatic, approximately 20 percent develop cirrhosis within 10 to 20 years (Dienstag, 2015b). When present, symptoms are nonspecific and usually include fatigue. In some patients, cirrhosis with liver failure or bleeding varices may be the presenting finding. Indeed, asymptomatic chronic viral hepatitis as a group remains the leading cause of liver cancer and the most frequent reason for liver transplantation.

Chronic viral hepatitis is usually diagnosed serologically (Table 55-3). With persistently abnormal biochemical tests, liver biopsy usually discloses active inflammation, continuing necrosis, and fibrosis that may lead to cirrhosis. Chronic hepatitis is classified by cause; by grade, defined by histological activity; and by stage, which is the degree of progression (Dienstag, 2015b).

TABLE 55-3

Simplified Diagnostic Approach in Patients with Hepatitis

	Serological Test			
Diagnosis	**HBsAg**	**IgM Anti-HAV**	**IgM Anti-HBc**	**Anti-HCV**
Acute hepatitis A	–	+	–	–
Acute hepatitis B	+	–	+	–
Chronic hepatitis B	+	–	–	–
Acute hepatitis A with chronic B	+	+	+	–
Acute hepatitis A and B	+	+	+	
Acute hepatitis C	–	–	–	+

HAV = hepatitis A virus; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Compiled from the Centers for Disease Control and Prevention, 2016b; Dienstag, 2015a.

Most young women with chronic viral hepatitis either are asymptomatic or have only mild liver disease. For seropositive asymptomatic women, there usually are no problems with pregnancy. With *symptomatic* chronic active hepatitis, pregnancy outcome depends primarily on disease and fibrosis severity, and especially on the presence of portal hypertension. The few women whom we have managed have done well, but their long-term prognosis is poor. Accordingly, they should be counseled regarding possible liver transplantation as well as abortion and sterilization options.

Hepatitis A

Vaccination has reduced the incidence of hepatitis by 95 percent since 1995. In 2014, the rate was 0.4 per 100,000 individuals (Centers for Disease Control and Prevention, 2016b). This 27-nm RNA picornavirus is transmitted by the fecal–oral route, usually by ingestion of contaminated food or water. The incubation period is approximately 4 weeks. Individuals shed virus in their feces, and during the relatively brief period of viremia, their blood is also infectious. Signs and symptoms are often nonspecific and usually mild, although jaundice develops in most patients. Symptoms usually last less than 2 months, although 10 to 15 percent of patients may remain symptomatic or relapse for up to 6 months (Dienstag, 2015a). Early serological testing identifies IgM anti-HAV antibody, which may persist for several months. During convalescence, IgG antibody predominates, and it persists and provides subsequent immunity. There is no chronic stage of hepatitis A.

Management of hepatitis A in pregnancy includes a balanced diet and diminished physical activity. Women with less severe illness may be managed as outpatients. In developed countries, the effects of hepatitis A on pregnancy outcomes are not dramatic (American College of Obstetricians and Gynecologists, 2015, 2016). Both perinatal and maternal mortality rates, however, are substantively increased in resource-poor countries. Hepatitis A virus is not teratogenic, and transmission to the fetus is negligible. Preterm birth rates may be increased, and neonatal cholestasis has been reported (Urganci, 2003). Although hepatitis A RNA has been isolated in breast milk, no cases of neonatal hepatitis A have been reported secondary to breastfeeding (Daudi, 2012).

Preventatively, vaccination during childhood with formalin- inactivated hepatitis viral vaccine is more than 90-percent effective. HAV vaccination is recommended by the American College of Obstetricians and Gynecologists (2016) and the Advisory Committee on Immunization (Kim, 2015a) for high-risk adults. This category includes behavioral and occupational populations and travelers to high-risk countries. These countries are listed in the CDC (2016c) Health Information for International Travel “yellow book,” which is available on the CDC website. Passive immunization for the pregnant woman recently exposed by close personal or sexual contact with a person with hepatitis A is provided by a 0.02 mL/kg dose of immune globulin (Kim, 2015a). Victor and colleagues (2007) reported that a single dose of HAV vaccine given in the usual dosage within 2 weeks of contact with an affected person was as effective as immune serum globulin to prevent hepatitis A. In both groups, HAV developed in 3 to 4 percent.

Hepatitis B

This double-stranded DNA virus is found worldwide. It is endemic in Africa, Central and Southeast Asia, China, Eastern Europe, the Middle East, and certain areas of South America, where prevalence rates reach 5 to 20 percent. The World Health Organization (WHO) (2009) estimates that more than 2 billion people worldwide are infected with HBV, and of these, 370 million have chronic infection. The CDC (2016b) estimated nearly 18,100 cases of acute hepatitis B in the United States in 2014. This is a substantial decline since vaccination was introduced in the 1980s.

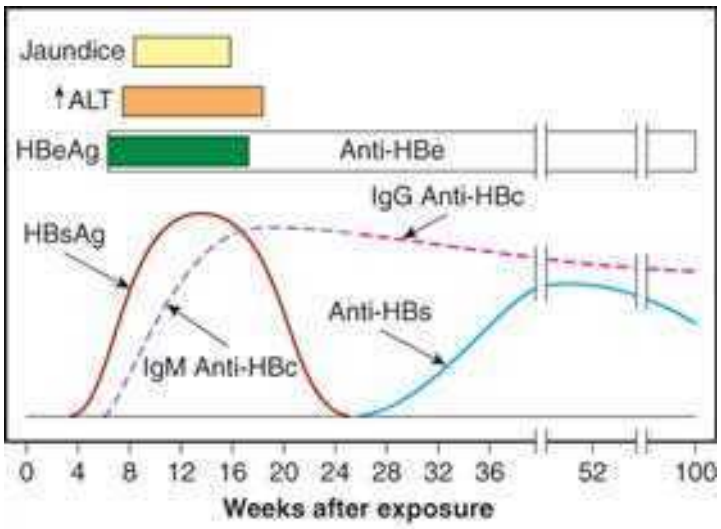
The hepatitis B virus is transmitted by exposure to blood or body fluids from infected individuals. In endemic countries, vertical transmission, that is, from mother to fetus or newborn, accounts for at least 35 to 50 percent of chronic HBV infections. In low-prevalence countries such as the United States, which has a prevalence <2 percent, the more frequent mode of HBV transmission is by sexual transmission or by sharing contaminated needles. HBV can be transmitted in any body fluid, but exposure to virus-laden serum is the most efficient.

Acute hepatitis B develops after an incubation period of 30 to 180 days with a mean of 8 to 12 weeks. At least half of acute infections are asymptomatic. If symptoms are present, they are usually mild and include anorexia, nausea, vomiting, fever, abdominal pain, and jaundice. Acute HBV accounts for half of cases of fulminant hepatitis. Symptoms completely resolve within 3 to 4 months in more than 90 percent of patients.

Figure 55-2 details the sequence of the various HBV antigens and antibodies in acute infection. The first serological marker to be detected is the hepatitis B surface antigen (HBsAg), often preceding the increase in transaminase levels. As HBsAg disappears, antibodies to the surface antigen develop (anti-HBs), marking complete resolution of disease. Hepatitis B core antigen is an intracellular antigen and not detectable in serum. However, anti-HBc is detectable within weeks of HBsAg appearance. The hepatitis Be antigen (HBeAg) is present during times of high viral replication and often correlates with detectable HBV DNA. After acute hepatitis, approximately 90 percent of adults recover completely. The 10 percent who remain chronically infected are considered to have chronic hepatitis B.

FIGURE 55-2

Sequence of various antigens and antibodies in acute hepatitis B. ALT = alanine transaminase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen. (Reproduced with permission from Dienstag JL: Acute viral hepatitis. In Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. New York, McGraw-Hill Education, 2015).



Chronic HBV infection is often asymptomatic but may be clinically suggested by persistent anorexia, weight loss, fatigue, and hepatosplenomegaly. Extrahepatic manifestations may include arthritis, generalized vasculitis, glomerulonephritis, pericarditis, myocarditis, transverse myelitis, and peripheral neuropathy. One risk factor for chronic disease is age at acquisition. It is more than 90 percent in newborns, 50 percent in young children, and less than 10 percent in immunocompetent adults. Another risk is an immunocompromised state such as those with human immunodeficiency virus (HIV) infection, transplant recipients, or persons receiving chemotherapy. Chronically infected persons may be asymptomatic carriers or have chronic disease with or without cirrhosis. Patients with chronic disease have persistent HBsAg serum positivity. The patients with evidence of high viral replication—HBV DNA with or without HBeAg—have the highest likelihood of developing cirrhosis and hepatocellular carcinoma. The WHO considers hepatitis B to be second only to tobacco among human carcinogens. HBV DNA has been found to be the best correlate of liver injury and disease progression risk.

Pregnancy and Hepatitis B

Hepatitis B infection is not a cause of excessive maternal morbidity and mortality. It is often asymptomatic and found only on routine prenatal screening (Stewart, 2013). A review of data from the National Inpatient Sample reported a modest increase in preterm birth rates in HBV-positive mothers but no effect on fetal growth restriction or preeclampsia rates (Reddick, 2011). Others have shown similar results (Chen, 2015). Transplacental viral infection is uncommon, and Towers and associates (2001) reported that viral DNA is rarely found in amnionic fluid or cord blood. Interestingly, HBV DNA has been found in the ovaries of HBV-positive pregnant women, although this may not be a significant factor in perinatal transmission (Jin, 2016b). The highest HBV DNA levels were found in women who transmitted the virus to their fetuses (Dunkelberg, 2015; Society for Maternal-Fetal Medicine, 2016).

In the absence of HBV immunoprophylaxis, 10 to 20 percent of women positive for HBsAg transmit viral infection to their infant. This rate increases to almost 90 percent if the mother is HBsAg and HBeAg positive. Immunoprophylaxis and hepatitis B vaccine given to newborns of HBV-infected mothers has

decreased transmission dramatically and prevented approximately 90 percent of infections (Smith, 2012). But, women with high HBV viral loads—10^6 to 10^8 copies/mL—or those who are HBeAg positive still have approximately a 10-percent vertical transmission rate, regardless of immunoprophylaxis (Yi, 2016).

The Society for Maternal–Fetal Medicine (2016) recommends antiviral therapy to decrease vertical transmission in women at highest risk because of high HBV DNA levels. Although lamivudine, a cytidine nucleoside analogue, significantly lowers the risk of fetal HBV infection in women with high HBV viral loads, recent data indicate that lamivudine may be less effective in the third trimester. Moreover, it is associated with the development of resistant mutations and is no longer recommended at a first-line agent. Newer drugs include the adenosine nucleoside analogue tenofovir and the thymidine analogue telbivudine. Both are associated with a lower risk of resistance than lamivudine (Ayres, 2014; Yi, 2016). Tenofovir has been recommended as the first-line agent during pregnancy by the Society for Maternal-Fetal Medicine (2016). These antiviral medications appear safe in pregnancy and are not associated with higher rates of congenital malformations or adverse obstetrical outcomes (Brown, 2016). Hepatitis B immunoglobulin (HBIG) given antepartum to women at highest risk of transmission is also cost-effective (Fan, 2016).

Newborns of seropositive mothers are given HBIG very soon after birth. This is accompanied by the first of a three-dose hepatitis B recombinant vaccine. Hill and colleagues (2002) applied this strategy in 369 infants and reported that the 2.4-percent transmission rate was not increased with breastfeeding if vaccination was completed. Although virus is present in breast milk, the incidence of transmission is not lowered by formula feeding (Shi, 2011). The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (2017) does not consider maternal HBV infection a contraindication to breastfeeding.

For high-risk mothers who are seronegative, hepatitis B vaccine can be given during pregnancy. The efficacy is similar to that for nonpregnant adults, and overall seroconversion rates approach 95 percent after three doses (Stewart, 2013). The traditional vaccination schedule of 0, 1, and 6 months may be difficult to complete during pregnancy, and compliance rates decline after delivery. Sheffield and coworkers (2011) reported that the three-dose regimen given prenatally—initially and at 1 and 4 months—resulted in seroconversion rates of 56, 77, and 90 percent, respectively. This regimen was easily completed during routine prenatal care.

Hepatitis D

Also called *delta hepatitis*, this is a defective RNA virus that is a hybrid particle with an HBsAg coat and a delta core. The virus must co-infect with hepatitis B either simultaneously or secondarily. It cannot persist in serum longer than hepatitis B virus. Transmission is similar to hepatitis B. Chronic co-infection with B and D hepatitis is more severe and accelerated than with HBV alone, and up to 75 percent of affected patients develop cirrhosis. HDV infection is detected by the presence of anti-HDV and HDV DNA. Neonatal transmission is unusual, as neonatal HBV vaccination usually prevents delta hepatitis.

Hepatitis C

This is a single-stranded RNA virus, and transmission occurs via blood and body fluids, although sexual transmission is inefficient. Up to a third of anti-HCV positive persons have no identifiable risk factors (Dienstag, 2015b). Screening for HCV is recommended for HIV-infected individuals, persons with injection drug use, hemodialysis patients, children born to mothers with HCV, persons exposed to HCV-positive blood or body fluids, persons with unexplained elevations in transaminase values, and recipients of blood or transplants before July 1992. Prenatal screening is recommended for high-risk women, and in the United States, seroprevalence rates reach 1 to 2.4 percent (American College of Obstetricians and Gynecologists, 2016; Arshad, 2011). It is higher in women who are infected with HIV. Santiago-Munoz and associates (2005) found that 6.3 percent of HIV-infected pregnant women at Parkland Hospital were co-infected with hepatitis B or C.

Acute HCV infection is usually asymptomatic or yields mild symptoms. Only 10 to 15 percent develop jaundice. The incubation period ranges from 15 to 160 days with a mean of 7 weeks. Transaminase levels are elevated episodically during the acute infection. Hepatitis C RNA testing is now preferred for HCV diagnosis. RNA levels may be found even before elevations of transaminase and anti-HCV levels. Specifically, anti-HCV antibody is not detected for an average of 15 weeks and in some cases up to a year (Dienstag, 2015a).

Nearly 80 to 90 percent of patients with acute HCV will be chronically infected. Although most remain asymptomatic, approximately 20 to 30 percent progress to cirrhosis within 20 to 30 years. Transaminase values fluctuate, and HCV RNA levels vary over time. Liver biopsy reveals chronic disease and fibrosis in up to 50 percent, however, these findings are often mild. Overall, the long-term prognosis for most patients is excellent.

Pregnancy and Hepatitis C

As expected, most pregnant women diagnosed with HCV have chronic disease. HCV infection was initially thought to have limited pregnancy effects. However, more recent reports have chronicled modestly increased fetal risks for low birthweight, NICU admission, preterm delivery, and mechanical ventilation (Berkley, 2008; Pergam, 2008; Reddick, 2011). In some women, these adverse outcomes may have been influenced by concurrent high-risk behaviors associated with HCV infection.

The primary adverse perinatal outcome is vertical transmission of HCV infection to the fetus-infant. This is higher in mothers with viremia (Indolfi, 2014; Joshi, 2010). Airoldi and Berghella (2006) cited a rate of 1 to 3 percent in HCV-positive, RNA-negative women compared with 4 to 6 percent in those who were RNA-positive. In a report from Dublin, the vertical transmission rate in 545 HCV-infected women was 7.1-percent in RNA-positive women compared with none in those who were RNA-negative (McMenamin, 2008). Some have found an even greater risk when the mother is co-infected with HIV (Snidjewind, 2015;

Tovo, 2016). Invasive prenatal diagnostic procedures have not been reported to increase transmission to the fetus. However, Rac and Sheffield (2014) note that few studies have addressed this possibility, and they recommend avoiding traversing the placenta during amniocentesis. Approximately two thirds of prenatal transmission cases occur peripartum. HCV genotype, invasive prenatal procedures, breastfeeding, and delivery mode are not associated with mother-to-child transmission. That said, invasive procedures such as internal electronic fetal heart rate monitoring are avoided. HCV infection is not a contraindication to breastfeeding.

No licensed vaccine is available for HCV prevention. The chronic HCV infection treatment has traditionally included alpha interferon (standard and pegylated), alone or in combination with ribavirin. This regimen is contraindicated in pregnancy because of the teratogenic potential of ribavirin in animals (Joshi, 2010). The initial 5-year review of the Ribavirin Pregnancy Registry found no evidence for human teratogenicity. However, the registry has enrolled fewer than half of the necessary numbers to allow a conclusive statement to be made (Roberts, 2010). The development and study of direct-acting and host-targeted antiviral drugs in the past decade shows great promise for chronic hepatitis C management (Liang, 2013; Lok, 2012; Poordad, 2013). Current interferon-free, ribavirin-free regimens are being evaluated, although no data are available for pregnant women.

Hepatitis E

This water-borne RNA virus usually is enterically transmitted by contaminated water supplies. Hepatitis E is probably the most common cause of acute hepatitis (Hoofnagle, 2012). It causes epidemic outbreaks in third-world countries with substantial morbidity and mortality rates. Pregnant women have a higher case-fatality rate than nonpregnant individuals. In a metaanalysis of nearly 4000 subjects from Asia and Africa, Jin and coworkers (2016a) reported maternal and fetal case-fatality rates of 21 and 34 percent, respectively. Fulminant hepatitis, although rare overall, is more common in gravidas and contributes to the increased mortality rates. An altered innate immune response to incipient hepatitis E infection during pregnancy, affecting macrophage function and toll-like receptor signaling, may be a factor in the development of fulminant hepatitis (Sehgal, 2015).

A recombinant HEV vaccine has been developed and licensed in China. It is >95 percent effective for 12 months after vaccination. Long-term efficacy is 87 percent, and protective titers are maintained for up to 4.5 years (Zhang, 2015). Preliminary data from inadvertently vaccinated pregnant women show no adverse maternal or fetal events (Wu, 2012). At this time, it is unclear if this Chinese-licensed vaccine is effective in other areas of the world where other genotypes predominate. Genotype 4 is most common in China, and types 2 and 3 are more common in the Americas. A Food and Drug Administration (FDA) approved vaccine is not available at this time.

Hepatitis E is found worldwide, and although the highest prevalence is in east Asia, the CDC (2015) lists Mexico as a highly endemic country. Seroprevalence rates vary by age and geography, but overall seroprevalence rates of 10 percent have been reported. Durango State has the highest rate (37 percent) (Fierro, 2016).

Hepatitis G

Hepatitis G is the former name of an RNA flavivirus now known as HPvG or human pegivirus. This blood-borne infection of the liver, spleen, bone marrow, and mononuclear cells of the peripheral blood does not actually cause hepatitis (Chivero, 2015). It is thought to infect 750 million people worldwide, with up to two times that many with evidence of past infection. It may modulate the immune response, particularly during co-infection with HIV. Currently, no treatment aside from basic blood and body fluid precautions is recommended. Vertical transmission (to the fetus/infant) and horizontal transmission (to peers) has been described (Trinks, 2014).

Autoimmune Hepatitis

This is a generally progressive chronic hepatitis that is important to distinguish from other forms. Autoimmune hepatitis is more common in women and frequently coexists with other types of autoimmune disease, particularly autoimmune thyroid disease and Sjögren syndrome. Symptoms are typical of acute and chronic hepatitis, but one quarter may be asymptomatic. Rates of cirrhosis vary worldwide, but in western countries autoimmune hepatitis is more common and is characterized by multiple autoimmune antibodies such as antinuclear antibodies (ANA) and anti–smooth muscle antibody. Type 2 autoimmune hepatitis has an even higher prevalence in females and typically a more aggressive presentation. The incidence peaks in childhood and adolescence, before peak reproductive years. Treatment employs corticosteroids, alone or combined with azathioprine. Failure to respond to these two agents is more frequent in those with type 2 disease, and nearly all women with type 2 disease require more intensive therapy that is sustained long term (Vierling, 2015). In some patients with progressive disease and cirrhosis, hepatocellular carcinoma develops. In general, autoimmune hepatitis—especially when severe—increases the risk of adverse pregnancy outcomes.

Westbrook and coworkers (2012) reported the outcomes of 81 pregnancies in 53 women. A third had a flare, and these were more common in those not taking medication and those with active disease in the year before conception. Maternal and fetal complications were higher among women with cirrhosis, particularly with respect to the risks of death or need for liver transplantation during the pregnancy or within 12 months postpartum. From one Swedish national database analysis, frequencies of preterm birth, low birthweight, and diabetes were higher, but not those of preeclampsia or cesarean delivery (Stokkeland, 2016). Danielsson Borssén (2016) reported stable or mild disease in 84 percent of 58 women who delivered 100 newborns. Nearly a fourth of cases were delivered before 38 weeks, and a postpartum flare developed in a third. Cirrhosis was present in 40 percent, and these women experienced more complications during pregnancy.

Iron and Copper Overload

Chronic hepatitis and cirrhosis can result from iron and copper overload. Iron overload may stem from a primary cause that is generally inherited, such as hereditary hemochromatosis, or originates secondary to complications of certain hemoglobinopathies. Many of the gene mutations underlying hereditary hemochromatosis involve hepcidin and result in dysregulated iron transport (Chap. 4, Iron Metabolism). Some of these mutations are more common in certain populations originating from northern Europe (Pietrangelo, 2016; Salgia, 2015). Cardiomyopathy, diabetes, joint disease, and skin changes can coexist with liver disease. Pregnancy outcomes associated with iron overload in hereditary hemochromatosis are driven by the degree of liver dysfunction, although higher iron levels may affect birthweight (Dorak, 2009).

A form of neonatal hemochromatosis that does not affect the mother is now thought to be alloimmune and is called *gestational alloimmune liver disease* (Anastasio, 2016). With this, maternal autoantibodies cross to the fetus and mediate dysfunction of iron homeostasis, although the antigenic target of these alloantibodies remains unclear. It is associated with significant neonatal morbidity and mortality, and frequently recurs in subsequent pregnancies. In these cases, antepartum treatment with intravenous immunoglobulin (IVIG) may improve outcomes (Feldman, 2013; Roumiantsev, 2015).

Copper overload leading to chronic hepatitis and cirrhosis is Wilson disease. This systematic condition can also manifest with cardiomyopathy, renal disease, neuropsychiatric symptoms, and certain endocrine abnormalities. A Kayser-Fleischer ring surrounding the iris is highly specific, but a suspected diagnosis generally requires genetic analysis. Autosomal recessive mutations of the *ATP7B* gene underlie this disorder. This gene codes for the P-type ATPase involved in copper transport to ceruloplasmin and bile (Bandman, 2015).

With Wilson disease, infertility may be present, but pregnancy outcomes among affected women who do conceive are influenced by disease severity. Malik and colleagues (2013) reported four cases in pregnancy, and three had associated gestational hypertension or preeclampsia. Maternal and neonatal outcomes were good, and the authors review chelation therapy with penicillamine and zinc sulfate in pregnancy. The American College of Gastroenterology states that few data guide which of the various chelating agents is best (Tran, 2016). These include penicillamine, zinc, and trientine, and any theoretical risks are outweighed by the risks of discontinuing therapy. The latter include not only hepatic decompensation, but also injury to the placenta and fetal liver. Accordingly, the American College of Gastroenterology recommends that pregnant women should continue their chelation therapy, although a dose reduction of 25 to 50 percent should be considered to promote wound healing in the event of a surgical delivery. As a reminder, copper ions regulate the activity of proteins essential to wound repair.

Nonalcoholic Fatty Liver Disease

This condition is frequently comorbid with obesity and is the most common chronic liver disease in the United States (Diehl, 2017). Its most severe form—*nonalcoholic steatohepatitis (NASH)*—is an increasingly recognized condition that may occasionally progress to hepatic cirrhosis. Nonalcoholic fatty liver disease (NAFLD) is a macrovesicular fatty liver condition that resembles alcohol-induced liver injury but is seen without this substance abuse. Obesity, type 2 diabetes, and hyperlipidemia—*syndrome X*—frequently coexist (Chap. 48, Pregnancy and Obesity). The current hypothesis suggests that these conditions may interact with other unknown etiological agents to cause multiple insults or "hits" leading to hepatic injury. For example, half of persons with type 2 diabetes have NAFLD, and insulin resistance has been postulated to act as one possible "hit" (Buzzetti, 2016). Browning and associates (2004) used MR spectroscopy to determine the prevalence of NAFLD in Dallas County and found that approximately a third of adults were affected. This varied by ethnicity, with 45 percent of Hispanics, 33 percent of whites, and 24 percent of blacks being affected. Most people—80 percent—found to have steatosis had normal liver enzymes. In a study of obese adolescents undergoing bariatric surgery, more than a third had fatty liver without hepatitis, whereas an additional 20 percent had borderline or definite NASH (Xanthakos, 2015).

Liver damage follows a progressive continuum from NAFLD to NASH and then to hepatic fibrosis that may progress to cirrhosis (Goh, 2016). Still, in most persons, the disease is usually asymptomatic, and it is a frequent explanation for elevated serum transaminase levels found in blood donors and during other routine screening. Indeed, NAFLD is the cause of elevated asymptomatic transaminase levels in up to 90 percent of cases in which other liver disease is ultimately excluded. It also is the most common cause of abnormal liver tests among adults in this country. Currently, weight loss along with control of diabetes and dyslipidemia is the only recommended treatment.

Fatty liver infiltration is probably much more common than realized in obese and diabetic gravidas. During the past decade, we encountered an increasing number of pregnant women with these disorders. Once severe liver injury, that is, acute fatty liver of pregnancy, is excluded, gravidas with fatty liver infiltration have no greater rates of adverse outcomes relative to liver involvement compared with pregnant women of similar weight. That said, some emerging data indicate that this condition may portend adverse pregnancy outcomes. In 110 pregnancies with NAFLD from the Swedish Medical Birth and the National Patient Registries, risks of gestational diabetes, preeclampsia, preterm birth, and low-birthweight newborns were two- to threefold greater than in unaffected women (Hagström, 2016). Yarrington and associates (2016) reported a high rate of gestational diabetes among nonobese women without liver disease, alcohol use, or diabetes, and who had elevated alanine transaminase levels in the first trimester. As the obesity endemic worsens, adverse effects of this liver disorder on pregnancy will be clarified.

Cirrhosis

Irreversible chronic liver injury with extensive fibrosis and regenerative nodules is the final common pathway for several disorders. *Laënnec cirrhosis* from chronic alcohol exposure is the most frequent cause in the general population. But in young women—including pregnant women—most cases are caused by

postnecrotic cirrhosis from chronic hepatitis B and C. Many cases of *cryptogenic cirrhosis* are now known to be caused by NAFLD (Goh, 2016). Clinical manifestations of cirrhosis include jaundice, edema, coagulopathy, metabolic abnormalities, and portal hypertension with gastroesophageal varices and with splenomegaly that may cause thrombocytopenia. The incidence of deep-vein thromboembolism is increased (Søgaard, 2009). The prognosis is poor, and 75 percent have progressive disease that leads to death in 1 to 5 years.

Women with symptomatic cirrhosis frequently are infertile. Those who become pregnant generally have poor outcomes. Common complications include transient hepatic failure, variceal hemorrhage, preterm delivery, fetal growth restriction, and maternal death (Tan, 2008). Outcomes are generally worse if esophageal varices coexist.

Another potentially fatal complication of cirrhosis arises from associated splenic artery aneurysms. Up to 20 percent of ruptures occur during pregnancy, and 70 percent of these rupture in the third trimester (Palatnik, 2017; Tan, 2008). In a review of 32 gravidas with aneurysm rupture, the mean aneurysm diameter was 2.25 cm, and in half of cases, the diameter was <2 cm (Ha, 2009). The 22-percent maternal mortality rate was likely related to the emergent presentation of these events. Parrish and colleagues (2015) described embolization of a 13 × 9 mm aneurysm in the third trimester leading to a splenic abscess and sepsis 3 weeks later.

Portal Hypertension and Esophageal Varices

In pregnant women, approximately half of cases of esophageal varices originate from cirrhosis or extrahepatic portal vein obstruction, which leads to portal system hypertension. Some cases of extrahepatic hypertension develop following portal vein thrombosis associated with one of the *thrombophilia syndromes* (Chap. 52, Thrombophilias). Others follow thrombosis from umbilical vein catheterization when the woman was a neonate, especially if she was born preterm.

With either intrahepatic or extrahepatic resistance to flow, portal vein pressure rises from its normal range of 5 to 10 mm Hg, and values may exceed 30 mm Hg. Collateral circulation develops that carries portal blood to the systemic circulation. Blood drains into the gastric, intercostal, and other veins to the esophageal system, where varices develop. Bleeding is usually from varices near the gastroesophageal junction, and hemorrhage can be torrential. Bleeding during pregnancy from varices occurs in a third to half of affected women and is the major cause of maternal mortality within this group (Tan, 2008).

Maternal prognosis with esophageal varices largely depends on whether these rupture. Mortality rates are higher if varices are associated with cirrhosis compared with rates for varices without cirrhosis—18 versus 2 percent, respectively. Perinatal mortality rates are high in women with varices and are worse if cirrhosis caused the varices. Increased rates of neonatal demise, preterm birth, low birthweight, preeclampsia, and postpartum hemorrhage have been reported (Puljic, 2016).

Treatment is the same as for nonpregnant patients. Preventatively, all patients with cirrhosis, including pregnant women, should undergo endoscopic screening for identification of variceal dilatation (Bacon, 2015). Beta-blocking drugs such as propranolol are given to reduce portal pressure and hence the bleeding risk (Bissonnette, 2015; Tran, 2016).

For acute bleeding and for prophylaxis, endoscopic band ligation is preferred to sclerotherapy as it avoids any potential risks of injecting sclerotherapeutic chemicals (Bissonnette, 2015; Tan, 2008). Acute medical management for bleeding varices verified endoscopically includes the intravenous (IV) vasoconstrictors octreotide or somatostatin along with endoscopic banding. Vasopressin is less often used (Bacon, 2015). *Balloon tamponade* using a triple-lumen tube placed into the esophagus and stomach to compress bleeding varices can be lifesaving if endoscopy is not available. An interventional radiology procedure—*transjugular intrahepatic portosystemic stent shunting (TIPSS)*—can also control bleeding from gastric varices that is unresponsive to other measures (Bissonnette, 2015; Tan, 2008). This procedure can be done electively in patients with prior variceal hemorrhage.

Acetaminophen Overdose Hepatotoxicity

This drug is the most common cause of acute liver failure in the United States (Lee, 2013). Acetaminophen is often used during pregnancy, and overdose–either accidentally or by attempted suicide–may lead to hepatocellular necrosis and acute liver failure (Bunchorntavakul, 2013). Massive necrosis causes a cytokine storm and multiorgan dysfunction. Early symptoms of overdose are nausea, vomiting, diaphoresis, malaise, and pallor. With an acute overdose, after a latent period of 24 to 48 hours, liver failure ensues and usually begins to resolve in 5 days. In a prospective Danish study, only 35 percent of patients who were treated for fulminant hepatic failure spontaneously recovered before being listed for liver transplantation (Schmidt, 2007).

The antidote is *N-acetylcysteine*, which must be given promptly. The drug is thought to increase glutathione levels, which aid metabolism of the toxic metabolite, *N*-acetyl-*p*- benzoquinoneimine. The need for treatment is based on projections of possible plasma hepatotoxic levels as a function of the time from acute ingestion. For this, many poison control centers use the nomogram established by Rumack and Matthew (1975). A plasma level is measured 4 hours after ingestion, and if the level is >150 µg/mL, treatment is given (Smilkstein, 1988). If plasma determinations are not available, empirical treatment is given if the ingested amount exceeded 7.5 g. An oral loading dose of 140 mg/kg of N-acetylcysteine is followed by 17 maintenance doses of 70 mg/kg every 4 hours for 72 hours of total treatment time. Both the oral and an equally efficacious IV dosing regimen have been reviewed by Hodgman and Garrard (2012). The drug has been reported to reach therapeutic concentrations in the fetus (Wiest, 2014).

After 14 weeks' gestation, the fetus has some cytochrome P450 activity necessary for metabolism of acetaminophen to the toxic metabolite. Riggs and colleagues (1989) reported follow-up data from the Rocky Mountain Poison and Drug Center in 60 women suffering overdose. The likelihood of maternal and

fetal survival was better if the antidote was given soon after overdose. At least one 33-week fetus appears to have died as a direct result of hepatotoxicity 2 days after maternal ingestion. In another case, Crowell and associates (2008) reported a case of acetaminophen overdose at 32 weeks' gestation. The woman had taken 9.75 grams of acetaminophen approximately 1.5 hours prior to arrival. With treatment, the patient survived and went on to deliver a healthy term neonate.

Focal Nodular Hyperplasia

This benign lesion of the liver is characterized in most cases by a well-delineated accumulation of normal but disordered hepatocytes that surround a central stellate scar. These usually can be differentiated from hepatic adenomas by magnetic resonance (MR) or computed tomographic (CT) imaging. Except in the rare situation of unremitting pain, surgery is rarely indicated, and most women remain asymptomatic during pregnancy. In one review of 20 cases in Germany, no woman had related complications during pregnancy (Rifai, 2013). Three women showed 20-percent tumor growth; in 10 patients, the tumor decreased in size; and the remaining seven were unchanged across pregnancy. Ramírez-Fuentes and associates (2013) studied 44 lesions with MR imaging in 30 women. Of the lesions, 80 percent were unchanged in size, and most of the remainder decreased in size. They concluded that size changes were unrelated to pregnancy, combination oral contraceptive (COC) use, or menopause. Notably, this lesion is not a contraindication to estrogen-containing contraceptives (Chap. 38, Transdermal Patch).

Hepatic Adenoma

This is an uncommon benign neoplasm but has a 5-percent risk of malignant transformation and a significant risk of rupture-associated hemorrhage, particularly in pregnancy. As just discussed, adenomas can usually be differentiated from focal nodular hyperplasia by MR or CT imaging. Adenomas have a 9:1 predominance among women and are strongly linked with COC use. The rupture risk progresses with lesion size, and surgery is generally recommended for tumors measuring >5 cm (Agrawal, 2015). Tran and colleagues (2016) recommend sonographic surveillance of hepatic adenomas during pregnancy. In one review of 27 cases in pregnancy, 23 became apparent in the third trimester and puerperium (Cobey, 2004). Bleeding complicated no tumors measuring <6.5 cm. However, 16 of 27 women (60 percent) with an adenoma presented with tumor rupture that resulted in seven maternal deaths and six fetal deaths. Of note, 13 of 27 women presented within 2 months postpartum, and in half, hemorrhage heralded rupture. Wilson and coworkers (2011) described two cases of bleeding hepatic adenoma during pregnancy. One was managed by laparoscopic segmental resection, and another, which followed liver biopsy, required open surgery. The authors discourage biopsy during pregnancy for suspected hepatic adenomas, and emphasize the feasibility of resection for problematic lesions.

Liver Transplantation

In 2013 in the United States, 5921 adult liver transplants were performed, and 34 percent of patients were women (Kim, 2015b). Currently, more than 65,000 recipients of liver transplant are living, and one literature review cited 450 pregnancies in 3026 women who had undergone transplantation (Deshpande, 2012). Although their live-birth rate of 80 percent and miscarriage rate compare favorably with those of the general population, risks of preeclampsia, cesarean delivery, and preterm birth are significantly elevated. A fourth of pregnancies were complicated by hypertension, approximately a third resulted in preterm birth, and in 10 percent, there was one or more rejection episodes (Table 55-4). Importantly, 4 percent of mothers had died within a year after delivery, but this rate is comparable to that in nonpregnant liver transplantation patients. Ghazali and associates (2016) analyzed the National Inpatient Sample database and found 2.1 liver transplants per 100,000 deliveries. Pregnancies after liver transplant had significantly greater risks of maternal and fetal complications, including hypertensive disorders, gestational diabetes, and postpartum hemorrhage. Rates of preterm birth, fetal growth restriction, and congenital anomalies were also increased. Mattila and colleagues (2017) found that half of the women they cared for had maternal complications.

TABLE 55-4

Pregnancy Complications (%) in 558 Pregnancies after Liver Transplantation

Series	No.	Preeclampsia/Hypertension	Cesarean Delivery	Rejection	Live Birth
Jain (2003)	49	2–8	45	24	100
Nagy (2003)	38	21	46	17	63
Christopher (2006)	71	13–28	28	17	70
Coscia (2010)	281	22–33	32	6	75
Jabiry-Zieniewicz (2011)	39	8–26	79	8	100
Blume (2013)	62	6	30	13	77
Weighted Average:	540	16–28	38	10	78

GALLBLADDER DISORDERS

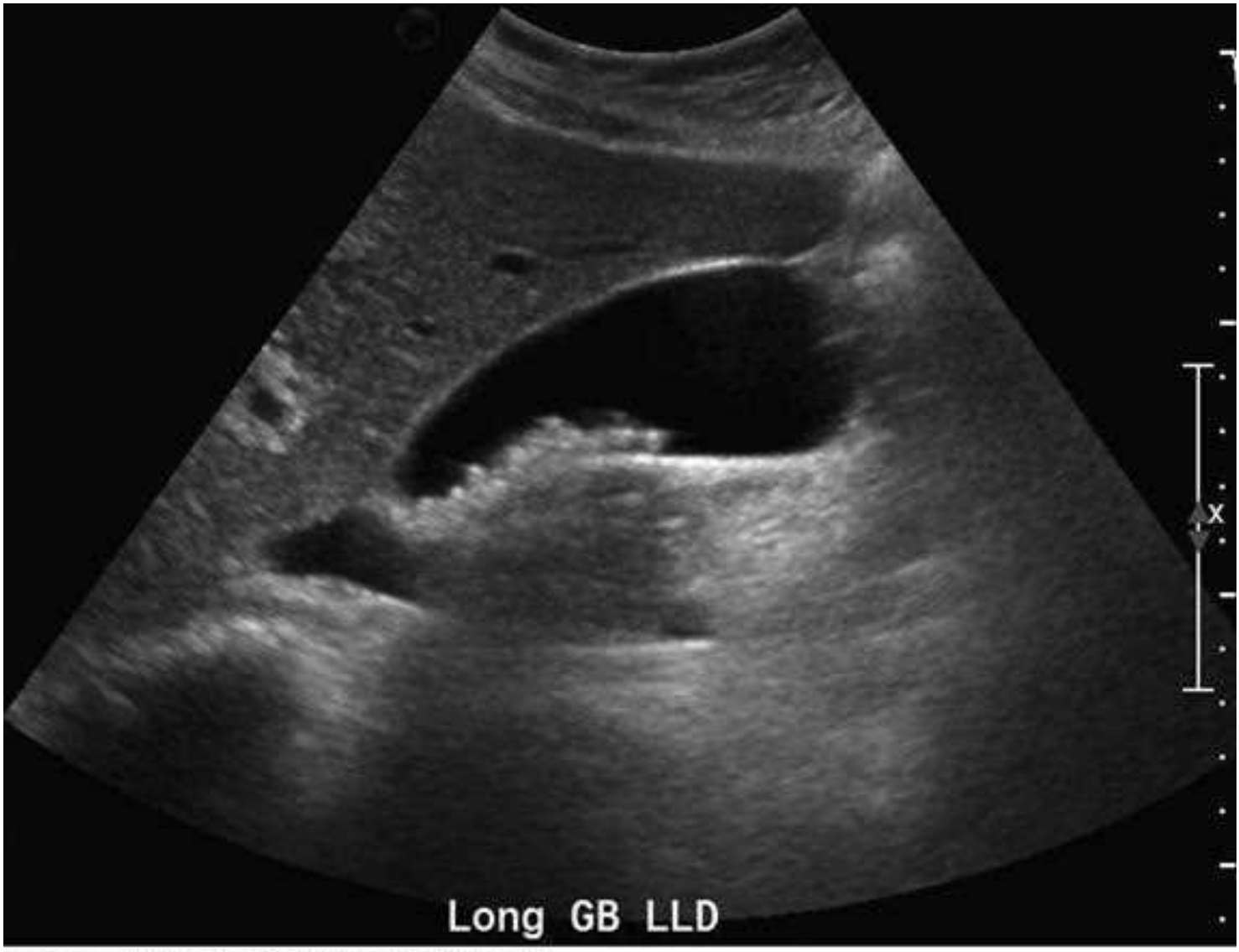
Cholelithiasis and Cholecystitis

In the United States, 20 percent of women older than 40 years have gallstones. Most stones contain cholesterol, and its oversecretion into bile is thought to be a major factor in stone formation. The cumulative risk of all patients with silent gallstones to require surgery for symptoms or complications is 10 percent at 5 years, 15 percent at 10 years, and 18 percent at 15 years (Greenberger, 2015). For these reasons, prophylactic cholecystectomy is not warranted for *asymptomatic* stones. For *symptomatic* gallstone disease, nonsurgical approaches have been used and include oral bile acid therapy with ursodeoxycholic acid and extracorporeal shock wave lithotripsy. Experience with these during pregnancy is lacking.

Acute cholecystitis usually develops when the cystic duct is obstructed. Bacterial infection plays a role in 50 to 85 percent of cases. In more than half of patients with acute cholecystitis, a history of prior right upper quadrant pain from cholelithiasis is elicited. With acute disease, pain is accompanied by anorexia, nausea and vomiting, low-grade fever, and mild leukocytosis. As shown in Figure 55-3, sonography can help visualize stones, and both false-positive and false-negative rates range from 2 to 4 percent (Greenberger, 2015). In acute cases, medical therapy consists of IV fluids, antimicrobials, analgesics, and in some instances, nasogastric suction, before surgical therapy. Laparoscopic cholecystectomy is the preferred treatment for most patients.

FIGURE 55-3

This sonogram shows multiple hyperechoic gallstones filling an anechoic gallbladder.



Gallbladder Disease During Pregnancy

After the first trimester, the gallbladder fasting volume and the residual volume after postprandial emptying are doubled. Incomplete emptying may result in retention of cholesterol crystals, a prerequisite for cholesterol gallstones. Maringhini and colleagues (1993) showed that the incidence of biliary sludge—which can be a forerunner to gallstones—and gallstones in pregnancy are 31 and 2 percent, respectively. Ko and colleagues (2014), however, cited a combined incidence of <5 percent. Others have identified asymptomatic gallstones in 2.5 to 10 percent of more than 1500 pregnant or postpartum women (Maringhini, 1993; Valdivieso, 1993).

Postpartum, sludge frequently regresses, and occasionally gallstones will resorb. Still, within a year after delivery, hospitalization for gallbladder disease remains relatively common, particularly for women managed conservatively in pregnancy. Jorge and coworkers (2015) reported that half of 53 women with symptomatic gallstones in pregnancy underwent postpartum cholecystectomy. In 80 percent of these women, recurrent symptoms developed prior to surgery, requiring readmission in half.

Medical versus Surgical Management

Acute cholecystitis during pregnancy or the puerperium is common and usually associated with gallstones or biliary sludge. Symptomatic cholecystitis is initially managed in a manner similar to that for nonpregnant women. In the past, most favored medical therapy. However, the recurrence rate during the same pregnancy is high, and 25 to 50 percent of women ultimately required cholecystectomy for persistent symptoms. Moreover, if cholecystitis recurs later in gestation, preterm labor is more likely and cholecystectomy is technically more difficult.

For these reasons, operative and endoscopic interventions are increasingly favored over conservative measures. Othman and coworkers (2012) showed that women managed conservatively had more pain, more recurrent visits to the emergency department, more hospitalizations, and a higher rate of cesarean delivery. Dhupar and associates (2010) reported more complications with conservative management of gallbladder disease compared with laparoscopic

cholecystectomy in pregnancy. These included multiple admissions, prolonged total parenteral nutrition, and unplanned labor induction for worsening gallbladder symptoms. Cholecystectomy was performed safely in all trimesters. Only one of 19 patients who underwent laparoscopic cholecystectomy had a complication, which did not require further surgery. A metaanalysis found that cholecystectomy does not increase the risk of preterm labor or of maternal or fetal mortality (Athwal, 2016). Management at Parkland Hospital has evolved to a more aggressive surgical approach, especially if there is concomitant biliary pancreatitis as subsequently discussed. During the past two decades, laparoscopic cholecystectomy has evolved as the favored surgical approach and is discussed in Chapter 46 (Medications and Surgeries).

Endoscopic Retrograde Cholangiopancreatography

Relief from symptomatic biliary duct gallstones during pregnancy has been greatly aided by use of endoscopic retrograde cholangiopancreatography (ERCP) (Fogel, 2014; Menees, 2006). The procedure is performed if common duct obstruction is suspected or proven. Approximately 10 percent of patients with symptomatic stone disease have common duct stones (Stinton, 2012). ERCP can be modified in many cases so that radiation exposure from fluoroscopy is avoided (Sethi, 2015).

Tang and associates (2009) reported results from 68 ERCP procedures performed in 65 pregnant women at Parkland Hospital. All but two women had gallstones, and sphincterotomy was performed in all but one woman. Common duct stones were identified in half of these 65 women, and in all but one, the stones were successfully removed. A biliary stent was placed in 22 percent of cases and removed after delivery. Complications were minimal, and post-ERCP pancreatitis developed in 16 percent. Pregnancy outcomes were not different than for the general obstetrical population. As a less invasive approach, MR cholangiopancreatography (MRCP) has been reported to have utility in pregnancy in small, retrospective case series. Wu and colleagues (2014) caution against its use in pregnancy, particularly for seriously ill women. Also, MRCP is not readily available, and this may lead to delayed definitive management.

Ascending cholangitis can complicate acute biliary obstruction. Nearly 70 percent of affected patients develop *Charcot triad*—jaundice, abdominal pain, and fever. The diagnosis is aided by sonography, and treatment is broad-spectrum antibiotics and biliary drainage by ERCP (Greenberger, 2015).

PANCREATIC DISORDERS

Pancreatitis

Acute pancreatic inflammation is triggered by factors that cause activation of pancreatic trypsinogen followed by autodigestion. It is characterized by cell-membrane disruption and proteolysis, edema, hemorrhage, and necrosis (Conwell, 2015; Fogel, 2014). Up to 10 percent of women develop necrotizing pancreatitis, which carries a mortality risk of 15 percent. This rate rises if infection develops (Cain, 2015).

In nonpregnant patients, acute pancreatitis is almost equally associated with gallstones and alcohol abuse. During pregnancy, however, cholelithiasis is almost always the predisposing condition. Other causes are hyperlipidemias, usually hypertriglyceridemia; hyperparathyroidism; congenital ductal anomalies; ERCP; some drugs; and rarely autoimmune pancreatitis (Cain, 2015; Ducarme, 2014). Nonbiliary pancreatitis occasionally develops postoperatively, or it is associated with trauma, drugs, or some viral infections. Certain metabolic conditions, including acute fatty liver of pregnancy and familial hypertriglyceridemia, also predispose to pancreatitis (Nelson, 2013). Cases of acute and chronic pancreatitis have been linked to numerous mutations of the cystic fibrosis transmembrane conductance regulator gene (Chang, 2015).

The incidence of pancreatitis varies with the population studied. At Parkland Hospital, with a predominant Mexican American population, acute pancreatitis complicated approximately 1 in 3300 pregnancies (Ramin, 1995). At Brigham and Women's Hospital, with a more diversely ethnic population, Hernandez and colleagues (2007) reported an incidence of 1 in 4450. In a multiple-institution Midwestern three-state review, the incidence of acute pancreatitis was 1 in 3450 (Eddy, 2008). In contrast, from California birth certificate data, the incidence approximated only 1 case in 6000 pregnancies (Hacker, 2015).

Diagnosis

Acute pancreatitis is characterized by mild to incapacitating epigastric pain, nausea and vomiting, and abdominal distention. Patients are usually distressed and have low-grade fever, tachycardia, hypotension, and abdominal tenderness. As many as 10 percent have systemic inflammatory response syndrome (SIRS), which causes endothelial activation and can lead to acute respiratory distress syndrome (Chap. 47, Sepsis Syndrome).

Of laboratory tests, serum amylase levels usually measure three times values considered the upper limit of normal. In 173 pregnant women with pancreatitis, the mean amylase value approximated 2000 IU/L, and the mean lipase value approached 3000 IU/L (Table 55-5). *Importantly, the degree of enzyme elevation and disease severity do not reliably correlate.* Indeed, by 48 to 72 hours, amylase levels may return to normal despite other evidence for continuing pancreatitis. Serum lipase activity is also increased and usually remains elevated with continued inflammation. Leukocytosis is usually found, and 25 percent of patients have hypocalcemia. Elevated serum bilirubin and aspartate transaminase levels may signify gallstone disease.

TABLE 55-5

Laboratory Values in 173 Pregnant Women with Acute Pancreatitis

Analyte	Mean	Range	Normal
Serum amylase (IU/L)	1980	111–8917	28–100
Serum lipase (IU/L)	3076	36–41,824	7–59
Total bilirubin (mg/dL)	1.7	0.1–8.71	0.2–1.3
Aspartate transferase (U/L)	115	11–1113	10–35
Leukocytes (per µL)	10,700	1000–27,200	3900–10,700

From Ramin, 1995; Tang, 2010; Turhan, 2010.

Several prognostic scoring systems have been used to classify pancreatitis severity, but not all of these are useful in pregnancy. For instance, two of the five Ranson criteria determined at admission include variables specific to nonpregnant patients. Similarly, certain criteria for the Apache II scoring system do not account for the changes in pregnancy physiology. In contrast, the Atlanta Classification incorporates the degree of organ failure as a measure of severity and may be more applicable in pregnancy (Banks, 2013; Cain, 2015).

Management

Medical treatment mirrors that for nonpregnant patients. This includes analgesics, IV hydration, and measures to decrease pancreatic secretion by interdiction of oral intake. Other than supportive therapy, antibiotics when appropriate, and targeted surgical interventions in the case of gallstone pancreatitis, no particular treatment schemes have improved outcomes. In a series by Ramin and colleagues (1995), all 43 affected pregnant women responded to conservative treatment and were hospitalized for a mean of 8.5 days. Nasogastric suction does not improve outcomes of mild to moderate disease, but enteral feeding may be helpful once pain improves and associated ileus resolves. For women with more severe pancreatitis and a prolonged disease course, total enteral nutrition using nasojejunal feeding is superior to total parenteral nutrition (Cain, 2015; Conwell, 2015). If there is bacterial superinfection of necrotizing pancreatitis, sepsis, or cholangitis, then broad-spectrum antimicrobials are administered. If common duct stones are found, then ERCP is indicated (Fogel, 2014; Tang, 2010). Cholecystectomy is considered after inflammation subsides because women with gallstonic pancreatitis carry an increased risk of recurrent pancreatitis (Cain, 2015).

Pregnancy outcomes are affected by acute pancreatitis severity. Eddy and associates (2008) reported a 30-percent preterm delivery rate, and 11 percent were delivered before 35 weeks' gestation. There were two pancreatitis-related maternal deaths. Importantly, almost a third of 73 women had recurrent pancreatitis during pregnancy. Of the 342 pregnancies complicated by pancreatitis in the California study, preterm delivery and fetal mortality rates were increased (Hacker, 2015). Also, preeclampsia risk was increased fourfold.

Pancreatic Transplantation

Few reports describe pregnancy following pancreas transplantation. Of 44 pregnancies in 73 women following pancreas-kidney transplantation, outcomes are encouraging, and vaginal delivery has been described (Mastrobattista, 2008). Although the incidence of hypertension, preeclampsia, preterm delivery, and fetal-growth restriction are high, there was only one perinatal death. Four rejection episodes developed during pregnancy and were treated successfully. Pancreatic islet autotransplantation may be performed to prevent diabetes following pancreatectomy, and at least three successful pregnancies have been reported (Jung, 2007).

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CHAPTER 56: Hematological Disorders

In the later months of pregnancy there is a slight increase in the amount of hemoglobin and red corpuscles and a slight increase in the number of white corpuscles, which become markedly accentuated during the first few days of the puerperium.

—J. Whitridge Williams (1903)

INTRODUCTION

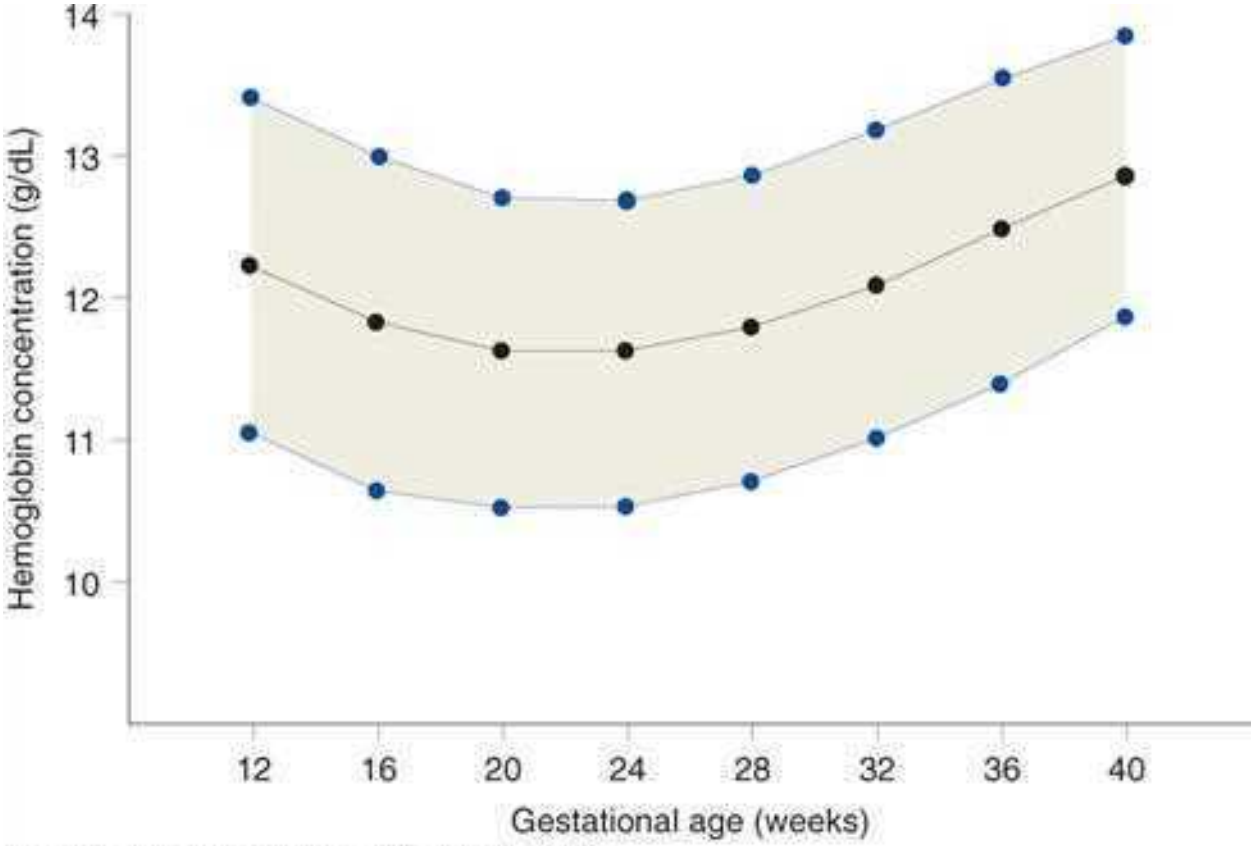
There is virtually nothing from the first edition of Williams' 1903 textbook that addresses the common anemias of pregnancy. Only pernicious anemia is devoted two paragraphs to say it occasionally appeared in pregnancy. Today, it is well known that pregnant women are susceptible to hematological abnormalities that may affect any woman of childbearing age. These include chronic disorders such as hereditary anemias, immunological thrombocytopenia, and malignancies such as leukemias and lymphomas. Other disorders arise during pregnancy because of pregnancy-induced demands. Two examples are iron deficiency and megaloblastic anemias. Pregnancy may also unmask underlying hematological disorders. Finally, any hematological disease may first arise during pregnancy. Importantly, pregnancy induces physiological changes that often confuse the diagnosis of these hematological disorders and assessment of their treatment (Chap. 4, Hematological Changes).

ANEMIAS

Definition and Incidence

Normal values for concentrations of many cellular elements during pregnancy are listed in the Appendix (Serum and Blood Constituents). The Centers for Disease Control and Prevention (1998) defined anemia in iron-supplemented pregnant women using a cutoff of the 5th percentile—11 g/dL in the first and third trimesters, and 10.5 g/dL in the second trimester (Fig. 56-1). The modest fall in hemoglobin levels and hematocrit values during pregnancy is caused by a relatively greater expansion of plasma volume compared with the increase in red cell volume. The disproportion between the rates at which plasma and erythrocytes are added to the maternal circulation is greatest during the second trimester. Late in pregnancy, plasma expansion essentially ceases, while hemoglobin mass continues to accrue.

FIGURE 56-1
Mean hemoglobin concentrations (*black line*) and 5th and 95th percentiles (*blue lines*) for healthy pregnant women taking iron supplements. (Data from the Centers for Disease Control and Prevention, 1989.)



The causes of more common anemias encountered in pregnancy are listed in Table 56-1. Their frequency is dependent on multiple factors such as geography, ethnicity, socioeconomic level, nutrition, preexisting iron status, and prenatal iron supplementation (American College of Obstetricians and Gynecologists, 2017a). In the United States, the prevalence of anemia in pregnancy is 3 to 38 percent (Centers for Disease Control and Prevention, 1989). In Latin America and the Caribbean, anemia prevalence ranges from 5 to 45 percent among women of childbearing age (Mujica-Coopman, 2015). Rates are also high in Israel, China, India, South Asia, and Africa (Azulay, 2015; Kumar, 2013, Stevens, 2013). Figure 56-2 highlights the global trends in hemoglobin concentrations and anemia thresholds in pregnant and nonpregnant women.

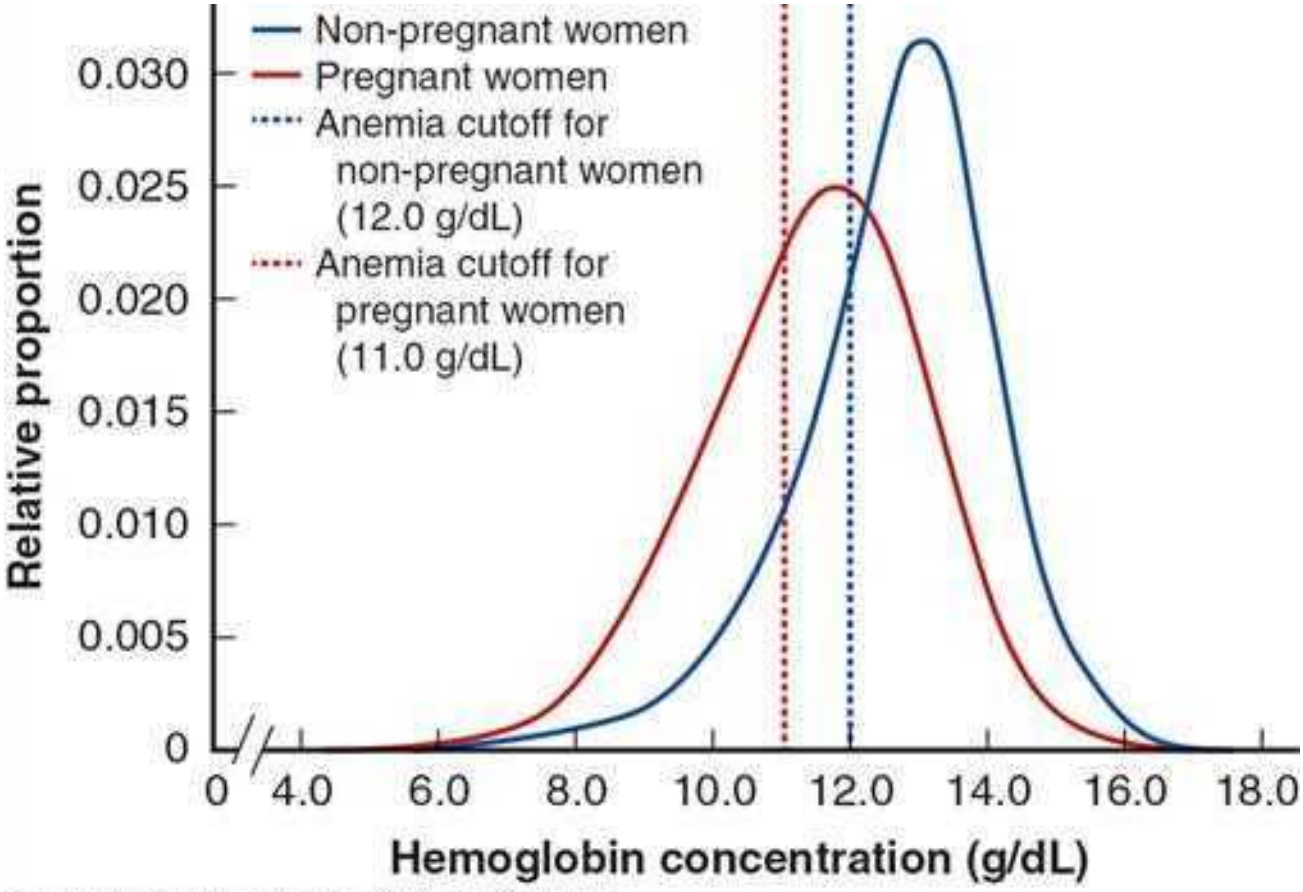
TABLE 56-1

Causes of Anemia During Pregnancy

Acquired
Iron-deficiency anemia
Anemia caused by acute blood loss
Anemia of inflammation or malignancy
Megaloblastic anemia
Acquired hemolytic anemia
Aplastic or hypoplastic anemia
Hereditary
Thalassemias
Sickle-cell hemoglobinopathies
Other hemoglobinopathies
Hereditary hemolytic anemias

FIGURE 56-2

Global trends in hemoglobin concentrations in pregnant and nonpregnant women. (Reproduced with permission from Stevens GA, Finucane MM, De-Regil LM, et al: Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data, Lancet Glob Health. 2013 Jul;1(1):e16–25.)



Effects on Pregnancy Outcomes

Most studies of anemia during pregnancy describe large populations and deal with nutritional anemias. Anemia is associated with several adverse pregnancy outcomes including preterm birth (Kidanto, 2009; Kumar, 2013; Rukuni, 2016). Children born to iron-deficient women and without iron supplementation are reported to have lower mental development scores (Drassinower, 2016; Tran, 2014).

A seemingly paradoxical finding is that healthy pregnant women with a higher hemoglobin concentration are also at greater risk for adverse perinatal outcomes (Murphy, 1986; von Tempelhoff, 2008). This may result from lower than average plasma volume expansion of pregnancy concurrent with normal red cell mass accrual. Scanlon and associates (2000) studied the relationship between maternal hemoglobin levels and rates of preterm or growth-restricted newborns in 173,031 pregnancies. Women whose hemoglobin concentration was three standard deviations *above* the mean at 12 or 18 weeks' gestation had a 1.3- to 1.8-fold greater incidence of fetal-growth restriction. Placental weight correlates negatively with maternal hemoglobin concentration (Larsen, 2016). These findings have led some to the illogical conclusion that withholding iron supplementation to cause iron-deficiency anemia will improve pregnancy outcomes (Ziaei, 2007).

Iron-Deficiency Anemia

The two most common causes of anemia during pregnancy and the puerperium are iron deficiency and acute blood loss. In a study of more than 1300 women, 21 percent had third-trimester anemia, and 16 percent had iron-deficiency anemia (Vandevijvere, 2013). In a typical singleton gestation, the maternal need for iron averages nearly 1000 mg. Multifetal gestational requirements are considerably higher (Ru, 2016). These amounts exceed the iron stores of most women and result in iron-deficiency anemia unless supplementation is given.

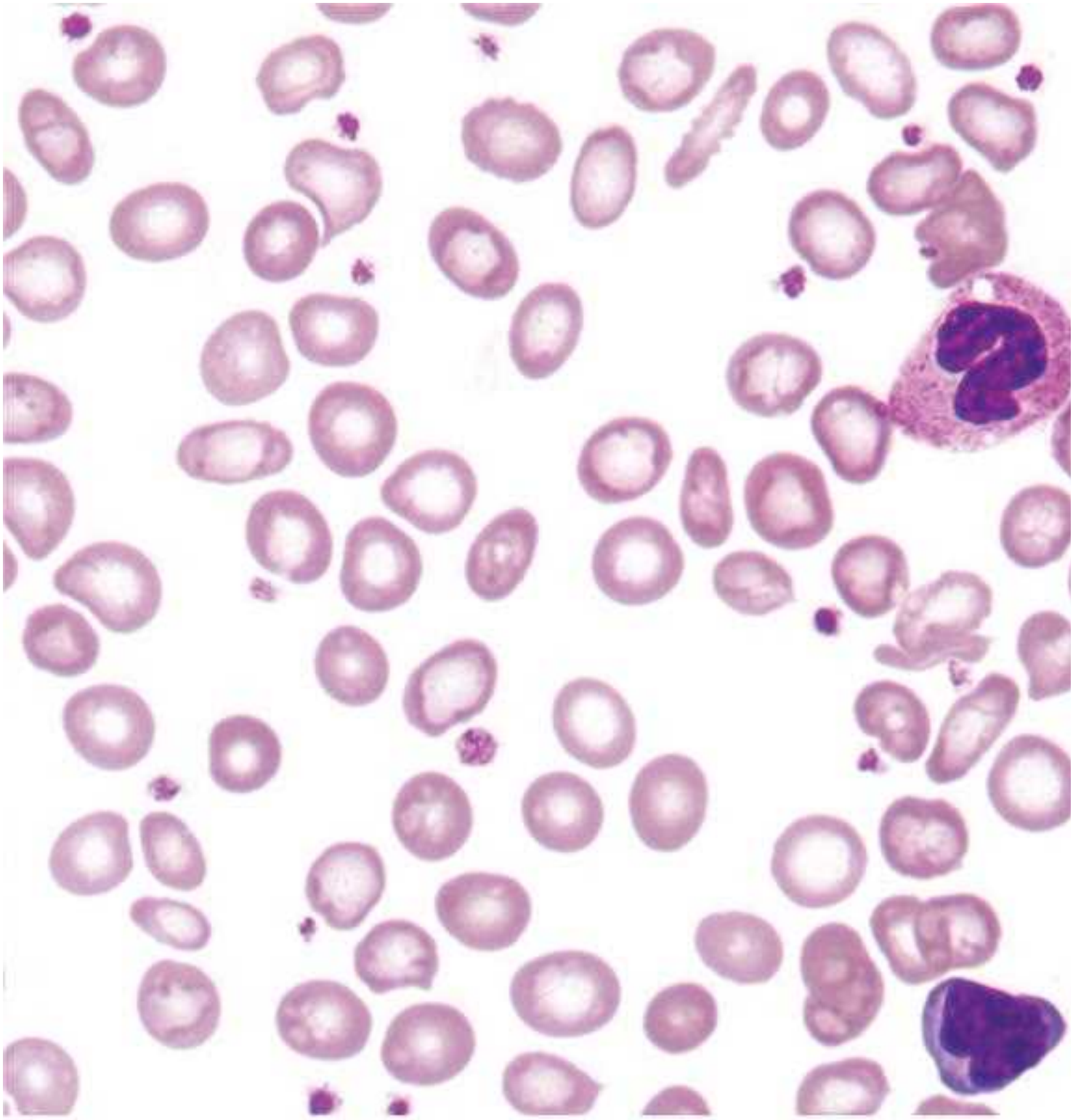
Iron deficiency is often manifested by an appreciable drop in hemoglobin concentration. In the third trimester, additional iron is needed to augment maternal hemoglobin and for transport to the fetus. Because the amount of iron diverted to the fetus is similar in a normal and in an iron-deficient mother, the newborn of a severely anemic mother does not suffer from iron-deficiency anemia. Neonatal iron stores are related to maternal iron status and to timing of cord clamping.

Diagnosis

Classic morphological evidence of iron-deficiency anemia is erythrocyte hypochromia and microcytosis (Fig. 56-3). This may be less prominent in the pregnant woman. Serum ferritin levels are lower. And, levels of *hepcidin*—the master regulator of iron availability—are decreased normally in pregnancy. With iron deficiency, hepcidin levels follow those of serum ferritin (Camaschella, 2015; Koenig, 2014).

FIGURE 56-3
This peripheral blood smear from a women with iron-deficiency anemia contains many scattered microcytic and hypochromic red cells with characteristic central pallor. These exhibit moderate anisopoikilocytosis, namely, varying sizes and shapes including occasional elliptocytes, which can be oval or pencil-shaped.

(Reproduced with permission from Werner CL, Richardson DL, Chang SY, et al (eds): Perioperative Considerations. In Williams Gynecology Study Guide, 3rd ed. New York, McGraw-Hill Education, 2016: Photo contributor: Dr. Weina Chen.)



The initial evaluation of a pregnant woman with moderate anemia includes measurements of hemoglobin, hematocrit, and red cell indices; careful examination of a peripheral blood smear; a sickle-cell preparation if the woman has African origin; and evaluation of serum iron or ferritin levels, or both (Appendix, Serum and Blood Constituents). Serum ferritin levels normally decline during pregnancy, and levels <10 to 15 mg/L confirm iron-deficiency anemia.

When pregnant women with moderate iron-deficiency anemia are given adequate iron therapy, a hematological response is detected by an elevated reticulocyte count. The rate of rise of hemoglobin concentration or hematocrit is typically slower than in nonpregnant women due to the increasing and larger blood volumes during pregnancy.

Treatment

Routinely in pregnancy, daily oral supplementation with 30 to 60 mg of elemental iron and 400 µg of folic acid is recommended (World Health Organization, 2012). A Cochrane review found that intermittent oral iron supplementation may also be appropriate (Peña-Rosas, 2015). For iron-deficiency anemia, resolution and restitution of iron stores can be accomplished with simple iron salts that provide approximately 200 mg daily of *elemental iron*. These include ferrous sulfate, fumarate, or gluconate. If a woman cannot or will not take oral iron preparations, then parenteral therapy is given. Although both are administered intravenously, ferrous sucrose is safer than iron-dextran (American College of Obstetricians and Gynecologists, 2017a; Camaschella, 2015; Shi, 2015). Hemoglobin and ferritin levels show equivalent rises in women treated with either oral or parenteral iron therapy (Breymann, 2017; Daru, 2016).

Anemia from Acute Blood Loss

In early pregnancy, anemia caused by acute blood loss is common with abortion, ectopic pregnancy, and hydatidiform mole. Postpartum, anemia commonly stems from obstetrical hemorrhage. Massive hemorrhage demands immediate treatment as described in Chapter 41 (Hypovolemic Shock). If a moderately anemic woman —defined by a hemoglobin value of approximately 7 g/dL—is hemodynamically stable, is able to ambulate without adverse symptoms, and is not septic, then blood transfusions are not indicated. Instead, oral iron therapy is given for at least 3 months (Krafft, 2005).

Anemia Associated with Chronic Disease

Various disorders, such as chronic renal insufficiency, cancer and chemotherapy, human immunodeficiency virus (HIV) infection, and chronic inflammation result in moderate and sometimes severe anemia, usually with slightly hypochromic and microcytic erythrocytes. It is the second most common form of anemia worldwide (Weiss, 2005).

During pregnancy, women with chronic disorders may develop anemia for the first time. In those with preexisting anemia, it may be intensified as plasma volume expands. Causes include chronic renal insufficiency, inflammatory bowel disease, and connective-tissue disorders. Others are granulomatous infections, malignant neoplasms, rheumatoid arthritis, and chronic suppurative conditions.

Chronic renal insufficiency is the most common disorder that we have encountered as a cause of this type of anemia during pregnancy. Some cases are accompanied by erythropoietin deficiency. As discussed in Chapter 53 (Chronic Kidney Disease), during pregnancy in women with mild chronic renal insufficiency, the degree of red cell mass expansion is inversely related to renal impairment. At the same time, plasma volume expansion usually is normal, and thus anemia is intensified (Cunningham, 1990).

For treatment, adequate iron stores must be ensured. *Recombinant erythropoietin* has been used successfully to treat anemia stemming from chronic disease (Weiss, 2005). In pregnancies complicated by chronic renal insufficiency, recombinant erythropoietin is usually considered when the hematocrit approximates 20 percent (Cyganek, 2011; Ramin, 2006). One worrisome side effect of this agent is hypertension, which is already prevalent in women with renal disease. Red cell aplasia and antierythropoietin antibodies have also been reported (Casadevall, 2002; McCoy, 2008).

Megaloblastic Anemia

These anemias are characterized by blood and bone-marrow abnormalities from impaired DNA synthesis. This leads to large cells with arrested nuclear maturation, whereas the cytoplasm matures more normally. Worldwide, the prevalence of megaloblastic anemia during pregnancy varies considerably. It is rare in the United States.

Folic Acid Deficiency

Megaloblastic anemia developing during pregnancy almost always results from folic acid deficiency. In the past, this condition was referred to as *pernicious anemia of pregnancy*. It usually is found in women who do not consume fresh green leafy vegetables, legumes, or animal protein. As folate deficiency and anemia worsen, anorexia often becomes intense and further aggravates the dietary deficiency. Drugs and excessive ethanol ingestion either cause or contribute (Hesdorffer, 2015).

In nonpregnant women, the folic acid requirement is 50 to 100 µg/d. During pregnancy, requirements are increased, and 400 µg/d is recommended. The earliest biochemical evidence is low plasma folic acid concentrations (Appendix, Serum and Blood Constituents). Early morphological changes usually include neutrophils that are hypersegmented and newly formed erythrocytes that are macrocytic. With preexisting iron deficiency, macrocytic erythrocytes cannot be detected by measurement of the mean corpuscular volume. Careful examination of a peripheral blood smear, however, usually demonstrates some macrocytes. As the anemia becomes more intense, peripheral nucleated erythrocytes appear, and bone marrow examination discloses megaloblastic erythropoiesis. Anemia may then become severe, and thrombocytopenia, leukopenia, or both may develop. The fetus and placenta extract folate from maternal circulation so effectively that the fetus is not anemic despite severe maternal anemia.

For treatment, folic acid is given along with iron, and a nutritious diet is encouraged. By 4 to 7 days after beginning folic acid treatment, the reticulocyte count is increased, and leukopenia and thrombocytopenia are corrected.

For prevention of megaloblastic anemia, a diet should contain sufficient folic acid. The role of folate deficiency in the genesis of neural-tube defects has been well studied (Chap. 13, Genetic Tests). Since the early 1990s, nutritional experts and the American College of Obstetricians and Gynecologists (2016a) have recommended that all women of childbearing age consume at least 400 µg of folic acid daily. More folic acid is given with multifetal pregnancy, hemolytic anemia, Crohn disease, alcoholism, and inflammatory skin disorders. Women with a family history of congenital heart disease may also benefit from higher doses (Huhta, 2015). Women who previously have had infants with neural-tube defects have a lower recurrence rate if a daily 4-mg folic acid supplement is given.

Vitamin B_{12} Deficiency

During pregnancy, vitamin B_{12} levels are lower than nonpregnant values because of decreased levels of binding proteins, namely, the transcobalamins. During pregnancy, megaloblastic anemia is rare from deficiency of vitamin B_{12}, that is, cyanocobalamin. Instead, a typical example is *Addisonian pernicious anemia,* which results from absent intrinsic factor that is requisite for dietary vitamin B_{12} absorption. This autoimmune disorder usually has its onset after age 40 years (Stabler, 2013).

In our limited experience, vitamin B_{12} deficiency in pregnancy is more likely encountered following gastric resection. Those who have undergone total gastrectomy require 1000 µg of vitamin B_{12} given intramuscularly each month. Those with a partial gastrectomy usually do not need supplementation, but adequate serum vitamin B_{12} levels should be ensured (Appendix, Serum and Blood Constituents). Other causes of megaloblastic anemia from vitamin B_{12} deficiency include Crohn disease, ileal resection, some drugs, and bacterial overgrowth in the small bowel (Hesdorffer, 2015; Stabler, 2013).

Hemolytic Anemia

Several conditions feature accelerated erythrocyte destruction. Damage may be stimulated by a congenital red-cell abnormality or in other cases by antibodies directed against red-cell membrane proteins. Hemolysis may be the primary disorder, and sickle-cell disease and hereditary spherocytosis are examples. In other cases, hemolysis develops secondary to an underlying condition such as systemic lupus erythematosus or preeclampsia. Microangiopathic hemolytic anemia due to malignancy has been reported in pregnancy (Happe, 2016).

Autoimmune Hemolysis

The cause of aberrant antibody production is unknown. Typically, both the direct and indirect antiglobulin (Coombs) tests are positive. Anemias caused by these factors may be due to warm-active autoantibodies (80 to 90 percent), cold-active antibodies, or a combination. These syndromes also may be classified as primary (idiopathic) or secondary due to underlying diseases or other factors. Examples of the latter include lymphomas and leukemias, connective-tissue diseases, infections, chronic inflammatory diseases, and drug-induced antibodies (Provan, 2000). *Cold-agglutinin disease* may be induced by infectious etiologies such as *Mycoplasma pneumoniae* or Epstein-Barr viral mononucleosis (Dhingra, 2007). Hemolysis and positive antiglobulin test results may be the consequence of either immunoglobulin M (IgM) or immunoglobulin G (IgG) antierythrocyte antibodies. When thrombocytopenia is comorbid, it is termed *Evans syndrome* (Wright, 2013).

In pregnancy, hemolysis can be markedly accelerated. Rituximab, along with prednisone, is first-line treatment (Luzzatto, 2015). Coincidental thrombocytopenia usually corrects with therapy. Transfusion of red cells is complicated by antierythrocyte antibodies, but warming the donor cells to body temperature may decrease their destruction by cold agglutinins.

Drug-Induced Hemolysis

These hemolytic anemias must be differentiated from other causes of autoimmune hemolysis. In most cases, hemolysis is mild, it resolves with drug withdrawal, and recurrence is prevented by avoidance of the drug. One mechanism is hemolysis induced through drug-mediated immunological injury to red cells. The drug may act as a high-affinity hapten when bound to a red-cell protein to which antidrug antibodies attach—for example, IgM antipenicillin or anticephalosporin antibodies. Some other drugs act as low-affinity haptens and adhere to cell membrane proteins. Examples include probenecid, quinidine, rifampin, and thiopental. A more common mechanism for drug-induced hemolysis is related to a congenital erythrocyte enzymatic defect. An example is glucose-6-phosphate dehydrogenase deficiency, which is common in African-American women and discussed later (Aplastic and Hypoplastic Anemia).

Drug-induced hemolysis is usually chronic and mild to moderate, but occasionally acute hemolysis is severe. Garratty and coworkers (1999) described seven women with severe Coombs-positive hemolysis stimulated by cefotetan given as prophylaxis for obstetrical procedures. Alpha-methyldopa can cause similar hemolysis (Grigoriadis, 2013). Moreover, maternal hemolysis has been reported after intravenous immune globulin therapy (Rink, 2013). Withdrawal of the offending drug frequently halts the hemolysis.

Pregnancy-Induced Hemolysis

Unexplained severe hemolytic anemia can develop during early pregnancy, and it resolves within months postpartum. A clear immune mechanism or red cell defects are not contributory (Starksen, 1983). Because the fetus-neonate also may demonstrate transient hemolysis, an immunological cause is suspected. Maternal corticosteroid treatment is often—but not always—effective (Kumar, 2001). We have cared for a woman who during each pregnancy developed intense severe hemolysis with anemia that was controlled by prednisone. Her fetuses were not affected, and in all instances, hemolysis abated spontaneously after delivery.

Pregnancy-Associated Hemolysis

In some cases, hemolysis is induced by conditions unique to pregnancy. Mild microangiopathic hemolysis with thrombocytopenia is relatively common with severe preeclampsia and eclampsia (Cunningham, 2015; Kenny, 2015). This HELLP (*hemolysis, elevated liver enzyme levels, low platelet count*) syndrome is discussed in Chapter 40 (Maternal Thrombocytopenia). Another is acute fatty liver of pregnancy, which is associated with moderate to severe hemolytic anemia (Nelson, 2013). It is discussed in Chapter 55 (Acute Fatty Liver of Pregnancy).

Paroxysmal Nocturnal Hemoglobinuria

Although commonly regarded as a hemolytic anemia, this hemopoietic stem cell disorder is characterized by formation of defective platelets, granulocytes, and erythrocytes. Paroxysmal nocturnal hemoglobinuria is acquired and arises from one abnormal clone of cells, much like a neoplasm (Luzzatto, 2015). One mutated X-linked gene responsible for this condition is termed *PIG-A* because it codes for phosphatidylinositol glycan protein A. Resultant abnormal anchor proteins of the

erythrocyte and granulocyte membrane make these cells unusually susceptible to lysis by complement (Provan, 2000). The most serious complication is thrombosis, which is heightened in the hypercoagulable state of pregnancy.

Chronic hemolysis has an insidious onset, and its severity ranges from mild to lethal. Hemoglobinuria develops at irregular intervals and is not necessarily nocturnal. Hemolysis may be initiated by transfusions, infections, or surgery. Almost 40 percent of patients suffer venous thromboses and may also experience renal failure, hypertension, and Budd-Chiari syndrome. Because of the thrombotic risk, prophylactic anticoagulation is recommended (Parker, 2005). The treatment of choice is eculizumab, an antibody that inhibits complement activation (Kelly, 2015). Median survival after diagnosis is 10 years, and bone marrow transplantation is the definitive treatment.

During pregnancy, paroxysmal nocturnal hemoglobinuria can be serious and unpredictable. Complications have been reported in up to three fourths of affected women, and the maternal mortality rate in the past was 10 to 20 percent (De Gramont, 1987; de Guibert, 2011). Complications more often develop postpartum, and half of affected women develop venous thrombosis (Fieni, 2006; Ray, 2000). Kelly and colleagues (2015) described 75 pregnancies in 61 affected women treated with eculizumab. In half of these, the dose was increased during pregnancy. They described no maternal deaths but 4 percent stillbirths.

Bacterial Toxins

The most fulminant acquired hemolytic anemia encountered during pregnancy is caused by the exotoxin of *Clostridium perfringens* or by group A β-hemolytic streptococcus (Chap. 47, Clinical Manifestations). Endotoxin of gram-negative bacteria, that is, lipopolysaccharide, may be accompanied by hemolysis and mild-to-moderate anemia (Cox, 1991). For example, anemia often accompanies acute pyelonephritis. With normal erythropoietin production, red cell mass is restored following infection resolution as pregnancy progresses (Cavenee, 1994; Dotters-Katz, 2013).

Inherited Erythrocyte Membrane Defects

The normal erythrocyte is a flexible biconcave disc that allows numerous cycles of reversible deformations. Several genes encode expression of erythrocyte structural membrane proteins or intraerythrocytic enzymes. Various mutations of these genes may result in inherited membrane defects or enzyme deficiencies that destabilize the lipid bilayer. The loss of lipids from the erythrocyte membrane causes a surface area deficiency and poorly deformable cells that undergo hemolysis. Anemia severity depends on the degree of rigidity or decreased distensibility. Erythrocyte morphology similarly is dependent on these factors, and these disorders are usually named after the most dominant red-cell shape characteristic of the disorder. Three examples are *hereditary spherocytosis, pyropoikilocytosis*, and *ovalocytosis*.

Hereditary Spherocytosis

Hemolytic anemias that compose this group of inherited membrane defects are among the most common hemolytic anemias found in gravidas. Mutations are usually an autosomally dominant, variably penetrant *spectrin* deficiency. Others are autosomally recessive or de novo gene mutations that result from deficiency of ankyrin, protein 4.2, moderate band 3, or combinations of these (Gallagher, 2010; Rencic, 2017; Yawata, 2000). The degrees of anemia and jaundice vary, and diagnosis is confirmed by identification of spherocytes on peripheral smear and increased osmotic fragility.

Spherocytic anemias may be associated with a so-called crisis that is characterized by severe anemia from accelerated hemolysis, and it develops in patients with an enlarged spleen. Infection can also accelerate hemolysis or suppress erythropoiesis to worsen anemia. An example of the latter is infection with parvovirus B19 (Chap. 64, Respiratory Viruses). In severe cases, splenectomy reduces hemolysis, anemia, and jaundice.

Pregnancy

In general, women with inherited red-cell membrane defects do well during pregnancy. Folic acid supplementation of 4 mg daily is given orally to sustain erythropoiesis. Women with hereditary spherocytosis cared for at Parkland Hospital had hematocrits ranging from 23 to 41 volumes percent—mean 31 (Maberry, 1992). Reticulocyte counts ranged from 1 to 23 percent. Among 50 pregnancies in 23 women, eight women miscarried. Four of 42 infants were born preterm, but none was growth restricted. Infection in four women intensified hemolysis, and three of these required transfusions. Similar results were reported by Pajor and coworkers (1993).

Because these disorders are inherited, the newborn may be affected. Celkan and Alhaj (2008) report prenatal diagnosis via cordocentesis at 18 weeks' gestation and testing for osmotic fragility. Newborns with hereditary spherocytosis may manifest hyperbilirubinemia and anemia shortly after birth.

Erythrocyte Enzyme Deficiencies

An intraerythrocytic deficiency of enzymes that permit anaerobic glucose metabolism may cause *hereditary nonspherocytic anemia*. Most of these mutations are autosomal recessive traits. As discussed earlier (Hemolytic Anemia), most episodes of severe anemia with enzyme deficiencies are induced by drugs or infections.

Pyruvate kinase deficiency is associated with variable anemia and hypertensive complications (Wax, 2007). Due to recurrent transfusions in homozygous carriers, iron overload is frequent, and associated myocardial dysfunction should be monitored (Dolan, 2002). The fetus that is homozygous for this mutation may develop *hydrops fetalis* from anemia and heart failure (Chap. 15, Hydrops Fetalis).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is complex because there are more than 400 known enzyme variants. The most common are caused by a base substitution that leads to an amino acid replacement and a broad range of phenotypic severity (Luzzatto, 2015; Puig, 2013). In the homozygous or A variant, both X chromosomes are affected, and erythrocytes are markedly deficient in G6PD activity. Approximately 2 percent of African-American women are affected, and the heterozygous variant is found in 10 to 15 percent (Mockenhaupt, 2003). In both instances, random X-chromosome inactivation—*lyonization*—results in variable enzyme activity.

During pregnancy, infections or drugs can induce hemolysis in G6PD deficiency heterozygotes or homozygotes, and severity is related to enzyme activity. Anemia is usually episodic, although some variants induce chronic nonspherocytic hemolysis. Because young erythrocytes contain more enzyme activity, anemia ultimately stabilizes and is corrected soon after the inciting cause is eliminated. Newborn screening for G6PD deficiency is not recommended by the American College of Obstetricians and Gynecologists (2016b).

Aplastic and Hypoplastic Anemia

Aplastic anemia is a grave complication that is characterized by pancytopenia and markedly hypocellular bone marrow (Young, 2015). There are multiple etiologies, and at least one is linked to autoimmune diseases (Stalder, 2009). The inciting cause can be identified in approximately a third of cases. These include drugs and other chemicals, infection, irradiation, leukemia, immunological disorders, and inherited conditions such as *Fanconi anemia* and *Diamond-Blackfan syndrome* (Green, 2009; Lipton, 2009). The functional defect appears to be a marked decrease in committed marrow stem cells.

Hematopoietic stem-cell transplantation is optimal therapy in a young patient (Killick, 2016). Immunosuppressive therapy is given, and in some nonresponders, *eltrombopag* has been successful (Olnes, 2012; Townsley, 2017). Definitive treatment is bone marrow transplantation, and approximately three fourths of patients have a good response and long-term survival (Rosenfeld, 2003). Umbilical cord blood-derived stem cells can also serve as a potential transplant source (Moise, 2005; Pinto, 2008). Previous blood transfusions and even pregnancy enhance the risk of graft rejection (Young, 2015).

Pregnancy

Hypoplastic or aplastic anemia complicating pregnancy is rare. A study of 60 pregnancies complicated by aplastic anemia found that half were diagnosed during pregnancy (Bo, 2016). There are a few well-documented cases of *pregnancy-induced hypoplastic anemia,* and the anemia and other cytopenias improve or remit following delivery or pregnancy termination (Bourantas, 1997; Choudhry, 2002). In some cases, anemia recurred in a subsequent pregnancy.

Diamond-Blackfan anemia is a rare form of pure red-cell hypoplasia. Approximately 40 percent of cases are familial and have autosomal dominant inheritance (Orfali, 2004). The response to glucocorticoid therapy is usually good. Continuous treatment is necessary, and most become at least partially transfusion dependent (Vlachos, 2008). In 64 pregnancies complicated by this syndrome, Faivre and associates (2006) reported that two thirds had problems related to placental vascular etiologies that included miscarriage, preeclampsia, preterm birth, fetal-growth restriction, or stillbirth.

Gaucher disease is an autosomally recessive lysosomal enzyme deficiency characterized by deficient activity of *acid* β-*glucosidase*. Affected women have anemia and thrombocytopenia that is usually worsened by pregnancy (Granovsky-Grisaru, 1995). Elstein and colleagues (1997) described six pregnant women whose disease improved when they were given *alglucerase* enzyme replacement. *Imiglucerase* therapy, which is human recombinant enzyme replacement therapy, has been available since 1994. European guidelines recommend treatment in pregnancy, whereas the Food and Drug Administration states it may be given with “clear indications” (Granovsky-Grisaru, 2011).

The major risks with hypoplastic anemia are hemorrhage and infection. Rates of preterm labor, preeclampsia, fetal-growth restriction, and stillbirth are increased (Bo, 2016). Management depends on gestational age, and supportive care includes continuous infection surveillance and prompt antimicrobial therapy. Granulocyte transfusions are given only during infections. Red cells are transfused to improve symptomatic anemia and routinely to maintain the hematocrit at or above 20 volumes percent. Platelet transfusions may be needed to control hemorrhage. Maternal mortality rates reported since 1960 have averaged nearly 50 percent, however, better outcomes have been reported more recently (Choudhry, 2002; Kwon, 2006).

Pregnancy after Bone Marrow Transplantation

Several reports describe successful pregnancies in women who have undergone bone marrow transplantation (Borgna-Pignatti, 1996; Eliyahu, 1994). In their review, Sanders and coworkers (1996) reported 72 pregnancies in 41 women who had undergone transplantation. In the 52 pregnancies resulting in a liveborn neonate, almost half were complicated by preterm delivery or hypertension. Our experiences with a few of these women indicate that they have normal pregnancy-augmented erythropoiesis and total blood volume expansion.

POLYCYTHEMIAS

Secondary Polycythemia

Excessive erythrocytosis during pregnancy is usually related to chronic hypoxia from maternal congenital cardiac disease or a chronic pulmonary disorder. Unusually heavy cigarette smoking can cause polycythemia. We have encountered otherwise healthy pregnant women who were heavy smokers, had chronic bronchitis, and had hematocrits ranging from 55 to 60 volumes percent! If polycythemia is severe, the probability of a successful pregnancy outcome is low.

Polycythemia Vera

This is a primary clonal myeloproliferative hemopoietic stem-cell disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic precursors (Spivak, 2015; Vannucchi, 2015). Virtually all patients have either a *JAK2*V617F or a *JAK2* exon 12 gene mutation (Harrison, 2009). Symptoms are related to increased blood viscosity, and thrombotic complications are common. Treatment of nonpregnant patients is with hydroxyurea or ruxolitinib (Vannucchi, 2015).

Fetal loss rates are high in women with polycythemia vera, and pregnancy outcome may be improved with aspirin therapy (Griesshammer, 2006; Robinson, 2005; Tefferi, 2000). Women with a history of venous thrombosis are given prophylaxis with low-molecular-weight heparin. If cytoreduction is required during pregnancy, interferon alpha may be considered (Kreher, 2014).

HEMOGLOBINOPATHIES

Sickle-Cell Hemoglobinopathies

Hemoglobin A is the most common hemoglobin tetramer and consists of two α- and two β-chains. In contrast, sickle hemoglobin (hemoglobin S) originates from a single β-chain substitution of glutamic acid by valine, which stems from an A-for-T substitution at codon 6 of the β-globin gene. Hemoglobinopathies that can result in clinical features of the *sickle-cell syndrome* include sickle-cell anemia (Hb SS); sickle-cell hemoglobin C disease (Hb SC); sickle-cell β-thalassemia disease (either Hb S/B^0 or Hb S/B^+); and sickle-cell E disease (Hb SE) (Benz, 2015). All are also associated with increased pregnancy morbidity.

Sickle-cell anemia results from the inheritance of the gene for S hemoglobin from each parent. In the United States, 1 of 12 African-Americans has sickle-cell trait, which results from inheritance of one gene for hemoglobin S and one for normal hemoglobin A. The computed incidence of sickle-cell anemia among African-Americans is 1 in 576 (1/12 × 1/12 × 1/4 = 1/576). But, the disease is less common in adults because of earlier mortality. Hemoglobin C originates from a single β-chain substitution of glutamic acid by lysine, which stems from a T-for-C substitution at codon 6 of the β-globin gene. Approximately 1 in 40 African-Americans has the gene for hemoglobin C. Thus, the theoretical incidence for coinheritance of the gene for hemoglobin S and an allelic gene for hemoglobin C in an African-American child is about 1 in 2000 (1/12 × 1/40 × 1/4). β-Thalassemia minor is approximately 1 in 40, thus S-β-thalassemia also is found in approximately 1 in 2000 (1/12 × 1/40 × 1/4).

Pathophysiology

Red cells with hemoglobin S undergo sickling when they are deoxygenated, and the hemoglobin aggregates. Constant sickling and unsickling cause membrane damage, and the cell may become irreversibly sickled. Events that slow erythrocyte transit through the microcirculation include adhesion to endothelial cells, erythrocytic dehydration, and vasomotor dysregulation. Clinically, the hallmarks of sickling episodes are periods during which there is ischemia and infarction in various organs. The *sickle-cell crisis* produces clinical symptoms, predominately pain, which is often severe. There may be aplastic, megaloblastic, sequestration, and hemolytic crises.

Chronic and acute changes from sickling include bony abnormalities such as osteonecrosis of femoral and humeral heads, renal medullary damage, autosplenectomy in homozygous SS patients and splenomegaly in other variants, hepatomegaly, ventricular hypertrophy, pulmonary infarctions, pulmonary hypertension, cerebrovascular accidents, leg ulcers, and a propensity for infection and sepsis (Benz, 2015; Gladwin, 2004). Other sequelae are cerebrovascular aneurysms and sickle-cell vasculopathy (Buonanno, 2016). Pulmonary hypertension can develop and is found in 20 percent of adults with SS hemoglobin (Gladwin, 2008).

Treatment

Good supportive care is essential to prevent mortality. Specific therapies are evolving, and many are still experimental. One treatment is hemoglobin F induction with drugs that stimulate gamma-chain synthesis. This increases hemoglobin F, which inhibits hemoglobin S polymerization. One example is *hydroxyurea,* which augments hemoglobin F production and reduces the number of sickling episodes (Platt, 2008). Hydroxyurea is teratogenic in animals, although a preliminary 17-year surveillance of antenatally exposed children was reassuring (Ballas, 2009; Briggs, 2015; Italia, 2010). A randomized trial showed no benefit from treatment with *prasugrel*, a platelet inhibitor (Henney, 2016). Treatment with *crizanlizumab*, an antibody against P-selectin, significantly lowered the incidence of adverse events (Ataga, 2017).

Various forms of hemopoietic cell transplantation are emerging as “cures” for sickle-cell syndromes and severe thalassemias (Hsieh, 2009). Oringanje and coworkers (2013) performed a Cochrane review and found that only observational studies have been reported. *Bone marrow transplantation* has 5-year survival rates that exceed 90 percent (Dalle, 2013). *Cord-blood stem-cell transplantation* from related donors also shows great promise (Shenoy, 2013). Finally, successful gene therapy has been accomplished by lentiviral vector-mediated addition of a beta globin gene into stem cells (Ribeil, 2017).

Pregnancy and Sickle-Cell Syndromes

Pregnancy is a serious burden to women with any of the major sickle hemoglobinopathies, particularly those with hemoglobin SS disease. Several large studies have defined this relationship. Villers and colleagues (2008) studied 17,952 births in women with sickle-cell syndromes. Chakravarty and associates (2008) studied 4352 pregnancies. A more recent cohort study of 1526 women was reported by Boulet and coworkers (2013). Last, a cohort study taken from more than 2 million women compared those with sickle-cell disease to normal controls (Kuo, 2016). Common obstetrical and medical complications and their relative risks from a composite of most of these studies are shown in Table 56-2.

TABLE 56-2

Pregnancy Morbidity with Hemoglobin SS and SC Disease

	Odds Ratios	
Outcome	**Hb SS**	**Hb SC**
Preeclampsia	2–3.1	2.0
Stillbirth	6.5	3.2
Preterm delivery	2–2.7	1.5
Growth restriction	2.8–3.9	1.5
Maternal mortality	11–23	11

Data from metaanalyses by Boafor, 2016; Oteng-Ntim, 2015.

Maternal morbidity common in pregnancy includes ischemic necrosis of multiple organs, especially bone marrow that causes episodes of severe pain. Pyelonephritis, pneumonia, and pulmonary complications are frequent. Although the maternal mortality rate has improved, perinatal morbidity and mortality rates remain formidable (Boga, 2016; Lesage, 2015; Yu, 2009). Perinatal outcomes include increased risks for preterm birth, fetal-growth restriction, and perinatal mortality.

Hemoglobin SC

In nonpregnant women, morbidity and mortality rates from SC disease are appreciably lower than those from sickle-cell anemia. Indeed, fewer than half of these women have symptoms before pregnancy. In our experiences, affected gravidas suffer attacks of severe bone pain and episodes of pulmonary infarction and embolization more commonly than when they are not pregnant (Cunningham, 1983). Some adverse pregnancy outcomes are shown in Table 56-2.

Management During Pregnancy

Women with sickle-cell hemoglobinopathies require close prenatal observation. Any factor that impairs erythropoiesis or increases red cell destruction aggravates the anemia. Prenatal folic acid supplementation with 4 mg daily is needed to support rapid red blood cell turnover.

One danger is that a symptomatic woman may categorically be considered to be suffering from a “sickle-cell crisis.” As a result, serious obstetrical or medical problems that cause pain, anemia, or both may be overlooked. Examples are ectopic pregnancy, placental abruption, pyelonephritis, or appendicitis. Thus, a diagnosis of sickle-cell crisis should be applied only after all other possible causes have been excluded. Pain with sickle-cell syndromes is caused by intense sequestration of sickled erythrocytes and infarction in various organs, especially bone marrow. These episodes may develop acutely, especially late in pregnancy, during labor and delivery, and early in the puerperium.

Guidelines for care of these women have been appropriately stressed by Rees and colleagues (2003). Marti-Carvajal and coworkers (2009) performed a Cochrane review and reported that no randomized trials have evaluated treatment during pregnancy. At minimum, intravenous fluids are given, and opioids are administered promptly for severe pain. Oxygen via nasal cannula may decrease the intensity of sickling at the capillary level. We have found that red cell transfusions after the onset of severe pain do not dramatically improve pain intensity and may not shorten its duration. Conversely, as discussed later, prophylactic transfusions almost always prevent further vasoocclusive episodes and pain crises. Recent reports suggest benefits from epidural analgesia (Verstraete, 2012; Winder, 2011). Long term, affected women can become habituated to narcotics. This problem is highlighted by the increased rates of neonatal abstinence syndrome, which is a constellation of withdrawal symptoms (Shirel, 2016).

Rates of covert bacteriuria and acute pyelonephritis are elevated substantively, and screening and treatment for bacteriuria are essential. If pyelonephritis develops, sickle cells are extremely susceptible to bacterial endotoxin, which can cause dramatic and rapid red cell destruction while simultaneously suppressing erythropoiesis. Pneumonia, especially due to *Streptococcus pneumoniae,* is common. The Centers for Disease Control and Prevention recommends specific vaccination for those with sickle-cell disease and all asplenic patients (Kim, 2016). These are polyvalent pneumococcal, *Haemophilus influenzae* type B, and meningococcal vaccines, and administration guidelines are found in Table 9-7.

Pulmonary complications are frequent. Of these, *acute chest syndrome* is characterized by pleuritic chest pain, fever, cough, lung infiltrates, and hypoxia, and usually also by bone and joint pain (Vichinsky, 2000). In addition to symptoms, radiographs show a new pulmonary infiltrate. There are four precipitants: infection, marrow emboli, thromboembolism, and atelectasis (Medoff, 2005). Bacterial or viral infection causes approximately half of cases. When acute chest syndrome develops, the mean duration of hospitalization is 10.5 days. Mechanical ventilation is required in approximately 15 percent, and the mortality rate approximates 3 percent (Gladwin, 2008). At least for nonpregnant adults, some recommend rapid simple or exchange transfusions to remove the “trigger” for acute chest syndromes (Gladwin, 2008). In a study of nonpregnant patients, Turner and colleagues (2009) reported that there were no increased benefits of exchange versus simple transfusions, and the former were associated with fourfold increased blood usage.

Women with sickle-cell disease usually have some degree of *cardiac dysfunction* from ventricular hypertrophy. Chronic hypertension worsens the dysfunction (Gandhi, 2000). During pregnancy, the basal hemodynamic state characterized by high cardiac output and increased blood volume is augmented (Veille, 1994). Although most women tolerate pregnancy without problems, complications such as severe preeclampsia or serious infections may result in ventricular failure (Cunningham, 1986). Heart failure caused by pulmonary hypertension must also be considered (Chakravarty, 2008).

In 4352 pregnancies in women with sickle-cell syndromes, Chakravarty and associates (2008) reported significantly higher pregnancy complication rates. Compared with controls, women with sickling disorders had a 63-percent rate of nondelivery-related admissions. They had a 1.8-fold greater incidence of hypertensive disorders—19 percent; a 2.9-fold higher rate of fetal-growth restriction—6 percent; and a 1.7-fold increased cesarean delivery rate—45 percent.

Prophylactic Red Cell Transfusions

Chronic transfusion therapy prevents strokes in high-risk children (DeBaun, 2014). During pregnancy, the most dramatic benefit of prophylactic transfusions has been on maternal morbidity rates (Benites, 2016). In an observational 10-year prospective study at Parkland Hospital, we offered prophylactic transfusions to all pregnant women with sickle-cell syndromes. Transfusions were given throughout pregnancy to maintain the hematocrit above 25 volumes percent and the portion of hemoglobin S <60 percent (Cunningham, 1979). Maternal morbidity was minimal, and erythropoiesis suppression was not problematic. Their outcomes were compared with historical controls who were not routinely transfused. Overall, morbidity and hospitalization rates were significantly reduced in the transfused group (Asma, 2015; Cunningham, 1983; Grossetti, 2009). Still, adverse perinatal outcomes are prevalent (Ngô, 2010).

In a multicenter trial, Koshy and coworkers (1988) randomly assigned 72 pregnant women with sickle-cell syndromes to prophylactic or indicated transfusions. They reported a significant decline in the incidence of painful sickle-cell crises with prophylactic transfusions but no differences in perinatal outcomes. Because of risks inherent with blood administration, they concluded that prophylactic transfusions were not indicated. A metaanalysis of 12 studies found prophylactic transfusions improved rates of some adverse maternal and neonatal outcomes, including maternal mortality, pulmonary complications, and perinatal mortality (Malinowski, 2015).

Undoubtedly, morbidity from multiple transfusions is significant. Up to 10 percent of women had a delayed hemolytic transfusion reaction, and infections are major concerns. Garratty (1997) reviewed 12 studies and found alloimmunization developed in a fourth of women. Finally, in liver biopsies in these women, we found no evidence of transfusion-related iron overload, hemochromatosis, or chronic hepatitis (Yeomans, 1990).

Because of what some consider marginal benefits, routine prophylactic transfusions during pregnancy remain controversial (American College of Obstetricians and Gynecologists, 2015; Okusayna, 2013). Current consensus is that their use should be individualized.

Fetal Assessment

Because of the high incidence of fetal-growth restriction and perinatal mortality, serial fetal assessment with sonography and antepartum surveillance is recommended (American College of Obstetricians and Gynecologists, 2015). Anyaegbunam and colleagues (1991) reported nonreactive stress tests during sickling crises, which resumed reactivity with crisis resolution. They concluded that transient effects of sickle-cell crisis do not compromise umbilical blood flow.

Labor and Delivery

Management is essentially identical to that for women with cardiac disease (Chap. 49, Labor and Delivery). Women should be kept comfortable, but not oversedated. Conduction analgesia is ideal (Camous, 2008). Compatible blood should be available. If a difficult vaginal or cesarean delivery is contemplated, and the hematocrit is <20 volumes percent, then packed erythrocyte transfusions are administered. There is no categorical contraindication to vaginal delivery, and cesarean delivery is reserved for obstetrical indications (Rogers, 2010).

Contraception and Sterilization

Many clinicians do not recommend combination hormonal contraception because of potential adverse vascular and thrombotic effects. In their systematic review, however, Haddad and coworkers (2012) found that complication rates were not higher with their use in women with sickle-cell syndromes. The Centers for Disease Control and Prevention categorizes combination hormonal contraception, intrauterine devices, implants, and progestin-only contraception as having no risk or as having advantages that generally outweigh theoretical or proven risks (Curtis, 2016).

Sickle-Cell Trait

The frequency of sickle-cell trait among African-Americans averages 8 percent. Carriers have occasional hematuria, renal papillary necrosis, and hyposthenuria, which is urine of low specific gravity (Tsaras, 2009). And although controversial, sickle-cell trait does not appear to be associated with increased rates of abortion, perinatal mortality, low birthweight, or pregnancy-induced hypertension (Pritchard, 1973; Tita, 2007; Tuck, 1983). One unquestioned relationship is the twofold increased incidence of asymptomatic bacteriuria and urinary infection. Sickle-cell trait should not be considered a deterrent to pregnancy or to hormonal contraception.

Inheritance is a concern for the fetus of a mother with sickle-cell trait whenever the father carries a gene for abnormal hemoglobins that include S, C, and D or for β-thalassemia trait. Prenatal diagnosis is discussed in Chapter 14 (Sickle Hemoglobinopathies).

Hemoglobin C and C-β-Thalassemia

Approximately 2 percent of African-Americans are heterozygous for hemoglobin C, but even if homozygous, hemoglobin C is innocuous (Nagel, 2003). Only when coinherited with sickle-cell trait to yield hemoglobin SC is the trait problematic. Pregnancy in women with homozygous hemoglobin CC disease or C-β-thalassemia carries relatively benign associations. Table 56-3 shows our experiences from Parkland Hospital (Maberry, 1990). Other than mild-to-moderate anemia, pregnancy outcomes were not abnormal. Supplementation with folic acid and iron is indicated.

TABLE 56-3

Outcomes in 72 Pregnancies Complicated by Hemoglobin CC and C-β-Thalassemia

	Hemoglobin CC	C-β-Thalassemia
Women (no.)	15	5
Pregnancies (no.)	49	23
Hematocrit (range)	27 (21–33)	30 (28–33)
Birthweight (g)		
Mean	2990	2960
Range	1145–4770	2320–3980
Perinatal deaths	1	2
Surviving infants	42	20

Data from Maberry, 1990.

Hemoglobin E

Although uncommon in the United States, hemoglobin E is the second most frequent hemoglobin variant worldwide. The heterozygous E trait is common in Southeast Asia. Hurst and coworkers (1983) identified homozygous hemoglobin E, hemoglobin E plus β-thalassemia, or hemoglobin E trait in 36 percent of Cambodians and 25 percent of Laotians. Hemoglobin EE is associated with little or no anemia, hypochromia, marked microcytosis, or erythrocyte targeting. Kemthong and colleagues (2016) studied 1073 women and 2146 controls and found that hemoglobin E trait does not increase pregnancy risks other than asymptomatic bacteriuria. Conversely, doubly heterozygous E-β-thalassemia is a common cause of severe childhood anemia in Southeast Asia (DeLoughery, 2014). In a cohort study of 54 women with singleton pregnancies, Luewan and associates (2009) reported a threefold greater risk of preterm birth and fetal-growth restriction in affected women. It is unclear if hemoglobin SE disease is ominous during pregnancy.

Hemoglobinopathy in the Newborn

Neonates with homozygous SS, SC, and CC disease can be identified accurately at birth by cord blood electrophoresis. The United States Preventive Services Task Force recommends that all newborns be tested for sickle-cell disease (Lin, 2007). In most states, such screening is mandated by law and performed routinely (Chap. 32, Routine Newborn Care).

Prenatal Diagnosis

Many tests are available to detect sickle-cell disease antenatally. Most are DNA based and use chorionic villus samples or amnionic fluid specimens (American College of Obstetricians and Gynecologists, 2015). Several mutations that encode hemoglobin S and other abnormal hemoglobins can be detected by targeted mutation analysis and polymerase chain reaction-based techniques (Chap. 13, Genetic Tests).

THALASSEMIA SYNDROMES

Hundreds of mutations affect genes that control hemoglobin production. Some of these impair synthesis of one or more of the normal globin peptide chains and may result in a clinical syndrome characterized by varying degrees of ineffective erythropoiesis, hemolysis, and anemia (Benz, 2015). Thalassemias are classified according to the globin chain that is deficient. The two major forms involve impaired production or instability of α-peptide chains to cause α-thalassemia or of β-chains to cause β-thalassemia. These may form from point mutations, deletions, or translocations involving the α- or non-α-globin gene (Leung, 2012).

Alpha Thalassemias

Because there are four α-globin genes, the inheritance of α-thalassemia is more complicated than for β-thalassemia (Piel, 2014). Possible genotypes and phenotypes are shown in Table 56-4. Clinical severity closely correlates with the degree of α-globin chains synthesis impairment. In most populations, the α-globin chain "cluster" or gene loci are doubled on chromosome 16. Similarly, the γ chains are duplicated. Thus, the normal genotype for diploid cells can be expressed as αα/αα and γγ/γγ. There are two main groups of α-thalassemia determinants: α^0-thalassemia is the deletion of both loci from one chromosome

TABLE 56-4

Genotypes and Phenotypes of α-Thalassemia Syndromes

Genotype	Genotype	Phenotype
Normal	αα/αα	Normal
α^+-Thalassemia heterozygote	–α/αα αα/–α	Normal; silent carrier
α^+-Thalassemia homozygote[a] α^0-Thalassemia heterozygote[b]	–α/–α ––/αα	α-Thalassemia minor—mild hypochromic microcytic anemia
Compound heterozygous α^0/α^+	––/–α	Hgb H (β_4) with moderate-to-severe hemolytic anemia
Homozygous α-thalassemia	––/––	Hgb Bart (γ_4) disease, hydrops fetalis

[a]More common in African Americans.

[b]More common in Asian Americans.

(––/αα), whereas α^+-thalassemia is the loss of a single locus from one allele (–α/αα heterozygote) or a loss from each allele (–α/–α homozygote).

There are two major phenotypes. The deletion of all four α-globin chain genes (––/––) characterizes *homozygous* α-thalassemia. Because α-chains are contained in fetal hemoglobin, the fetus is affected. When none of the four genes are expressed, no α-globin chains are produced, and instead hemoglobin Bart (γ_4) and hemoglobin H (β_4) are formed as abnormal tetramers that cannot transport oxygen (Chap. 7, Hemopoiesis).

Frequency

The relative frequency of α-thalassemia minor, hemoglobin H disease, and hemoglobin Bart disease varies remarkably among racial groups. All of these variants are encountered in Asians. In those of African descent, although α-thalassemia minor has a frequency approximating 2 percent, hemoglobin H disease is rare and hemoglobin Bart disease is unreported. This is because Asians usually have α^0-thalassemia minor inherited with both gene deletions typically from the same chromosome (––/αα), whereas blacks usually have α^+-thalassemia minor in which one gene is deleted from each chromosome (–α/–α).

Diagnosis of β-thalassemia minor and α-thalassemia major in the fetus can be accomplished by DNA analysis using molecular techniques (Piel, 2014). Fetal diagnosis of hemoglobin Bart has been described using capillary electrophoresis or high-performance liquid chromatography techniques (Sirichotiyakul, 2009; Srivorakun, 2009). Molecular genetic testing for *HBA1* and *HBA2* identifies 90 percent of deletions and 10 percent of point mutations in affected individuals (Galanello, 2011b).

Pregnancy

Important obstetrical aspects of some α-thalassemia syndromes depend on the number of gene deletions in a given woman. The silent carrier state with one gene deletion is of no consequence. Deletion of two genes resulting in *α*-thalassemia minor is characterized by minimal-to-moderate hypochromic microcytic anemia. This is due to either α^0- or α^+-thalassemia trait, and thus genotypes may be –α/–α or ––/αα. Differentiation is possible only by DNA analysis (Piel, 2014). Because no other clinical abnormalities accompany either form of α-thalassemia minor, it often goes unrecognized and is usually of no maternal consequence (Hanprasertpong, 2013). The fetus with these forms of thalassemia minor will have hemoglobin Bart at birth, but as its levels drop, it is not replaced by hemoglobin H. Red cells are hypochromic and microcytic, and the hemoglobin concentration is normal to slightly depressed.

Hemoglobin H disease (β_4) results from the compound heterozygous state for α^0- plus α^+-thalassemia with deletion of three of four alpha genes (––/–α). With only one functional α-globin gene per diploid genome, the newborn will have abnormal red cells containing a mixture of hemoglobin Bart (γ_4), hemoglobin H (β_4), and hemoglobin A. The neonate appears normal but soon develops hemolytic anemia as most of the hemoglobin Bart is replaced by hemoglobin H. In adults, anemia is moderate to severe and usually worsens during pregnancy.

Inheritance of all four abnormal α genes causes homozygous α-thalassemia with predominant production of hemoglobin Bart, which has an appreciably increased affinity for oxygen. This is incompatible with extended survival. Hsieh and colleagues (1989) reported that blood obtained by funipuncture from 20 hydropic fetuses contained 65 to 98 percent Bart hemoglobin. These fetuses are stillborn, or they are hydropic and usually die very soon after birth.

Sonographic measurement of the fetal cardiothoracic ratio at 12 to 13 weeks' gestation can be used to identify affected fetuses (Lam, 1999; Zhen, 2015). Sonographic assessment of myocardial performance—the *Tei index*—in the first half of pregnancy has been evaluated. Changes predate hydrops in affected fetuses (Luewan, 2013). Severe anemia can be detected using Doppler velocimetry of the middle cerebral artery. Hemopoietic cell transplantation has been described for treatment (Galanello, 2011a).

Beta Thalassemias

The β-thalassemias are the consequences of impaired β-globin chain production or α-chain instability. Genes that encode control of β-globin synthesis are in the δγβ-gene "cluster" located on chromosome 11 (Chap. 7, Hemopoiesis). More than 150 point mutations in the β-globin gene have been described (Weatherall, 2010). In β-thalassemia, β-chain production is decreased, and excess α-chains precipitate to cause cell-membrane damage. Other forms of β-thalassemias are caused by α-chain instability (Kihm, 2002).

The heterozygous trait is β-thalassemia minor, and those most commonly encountered have elevated hemoglobin A_2 levels. This hemoglobin is composed of two α- and two δ-globin chains, and concentrations are usually more than 3.5 percent. Hemoglobin F—composed of two α- and two γ-globin chains—also usually has increased concentrations that exceed 2 percent. Some patients with heterozygous β-thalassemia minor do not have anemia, and others have mild-to-moderate anemia characterized by hypochromia and microcytosis.

Homozygous β-thalassemia—also called β-thalassemia major or *Cooley anemia*—is a serious and frequently fatal disorder. Hemolysis is intense and leads to severe anemia. Many patients become transfusion dependent, and the subsequent iron load, along with abnormally increased gastrointestinal iron absorption, leads to hemochromatosis, which is fatal in many cases. Stem cell transplantation has been used to treat β-thalassemia major (Jagannath, 2014). A heterozygous form of β-thalassemia that clinically manifests as *thalassemia intermedia* produces moderate anemia.

Pregnancy

During pregnancy, women with β-thalassemia minor may have mild anemia (Charoenboon, 2016). Iron and folate supplements are given. In some women, anemia will worsen because normal plasma volume expansion may be accompanied by slightly subnormal erythropoiesis.

Thalassemia major and some of the other severe forms were uncommonly encountered during pregnancy before the advent of transfusion and iron chelation therapy. With such management, 63 pregnancies were reported and suffered no serious complications (Aessopos, 1999; Daskalakis, 1998). Pregnancy is considered reasonably safe if maternal cardiac function is normal. Transfusions are given throughout pregnancy to maintain the hemoglobin concentration at 10 g/dL. This is coupled with surveillance of fetal growth (American College of Obstetricians and Gynecologists, 2015; Sheiner, 2004).

Prenatal Diagnosis

Because β-thalassemia major is caused by numerous mutations, prenatal diagnosis is difficult. For a given individual, targeted mutation analysis is done that requires prior identification of the familial mutation. The analysis is done using chorionic villus sampling and other techniques discussed in Chapter 14 (Chorionic Villus Sampling). Noninvasive testing of circulating fetal nucleic acids in maternal plasma for the diagnosis of β-thalassemia has been described (Leung, 2012; Xiong, 2015).

PLATELET DISORDERS

Thrombocytopenia

Platelet abnormalities may precede pregnancy, develop during pregnancy coincidentally, or be induced by pregnancy. Thrombocytopenia—defined by a platelet count <150,000/μL—is identified in nearly 10 percent of gravidas (American College of Obstetricians and Gynecologists, 2016c). Of these cases, 75 percent are *gestational thrombocytopenia,* whereas 25 percent are due to other various causes. One other common cause is HELLP syndrome. Thrombocytopenia may be inherited or idiopathic, acute or chronic, and primary or associated with other disorders. Examples are shown in Table 56-5.

TABLE 56-5

Some Causes of Thrombocytopenia in Pregnancy

Gestational thrombocytopenia—75 percent
Preeclampsia and HELLP syndromes—20 percent
Obstetrical coagulopathies—DIC, MTP
Immune thrombocytopenic purpura
Systemic lupus erythematosus and APAS
Infections—viral and sepsis syndrome
Drugs
Hemolytic anemias
Thrombotic microangiopathies
Malignancies

APAS = antiphospholipid antibody syndrome; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; MTP = massive transfusion protocol.

Data from American College of Obstetrics and Gynecologists, 2016c; Aster, 2007; Diz-Küçükkāya, 2016.

Gestational Thrombocytopenia

Burrows and Kelton (1993) reported that 6.6 percent of 15,471 pregnant women had a platelet count <150,000/μL, and in 1.2 percent, it was <100,000/μL. They further noted that almost 75 percent of 1027 women whose platelet counts were <150,000/μL were found to have normal-variant incidental thrombocytopenia. Of the remainder, 21 percent had a hypertensive disorder of pregnancy, and 4 percent had an immunological disorder. A platelet count of <80,000/μL should trigger an evaluation for etiologies other than incidental or gestational thrombocytopenia, which is unlikely to have a platelet count <50,000/μL (Gernsheimer, 2013).

The physiological decline in platelet concentration seen with gestational thrombocytopenia is usually evident in the third trimester and is thought to be predominantly due to hemodilution. The normal increased splenic mass characteristic of pregnancy may also be contributory (Maymon, 2006). Most evidence shows that platelet life span is unchanged in normal pregnancy (Kenny, 2015).

Inherited Thrombocytopenias

Bernard-Soulier syndrome is characterized by lack of platelet membrane glycoprotein (GPIb/IX) and causes severe dysfunction. Moreover, women exposed to fetal platelets carrying this glycoprotein can develop antibodies against this fetal GPIb/IX antigen to cause alloimmune fetal thrombocytopenia (Fujimori, 1999; Peng, 1991).

A systematic review of 30 pregnancies in 18 women reported a 33-percent rate of primary postpartum hemorrhage, and half of women with bleeding required blood transfusion (Peitsidis, 2010). The reviewers also described six cases of neonatal alloimmune thrombocytopenia and two perinatal deaths. Close monitoring throughout pregnancy and 6 weeks postpartum is critical due to the possibility of life-threatening hemorrhage (Prabu, 2006).

May-Hegglin anomaly is an autosomal dominant disorder characterized by thrombocytopenia, giant platelets, and leukocyte inclusions (Chatwani, 1992). Urato and Repke (1998) described such a woman who was delivered vaginally. Despite a platelet count of 16,000/μL, she did not bleed excessively. The neonate inherited the anomaly but also had no bleeding despite a platelet count of 35,000/μL. A systematic review of 26 studies containing 75 pregnancies in 40 women reported four cases of postpartum hemorrhage, 34 cases of neonatal thrombocytopenia, and two fetal deaths (Hussein, 2013).

Immune Thrombocytopenic Purpura

The primary form—also termed *idiopathic thrombocytopenic purpura (ITP)*—is usually caused by a cluster of IgG antibodies directed against one or more platelet glycoproteins (Konkle, 2015). Antibody-coated platelets are destroyed prematurely in the reticuloendothelial system, especially the spleen. Although not proven, the disorder is probably mediated by autoantibodies directed at platelet-associated immunoglobulins—PAIgG, PAIgM, and PAIgA. In adults, immune thrombocytopenia most often is a chronic disease that rarely resolves spontaneously.

As shown in Table 56-5, secondary forms of immune-mediated chronic thrombocytopenia appear in association with systemic lupus erythematosus, lymphomas, leukemias, and several systemic diseases. Approximately 2 percent of thrombocytopenic patients have positive serological tests for lupus, and in some cases, levels of anticardiolipin antibodies are high. Finally, approximately 10 percent of HIV-positive patients have associated thrombocytopenia (Scaradavou, 2002).

Diagnosis and Management

Only a few adults with primary immune thrombocytopenia recover spontaneously, and for those who do not, platelet counts usually range from 10,000 to 100,000/μL (George, 2014). Evidence does not suggest that pregnancy increases the risk of relapse in women with previously diagnosed disease or worsens thrombocytopenia in women with active disease. That said, it is certainly not unusual for women who have been in clinical remission for several years to have recurrent thrombocytopenia during pregnancy. Although this may be from closer surveillance, hyperestrogenemia has also been implicated.

Therapy is considered if the platelet count is below 30,000 to 50,000/μL (American College of Obstetricians and Gynecologists, 2016c). Primary treatment includes corticosteroids or intravenous immune globulin (IVIG) (Neunert, 2011). Initially, prednisone, 1 mg/kg daily, is given to suppress the phagocytic activity of the splenic monocyte-macrophage system. IVIG given in a total dose of 2 g/kg during 2 to 5 days is also effective.

In pregnant women with no response to corticosteroid or IVIG therapy, open or laparoscopic splenectomy may be effective. In late pregnancy, cesarean delivery may be necessary for surgical exposure. Improvement usually follows splenectomy in 1 to 3 days and peaks at approximately 8 days. Cytotoxic agents are typically avoided in pregnancy due to teratogenicity risks. Azathioprine and rituximab, however, which are used in nonpregnant persons with ITP, have been used for other conditions in pregnancy. Finally, the thrombopoietin agonist *romiplostim* has stimulated responses in some patients (Decrooq, 2014; Imbach, 2011; Kuter, 2010).

Fetal and Neonatal Effects

Pregnancy complications that are increased with ITP include stillbirth, fetal loss, and preterm birth (Wyszynski, 2016). Platelet-associated IgG antibodies cross the placenta, and fetal death from hemorrhage occurs occasionally (Webert, 2003). The severely thrombocytopenic fetus is at increased risk for intracranial hemorrhage with labor and delivery, but fortunately this is unusual. Payne and associates (1997) reviewed studies of maternal ITP published since 1973. Of 601 newborns, 12 percent had severe thrombocytopenia with counts <50,000/μL. Six infants had intracranial hemorrhage, and in three, their initial platelet count was >50,000/μL. This is consistent with a study of 127 pregnancies in women with ITP in which 10 to 15 percent of neonates had transient ITP (Koyama, 2012).

Investigators concur that fetal and maternal platelet counts lack strong correlation (George, 2009; Hachisuga, 2014). Because of this, maternal IgG free platelet antibody levels and platelet-associated antibody levels have been evaluated to predict fetal platelet counts. Again, however, there is little concurrence with these.

Investigators have also examined the association between the specific cause of thrombocytopenia and risk of a thrombocytopenic fetus. Four researched causes include gestational thrombocytopenia, hypertension-associated thrombocytopenia, immune thrombocytopenia, and alloimmune thrombocytopenia. Burrows and Kelton (1993) reported neonatal umbilical cord platelet counts measuring <50,000/μL in 19 of 15,932 consecutive newborns (0.12 percent). Only one of 756 mothers with gestational thrombocytopenia had an affected newborn. Of 1414 hypertensive women with thrombocytopenia, five neonates had thrombocytopenia. In

contrast, of 46 mothers with immunological thrombocytopenia, four infants had thrombocytopenia. Alloimmune thrombocytopenia was associated with profound thrombocytopenia and cord platelet counts <20,000/µL. One of these fetuses died, and two others had intracranial hemorrhage.

Detection of Fetal Thrombocytopenia

Because no test accurately predicts fetal platelet counts, direct fetal blood sampling is necessary. Scott and coworkers (1983) obtained intrapartum scalp blood samples and recommended cesarean delivery for fetuses with platelet counts <50,000/µL. Daffos and colleagues (1985) reported that percutaneous umbilical cord blood sampling (PUBS) for this indication had a high complication rate (Chap. 14, Fetal Blood Sampling). Conversely, Berry and associates (1997) reported no complications and described poor reliability to predict severe thrombocytopenia, but noted a high negative-predictive value. Payne and coworkers (1997) summarized six studies in which fetal blood sampling was done for platelet estimation. Of the total of 195 fetuses, severe neonatal thrombocytopenia <50,000/µL was found in 7 percent. But, serious complications from cordocentesis were noted in 4.6 percent. Because of the low incidence of severe neonatal thrombocytopenia and morbidity, fetal platelet determinations and cesarean delivery are not recommended (Neunert, 2011).

Alloimmune Thrombocytopenia

Disparity between maternal and fetal platelet antigens can stimulate maternal production of antiplatelet antibodies. Such platelet alloimmunization can be severe, and its pathophysiology is identical to that caused by red cell antigens (Chap. 15, Fetal Thrombocytopenia).

Thrombocytosis

Also called *thrombocythemia*, thrombocytosis generally is defined as persistent platelet counts >450,000/µL. Common causes of *secondary* or *reactive thrombocytosis* are iron deficiency, infection, inflammatory diseases, and malignant tumors (Deutsch, 2013). Platelet counts seldom exceed 800,000/µL in these secondary disorders, and prognosis depends on the underlying disease. On the other hand, *primary* or *essential thrombocytosis* accounts for most cases in which platelet counts exceed 1 million/µL. It is a clonal disorder frequently due to an acquired mutation in the *JAK2* gene (Konkle, 2015). Thrombocytosis usually is asymptomatic, but arterial and venous thromboses may develop, and thrombosis is associated with pregnancy complications (Rabinerson, 2007; Randi, 2014). These cases must be differentiated from the *sticky platelet syndrome,* which is also associated with thromboses (Rac, 2011).

Normal pregnancies have been described in women whose mean platelet counts were >1.25 million/µL (Beard, 1991; Randi, 1994). Others report more adverse outcomes. Niittyvuopio and associates (2004) described 40 pregnancies in 16 women with essential thrombocythemia. Almost half had a spontaneous abortion, fetal demise, or preeclampsia. In 63 pregnancies in 36 women cared for at the Mayo Clinic, a third had a spontaneous miscarriage, but other pregnancy complications were uncommon (Gangat, 2009). In this observational study, aspirin therapy was associated with a significantly lower abortion rate than that in untreated women—1 versus 75 percent, respectively.

Suggested treatments during pregnancy include aspirin, low-molecular-weight heparin, and interferon-α (Finazzi, 2012). Interferon-α therapy during pregnancy was successful in 11 women in the review by Delage and coworkers (1996). One of these women had transient blindness at midpregnancy when her platelet count was 2.3 million/µL.

Thrombotic Microangiopathies

Although not a primary platelet disorder, some degree of thrombocytopenia accompanies the thrombotic microangiopathies, which include *thrombotic thrombocytopenic purpura (TTP)* and *hemolytic uremic syndrome (HUS).* These syndromes have an incidence of 2 to 6 per million persons per year (Miller, 2004). Their similarities to HELLP syndrome allude to their obstetrical ramifications (George, 2014).

Etiopathogenesis

Although different causes account for the variable findings within these syndromes, clinically, they frequently are indistinguishable. Most cases of TTP are thought to be caused by antibodies to or a plasma deficiency of ADAMTS13 (Ganesan, 2011; Sadler, 2010). This endothelium-derived protease cleaves von Willebrand factor (vWF) to decrease its activity. Conversely, HUS is usually due to endothelial damage incited by viral or bacterial infections and is seen primarily in children (Ardissino, 2013; George, 2014).

With TTP, intravascular platelet aggregation stimulates a cascade of events leading to end-organ failure. There is endothelial activation and damage, but it is unclear whether this is a consequence or a cause. Elevated levels of unusually large multimers of vWF are identified with active TTP. Various defects in the *ADAMTS13* gene create differing clinical presentations of thrombotic microangiopathy (Camilleri, 2007; Moake, 2002, 2004). In another scheme, antibodies raised against ADAMTS13 neutralize its action to cleave vWF multimers during an acute episode. The end result is microthrombi of hyaline material consisting of platelets and small amounts of fibrin within arterioles and capillaries. When sufficient in number or size, these aggregates produce ischemia or infarctions in various organs.

Clinical and Laboratory Manifestations

Thrombotic microangiopathies are characterized by thrombocytopenia, fragmentation hemolysis, and variable organ dysfunction. TTP is characterized by the pentad of thrombocytopenia, fever, neurological abnormalities, renal impairment, and hemolytic anemia. HUS typically has more profound renal involvement and fewer neurological aberrations.

Thrombocytopenia is usually severe, but fortunately, even with very low platelet counts, spontaneous severe hemorrhage is uncommon. Microangiopathic hemolysis is associated with moderate-to-marked anemia, and erythrocyte transfusions are frequently necessary. The blood smear is characterized by erythrocyte fragmentation with schizocytosis. Reticulocytes and nucleated red blood cells are increased, lactate dehydrogenase (LDH) levels are high, and haptoglobin concentrations are decreased. Consumptive coagulopathy, although common, is usually subtle and clinically insignificant.

Treatment

The cornerstone of treatment is plasmapheresis with fresh-frozen plasma replacement. Plasma exchange removes inhibitors and replaces the ADAMTS13 enzyme (George, 2014; Michael, 2009). Treatment with caplacizumab, the anti-vWF immunoglobulin, inhibits the interaction between ultralarge vWF multimers and platelets (Peyandi, 2016).

These treatments have remarkably improved outcomes in patients with these formerly fatal syndromes. Red cell transfusions are imperative for life-threatening anemia. Treatment is usually continued until the platelet count is >150,000/μL. Unfortunately, relapses are common. Additionally, there may be long-term sequelae such as renal impairment (Dashe, 1998; Vesely, 2015). Treatment for pregnancy-associated HUS, which is complement mediated, uses the anti-C5 humanized monoclonal antibody eculizumab (Ardissino, 2013; Cañigral, 2014; Fakhouri, 2016).

Pregnancy

As shown in the Appendix (Serum and Blood Constituents), ADAMTS13 enzyme activity decreases across pregnancy by up to 50 percent (Sánchez-Luceros, 2004). Levels drop even further with the preeclampsia syndrome. This is consonant with prevailing opinions that TTP is more commonly seen during pregnancy. The Parkland Hospital experiences were described by Dashe and coworkers (1998), who identified 11 pregnancies complicated by these syndromes among nearly 275,000 obstetrical patients—a frequency of 1 in 25,000.

It seems likely that some of the disparately higher incidence in pregnancy reported by others is because of inclusion of women with severe preeclampsia and eclampsia (Hsu, 1995; Magann, 1994). Differences that usually allow appropriate diagnosis are listed in Table 56-6. For example, moderate-to-severe hemolysis is a rather constant feature of thrombotic microangiopathies. But, this is seldom severe with the preeclampsia syndrome, even when complicated by HELLP syndrome (Chap. 40, Maternal Thrombocytopenia). And, although there is deposition of hyaline microthrombi within the liver with thrombotic microangiopathy, hepatocellular necrosis with elevated serum hepatic aminotransferase levels characteristic of preeclampsia is not a common feature (Ganesan, 2011; Sadler, 2010). Importantly, whereas delivery is imperative to reverse the preeclampsia syndrome, no evidence shows that thrombotic microangiopathy is improved by delivery (Dashe, 1998; Letsky, 2000). Finally, microangiopathic syndromes are usually recurrent and frequently unassociated with pregnancy. For example, seven of 11 women described by Dashe and colleagues (1998) had recurrent disease either when not pregnant or within the first trimester of a subsequent pregnancy. George (2009) reported recurrent TTP in only five of 36 subsequent pregnancies. That said, the risk for preeclampsia in these women is increased (Jiang, 2014).

TABLE 56-6

Some Differential Factors between HELLP Syndrome and Thrombotic Microangiopathies[a]

	HELLP Syndrome	Thrombotic Microangiopathies
Thrombocytopenia	Mild/mod.	Mod./severe
Microangiopathic hemolysis (schizocytosis)	Mild	Severe
ADAMTS13 def.	Mild/mod.	Severe
DIC	Mild	Mild
Transaminitis (AST, ALT)	Mod./severe	None/mild
Treatment	Delivery	Plasmapheresis

[a]Includes thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).

ADAMTS13 = ADAM metallopeptidase with thrombospondin type 1 motif, 13; AST = aspartate transaminase; ALT = alanine transaminase; def. = deficiency; DIC = disseminated intravascular coagulopathy; HELLP = hemolysis, elevated liver enzyme levels, low platelet count; Mod. = moderate.

Unless the diagnosis is unequivocally one of these thrombotic microangiopathies, rather than severe preeclampsia, the response to pregnancy termination should be evaluated before resorting to plasmapheresis and exchange transfusion, massive-dose glucocorticoid therapy, or other therapy. Unfortunately, recall that determination of ADAMTS13 enzyme activity may be difficult to interpret with HELLP syndrome (Franchini, 2007*). Plasmapheresis is not indicated for preeclampsia-eclampsia complicated by hemolysis and thrombocytopenia.*

During the past two decades, and coincidental with plasmapheresis and plasma exchange, maternal survival rates from thrombotic microangiopathy have improved dramatically (Dashe, 1998). Although previously fatal in up to half of mothers, with such treatment, Egerman and coworkers (1996) reported two maternal and three fetal deaths in 11 pregnancies. Hunt and associates (2013) reported that TTP accounted for 1 percent of maternal deaths in the United Kingdom from 2003 to 2008.

Long-Term Prognosis

Women who are diagnosed with thrombotic microangiopathy during pregnancy are at risk for serious long-term complications (Egerman, 1996). The Parkland experiences included a mean 9-year surveillance period (Dashe, 1998). These women had multiple recurrences; renal disease requiring dialysis, transplantation, or both; severe chronic hypertension; and transfusion-acquired infectious diseases. Two women died remote from pregnancy—one from dialysis complications and one from transfusion-acquired HIV infection.

In nonpregnant women who have recovered from thrombotic microangiopathies, persistent cognitive defects and physical disabilities have been reported (Kennedy, 2009; Lewis, 2009). Interestingly, as discussed in Chapter 40 (Renal Sequelae), these cognitive defects are very similar to those found in long-term surveillance studies of women who had eclampsia (Aukes, 2009, 2012; Wiegman, 2012).

INHERITED COAGULATION DEFECTS

Hemophilias A and B

Obstetrical hemorrhage may infrequently be the consequence of an inherited defect in a protein that controls coagulation. Both types of hemophilia are examples. Severity reflects plasma factor levels and is categorized as mild—levels of 6 to 30 percent; moderate—2 to 5 percent; or severe—less than 1 percent (Arruda, 2015).

Hemophilia A is an X-linked recessively transmitted disorder characterized by a marked deficiency of factor VIII. It is rare among women compared with men, in whom the heterozygous state is responsible for the disease. Heterozygous women have diminished factor VIII levels, but almost invariably, the homozygous state is requisite for hemophilia A. In a few instances, it appears in women spontaneously from a newly mutated gene. Pregnancy-associated acquired hemophilia A from antibodies may result in severe bleeding-related morbidity (Tengborn, 2012). *Christmas disease* or *hemophilia B* is caused by severe deficiency of factor IX and has similar genetic and clinical features.

Pregnancy

The risk of obstetrical bleeding with these is directly related to factor VIII or IX levels. Affected women have a range of activity that is determined by random X-chromosome inactivation—lyonization—although activity is expected to average 50 percent (Letsky, 2000). Levels below 10 to 20 percent pose hemorrhage risks. If levels fall to near zero, this risk is substantial. Pregnancy does afford some protection, however, because concentrations of both these clotting factors rise appreciably during normal pregnancy (Appendix, Serum and Blood Constituents). Treatment with desmopressin may also stimulate factor VIII release. Risks are further reduced by avoiding lacerations, minimizing episiotomy use, and maximizing postpartum uterine contractions. Operative vaginal deliveries should be avoided.

There are few published experiences during pregnancy. Kadir and coworkers (1997) reported that 20 percent of carriers had postpartum hemorrhage. Guy and associates (1992) reviewed five pregnancies in women with hemophilia B, and in all, outcomes were favorable. They recommended factor IX administration if levels are below 10 percent. Desmopressin has been shown in selected cases to reduce obstetrical bleeding complications (Trigg, 2012).

If a male fetus has hemophilia, the risk of hemorrhage increases after delivery in the neonate. This is especially true if circumcision is attempted.

Inheritance

If a mother has hemophilia A or B, all of her sons will have the disease, and all of her daughters will be carriers. If she is a carrier, half of her sons will inherit the disease, and half of her daughters will be carriers. Prenatal diagnosis of hemophilia is possible in some families using chorionic villus biopsy (Chap. 14, Chorionic Villus Sampling). Preimplantation genetic diagnosis for hemophilia was reviewed by Lavery (2009).

Factor VIII or IX Inhibitors

Rarely, antibodies directed against factor VIII or IX are acquired and may lead to life-threatening hemorrhage. Patients with hemophilia more commonly develop antibodies, and their acquisition in patients without hemophilia is extraordinary. It has been identified rarely in women during the puerperium (Santoro, 2009). The prominent clinical feature is severe, protracted, repetitive hemorrhage from the reproductive tract starting a week or so after an apparently uncomplicated delivery (Gibson, 2016). The activated partial thromboplastin time is markedly prolonged. Treatment has included multiple transfusions of blood component, immunosuppressive therapy, and attempts at various surgical procedures, especially curettage and hysterectomy. A recombinant activated factor VII (NovoSeven) stops bleeding in up to 75 percent of patients with these inhibitors (Arruda, 2015; Gibson, 2016).

Von Willebrand Disease

There are at least 20 heterogeneous clinical disorders involving aberrations of factor VIII complex and platelet dysfunction—collectively termed *von Willebrand disease (vWD)*. These abnormalities are the most frequently inherited bleeding disorders, and their prevalence is as high as 1 to 2 percent (Arruda, 2015; Pacheco, 2010). Most von Willebrand variants are inherited as autosomal dominant traits, and types I and II are the most common. Specifically, type I accounts for 75 percent of von Willebrand variants. Type III, which is the most severe, is a recessive trait. Although most cases of acquired vWD develop after age 50 years, some have been reported in pregnant women (Lipkind, 2005).

Pathogenesis

The *von Willebrand factor* is a series of large plasma multimeric glycoproteins that form part of the factor VIII complex. It is essential for normal platelet adhesion to subendothelial collagen and formation of a primary hemostatic plug. It also plays a major role in stabilizing the coagulant properties of factor VIII. The procoagulant component is factor VIII, a glycoprotein synthesized by the liver. Conversely, von Willebrand precursor, which is present in platelets and plasma, is synthesized by endothelium and megakaryocytes. The von Willebrand factor antigen (vWF:Ag) is the antigenic determinant measured by immunoassays.

Clinical Presentation

Symptomatic patients typically present with easy bruising, epistaxis, mucosal hemorrhage, and excessive bleeding with trauma, including surgery. The classic autosomal dominant forms usually cause symptoms in the heterozygous state. With vWD, laboratory features often include a prolonged bleeding time, prolonged partial thromboplastin time, decreased vWF antigen levels, decreased factor VIII immunological and coagulation-promoting activity, and inability of platelets from an affected person to react to various stimuli.

Pregnancy

During normal pregnancy, maternal levels of both factor VIII and vWF antigen increase substantively (Appendix, Serum and Blood Constituents). Because of this, pregnant women with vWD often develop normal levels of factor VIII coagulant activity and vWF antigen, although their measured bleeding time still may be prolonged. If factor VIII activity is very low or if there is bleeding, treatment is recommended. Desmopressin by infusion transiently increases factor VIII and vWF levels (Arruda, 2015; Kujovich, 2005). With significant bleeding, 15 or 20 units of cryoprecipitate are transfused every 12 hours. Alternatively, factor VIII concentrates (Alfanate, Hemate-P) may be given that contain high-molecular-weight vWF multimers. Lubetsky and colleagues (1999) described continuous infusion with Hemate-P in a woman during a vaginal delivery. According to Chi and coworkers (2009), conduction analgesia can be provided safely if coagulation defects have normalized or if hemostatic agents are administered prophylactically.

Pregnancy outcomes in women with vWD are generally good, but postpartum hemorrhage is encountered in up to half of cases. In a fourth of 38 cases summarized by Conti and associates (1986), bleeding was reported with abortion, with delivery, or in the puerperium. Kadir and coworkers (1998) reported their experiences with 84 pregnancies. They described a 20-percent incidence of immediate postpartum hemorrhage and another 20-percent incidence of late hemorrhage. Most cases were associated with low vWF levels in untreated women, and none given treatment peripartum had hemorrhage. More recently, Stoof and colleagues (2015) reviewed 185 deliveries in 154 affected women and found the risk for postpartum hemorrhage to be highest in deliveries with lowest factor levels.

Inheritance

Although most patients with vWD have heterozygous variants and associated minor bleeding complications, the disease can be severe. Moreover, homozygous offspring develop serious clotting dysfunction. Chorionic villus sampling with DNA analysis to detect the missing genes has been described. Some authorities recommend cesarean delivery to avoid trauma to a possibly affected fetus if the mother has severe disease.

Other Factor Deficiencies

In general, the activity of most procoagulant factors rises across pregnancy (Appendix, Serum and Blood Constituents). *Factor VII deficiency* is a rare autosomal recessive disorder. Levels of this factor normally increase during pregnancy, but these may rise only mildly in women with factor VII deficiency (Fadel, 1989). A systematic review of 94 births found no difference in postpartum hemorrhage rates with or without prophylaxis with recombinant factor VIIa (Baumann Kreuziger, 2013).

Factor X or *Stuart-Prower factor* deficiency is rare and is inherited as an autosomal recessive trait. Factor X levels typically rise by 50 percent during normal pregnancy. Konje and colleagues (1994) described a woman who had 2-percent factor activity. She was given prophylactic treatment with plasma-derived factor X, which raised her plasma levels to 37 percent. Despite this, she suffered an intrapartum placental abruption. Bofill and coworkers (1996) gave intrapartum fresh-frozen plasma to a woman with less than 1-percent factor X activity. She delivered spontaneously without incident. Beksaç and associates (2010) described a woman with severe factor X deficiency who was successfully managed with prophylactic prothrombin complex concentrate. Nance and colleagues (2012) reported on 24 pregnancies, of which 18 resulted in a healthy baby.

Factor XI—plasma thromboplastin antecedent—deficiency is inherited as an autosomal trait. It manifests as severe disease in homozygotes but only as a minor defect in heterozygotes. It is most prevalent in Ashkenazi Jews and is rarely seen in pregnancy. Musclow and coworkers (1987) reported 41 deliveries in 17 affected women, and none required transfusion. In 105 pregnancies from 33 affected women, Myers and colleagues (2007) reported an uneventful pregnancy and delivery in 70 percent. They recommended peripartum treatment with factor XI concentrate if cesarean delivery is performed and advised against epidural analgesia unless factor XI is given. From their review, Martin-Salces and associates (2010) found that factor XI levels and bleeding severity correlated poorly in women with severe deficiency. Wiewel-Verschueren and colleagues (2015) performed a systematic review of 27 studies with 372 women and reported that 18 percent had postpartum hemorrhage.

Factor XII deficiency is another autosomal recessive disorder that rarely complicates pregnancy. A greater incidence of thromboembolism is encountered in nonpregnant patients with this deficiency. Lao and coworkers (1991) reported an affected pregnant woman in whom placental abruption developed at 26 weeks' gestation.

Factor XIII deficiency is an autosomal recessive trait and may be associated with maternal intracranial hemorrhage (Letsky, 2000). In their review, Kadir and associates (2009) cited an increased risk of recurrent miscarriage and placental abruption. It has also been reported to cause umbilical cord bleeding (Odame, 2014). Treatment is fresh frozen plasma. Naderi and colleagues (2012) described 17 successful pregnancies in women receiving weekly prophylaxis with Factor XIII concentrate.

Fibrinogen abnormalities—either qualitative or quantitative—also may cause coagulation abnormalities. Autosomally inherited abnormalities usually involve the formation of a functionally defective fibrinogen—commonly referred to as *dysfibrinogenemia* (Edwards, 2000). Familial *hypofibrinogenemia* and sometimes *afibrinogenemia* are infrequent recessive disorders. In some cases, both are found—*hypodysfibrinogenemia* (Deering, 2003). Our experience suggests that hypofibrinogenemia represents a heterozygous autosomal dominant state. The thrombin-clottable protein level in these patients typically ranges from 80 to 110 mg/dL when nonpregnant, and this increases by 40 or 50 percent in normal pregnancy. Those pregnancy complications that give rise to acquired

hypofibrinogenemia, such as placental abruption, are more common with fibrinogen deficiency. Trehan and Fergusson (1991) and Funai and coworkers (1997) described successful outcomes in two affected women in whom fibrinogen or plasma infusions were given throughout pregnancy.

Conduction Analgesia with Bleeding Disorders

Most serious bleeding disorders would logically preclude the use of epidural or spinal analgesia for labor or delivery. If the bleeding disorder is controlled, however, conduction analgesia may be considered. Chi and colleagues (2009) reviewed intrapartum outcomes in 80 pregnancies in 63 women with an inherited bleeding disorder. These included those with factor XI deficiency, hemophilia carrier status, vWD, platelet disorders, or a deficiency of factor VII, XI, or X. Regional block was used in 41. Of these, 35 had spontaneously normalized hemostatic dysfunction, and others were given prophylactic replacement therapy. The reviewers reported no unusual complications. Singh and associates (2009) reviewed 13 women with factor XI deficiency. Nine received neuraxial analgesia without complications, but only after fresh-frozen plasma was transfused to most to correct the activated partial thromboplastin time.

THROMBOPHILIAS

Several important regulatory proteins act as inhibitors at strategic sites in the coagulation cascade to maintain blood fluidity. Inherited deficiencies of these inhibitory proteins are caused by gene mutations. Because they may be associated with recurrent thromboembolism, they are collectively referred to as *thrombophilias.* These are discussed in Chapter 52 (Thrombophilias) and reviewed by the American College of Obstetricians and Gynecologists (2017b).

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CHAPTER 57: Diabetes Mellitus

Diabetes may exist before the inception of pregnancy, or may not appear until labour. The prognosis is generally believed to be ominous for mother and child, but a review of the literature shows that less than 25 percent of the mothers died from diabetic coma, while premature labour occurred in only one third of the cases.

—J. Whitridge Williams (1903)

INTRODUCTION

In the early 1900s, overt diabetes complicating pregnancy was associated with horrific morbidity and mortality for a mother and her fetus. Although tremendously mitigated by the discovery of insulin, overt and gestational diabetes still are formidable complications of pregnancy.

According to the Centers for Disease Control and Prevention (2017), the number of adults diagnosed with diabetes in the United States is 23.1 million. And, almost a quarter of people with diabetes in the United States remain undiagnosed. Reasons for these substantial rates include an aging population more likely to develop type 2 diabetes, population growth within minority group at particular risk for type 2 diabetes, and a dramatic rise in obesity rates —also referred to as *diabesity*. The term reflects the strong relationship of diabetes and the current obesity epidemic in the United States and underlines the critical need for diet and lifestyle interventions to change the trajectory of both.

There is keen interest in events that precede diabetes, and this includes the intrauterine environment. Here, early imprinting is believed to have effects later in life (Saudek, 2002). For example, in utero exposure to maternal hyperglycemia leads to fetal hyperinsulinemia, causing an increase in fetal fat cells. This leads to obesity and insulin resistance in childhood (Feig, 2002). These factors in turn lead to impaired glucose tolerance and diabetes in adulthood. This cycle of fetal exposure to diabetes leading to childhood obesity and glucose intolerance is discussed further in Chapter 48 (Antepartum Management).

TYPES OF DIABETES

In nonpregnant individuals, the type of diabetes is based on its presumed etiopathogenesis and its pathophysiological manifestations. Absolute insulin deficiency, generally autoimmune in etiology, characterizes *type 1 diabetes*. In contrast, insulin resistance, relative insulin deficiency, or elevated glucose production characterizes *type 2 diabetes* (Table 57-1). Both types are generally preceded by a period of abnormal glucose homeostasis often referred to as prediabetes. The terms insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM) are now obsolete. Pancreatic β-cell destruction can begin at any age, but type 1 diabetes is clinically apparent most often before age 30. Type 2 diabetes usually develops with advancing age but is increasingly identified in younger obese adolescents.

TABLE 57-1

Etiological Classification of Diabetes Mellitus

Type 1: β-Cell destruction, usually absolute insulin deficiency
Immune-mediated
Idiopathic
Type 2: Ranges from predominantly insulin resistance to predominantly an insulin secretory defect with insulin resistance
Other types
Genetic mutations of β-cell function—MODY 1–6, others
Genetic defects in insulin action
Genetic syndromes—Down, Klinefelter, Turner
Diseases of the exocrine pancreas—pancreatitis, cystic fibrosis
Endocrinopathies—Cushing syndrome, pheochromocytoma, others
Drug or chemical induced—glucocorticosteroids, thiazides, β-adrenergic agonists, others
Infections—congenital rubella, cytomegalovirus, coxsackievirus
Gestational diabetes

MODY = maturity-onset diabetes of the young.

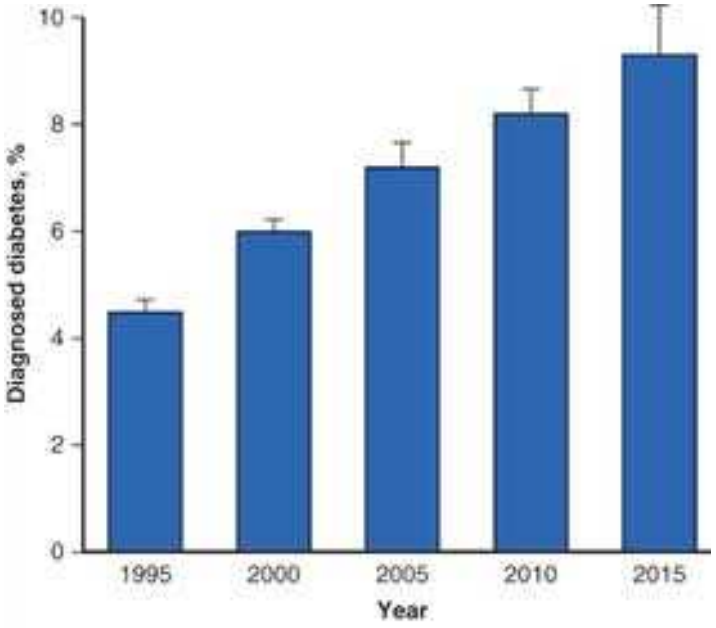
Data from Powers, 2012.

Classification During Pregnancy

Diabetes is the most common medical complication of pregnancy. Women can be separated into those who were known to have diabetes before pregnancy—*pregestational* or *overt*, and those diagnosed during pregnancy—*gestational diabetes*. The proportion of pregnancies complicated by diabetes more than doubled between 1994 and 2008, after which rates seem to have stabilized (Jovanovič, 2015). Almost 258,000—6.5 percent—of gravidas in the United States had pregnancies coexistent with some form of diabetes in 2015 (Martin, 2017). Prevalence of diabetes is highest among non-Hispanic blacks, Mexican-Americans, Puerto Rican-Americans, and Native Americans (Golden, 2012). The incidence of gestational diabetes during the past 20 years, shown in Figure 57-1, is reminiscent of similar statistics for obesity (Chap. 48, General Considerations).

FIGURE 57-1

Increasing prevalence of type 2 diabetes in the United States from 1995 to 2015. (Reproduced with permission from Centers for Disease Control and Prevention, 2017.)



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: Williams Obstetrics, 25th Edition

White Classification in Pregnancy

Until the mid-1990s, the classification by Priscilla White (1978) for diabetic pregnant women was the linchpin of management. Today, the White classification is used less frequently but still provides simple and useful information on pregnancy risks and prognosis (Bennett, 2015). And, because most currently cited literature also contains data from these older classifications, the one previously recommended by the American College of Obstetricians and Gynecologists (1986) is provided in Table 57-2.

TABLE 57-2

Classification Scheme Used from 1986 through 1994 for Diabetes Complicating Pregnancy

		Plasma Glucose Level		
Class	**Onset**	**Fasting**	**2-Hour Postprandial**	**Therapy**
A_1	Gestational	<105 mg/dL	<120 mg/dL	Diet
A_2	Gestational	>105 mg/dL	>120 mg/dL	Insulin
Class	**Age of Onset (yr)**	**Duration (yr)**	**Vascular Disease**	**Therapy**
B	Over 20	<10	None	Insulin
C	10 to 19	10 to 19	None	Insulin
D	Before 10	>20	Benign retinopathy	Insulin
F	Any	Any	Nephropathy[a]	Insulin
R	Any	Any	Proliferative retinopathy	Insulin
H	Any	Any	Heart	Insulin

[a]When diagnosed during pregnancy: proteinuria ≥500 mg/24 hr before 20 weeks' gestation.

Beginning several years ago, the American College of Obstetricians and Gynecologists no longer recommended the White classification. Instead, the current focus is whether diabetes antedates pregnancy or is first diagnosed during pregnancy. Many now recommend adoption of the classification

proposed by the American Diabetes Association (ADA), which is shown in Table 57-3.

TABLE 57-3

Proposed Classification System for Diabetes in Pregnancy

Gestational diabetes: diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes	
Type 1 Diabetes: Diabetes resulting from β-cell destruction, usually leading to absolute insulin deficiency a. Without vascular complications b. With vascular complications (specify which)	**Type 2 Diabetes:** Diabetes from inadequate insulin secretion in the face of increased insulin resistance a. Without vascular complications b. With vascular complications (specify which)
Other types of diabetes: genetic in origin, associated with pancreatic disease, drug-induced, or chemically induced	

Data from American Diabetes Association, 2017a.

PREGESTATIONAL DIABETES

The rising prevalence of type 2 diabetes, particularly in younger people, has led to an increasing number of affected pregnancies. For example, the CDC (2015) estimates that more than 5000 new cases of type 2 diabetes are diagnosed each year in youths before the age of 20 years. Feig and coworkers (2014) reported that the incidence of pregestational diabetes doubled from 7 per 1000 women in 1996 to 15 per 1000 in 2010. When considering the previously mentioned high percentage of diabetes that is undiagnosed, then many women identified to have gestational diabetes likely have type 2 diabetes previously unrecognized. In fact, 5 to 10 percent of women with gestational diabetes are found to have diabetes immediately after pregnancy.

Diagnosis

Women with high plasma glucose levels, glucosuria, and ketoacidosis present no diagnostic challenge. Women with a random plasma glucose level >200 mg/dL plus classic signs and symptoms such as polydipsia, polyuria, and unexplained weight loss, or those with a fasting glucose level >125 mg/dL are considered by the ADA (2017a) and the World Health Organization (2013) to have overt diabetes first detected in pregnancy. Women with only minimal metabolic derangement may be more difficult to identify. To diagnose overt diabetes in pregnancy, The International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (2010) recognizes the threshold values found in Table 57-4 for fasting or random plasma glucose and glycosylated hemoglobin (HbA_{1c}) levels at prenatal care initiation. The ADA (2017a) and the World Health Organization (2013) now also consider a plasma glucose level >200 mg/dL measured 2 hours after a 75 g oral glucose load to be diagnostic. No consensus has been reached as to whether such testing should be universal or limited to those women classified as high risk. Regardless, the tentative diagnosis of overt diabetes during pregnancy based on these thresholds should be confirmed postpartum. Risk factors for impaired carbohydrate metabolism in pregnant women include a strong familial history of diabetes, prior delivery of a large newborn, persistent glucosuria, or unexplained fetal losses.

TABLE 57-4

Diagnosis of Overt Diabetes in Pregnancy[a]

Measure of Glycemia	Threshold
Fasting plasma glucose	At least 7.0 mmol/L (126 mg/dL)
Hemoglobin A_{1c}	At least 6.5%
Random plasma glucose	At least 11.1 mmol/L (200 mg/dL) plus confirmation

[a]Apply to women without known diabetes antedating pregnancy. The decision to perform blood testing for evaluation of glycemia on all pregnant women or only on women with characteristics indicating a high risk for diabetes is based on the background frequency of abnormal glucose metabolism in the population and on local circumstances.

Data from International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010.

Impact on Pregnancy

With overt diabetes, the embryo, fetus, and mother frequently experience serious complications directly attributable to diabetes. Peterson and colleagues (2015) estimate that thousands of these complications might be prevented each year by preconceptional care for improved glycemic control. The likelihood of successful outcomes with overt diabetes, however, is not simply related to glucose control. The degree of underlying cardiovascular or renal disease may be more important. Thus, advancing stages of the White classification, seen in Table 57-2, are inversely related to favorable pregnancy outcomes. Shown in Table 57-5 are data that chronicle the deleterious pregnancy outcomes with overt diabetes. These maternal and fetal complications are described in the following sections.

TABLE 57-5

Pregnancy Outcomes of Births in Nova Scotia from 1988 to 2002 in Women with and without Pregestational Diabetes

Factor	Diabetic (n = 516) %	Nondiabetic (n = 150, 598) %	*p* value
Gestational hypertension	28	9	<.001
Preterm birth	28	5	<.001
Macrosomia	45	13	<.001
Fetal-growth restriction	5	10	<.001
Stillbirth	1.0	0.4	.06
Perinatal death	1.7	0.6	.004

Data from Yang, 2006.

Fetal Effects

Spontaneous Abortion

Several studies have shown that early miscarriage is associated with poor glycemic control (Chap. 18, First-Trimester Spontaneous Abortion). Up to 25 percent of diabetic gravidas have an early pregnancy loss (Galindo, 2006; Rosenn, 1994). Those whose HbA_{1c} concentrations were >12 percent or whose preprandial glucose concentrations were persistently >120 mg/dL had an elevated risk. Bacon and associates (2015) reviewed 89 pregnancies in women with maturity-onset diabetes of the young (MODY), which is a monogenic form of diabetes. These investigators found that only women with the causative glucose kinase gene (GCK) mutation were more likely to have a miscarriage. These women are characterized by hyperglycemic variability that is difficult to control.

Preterm Delivery

Overt diabetes is an undisputed risk factor for preterm birth. Eidem and associates (2011) analyzed 1307 births in women with type 1 diabetes from the Norwegian Medical Birth Registry. More than 26 percent were delivered preterm compared with 6.8 percent in the general obstetrical population. Moreover, almost 60 percent were indicated preterm births, that is, due to obstetrical or medical complications. In one review of more than 500,000 California births, 19 percent of women with pregestational diabetes had a preterm birth compared with 9 percent in controls (Yanit, 2012). In the Canadian study shown in Table 57-5, the incidence of preterm birth was 28 percent.

Malformations

The incidence of major malformations in women with type 1 diabetes is at least doubled and approximates 11 percent (Jovanovič, 2015). These account for almost half of perinatal deaths in diabetic pregnancies. As shown in Table 57-6, cardiovascular malformations accounted for more than half of the anomalies. In a cohort study of more than 2 million births in Canada, the risk of an isolated cardiac defect was fivefold higher in women with type 1 diabetes (Liu, 2013). The caudal regression sequence, described in Chapter 10 (Face and Neck), is a rare malformation frequently associated with maternal diabetes (Garne, 2012).

TABLE 57-6

Major Congenital Anomalies in 36,345 Neonates Born to Women with Diabetes between 2004 and 2011

Organ System	Type 1 DM n = 482	Type 2 DM n = 4166	GDM n = 31,700
Total	55	454	2203
Cardiac	38	272	1129
Musculoskeletal	1	31	231
Urinary	3	28	260
CNS	1	13	64
GI	1	30	164
Other	11	80	355

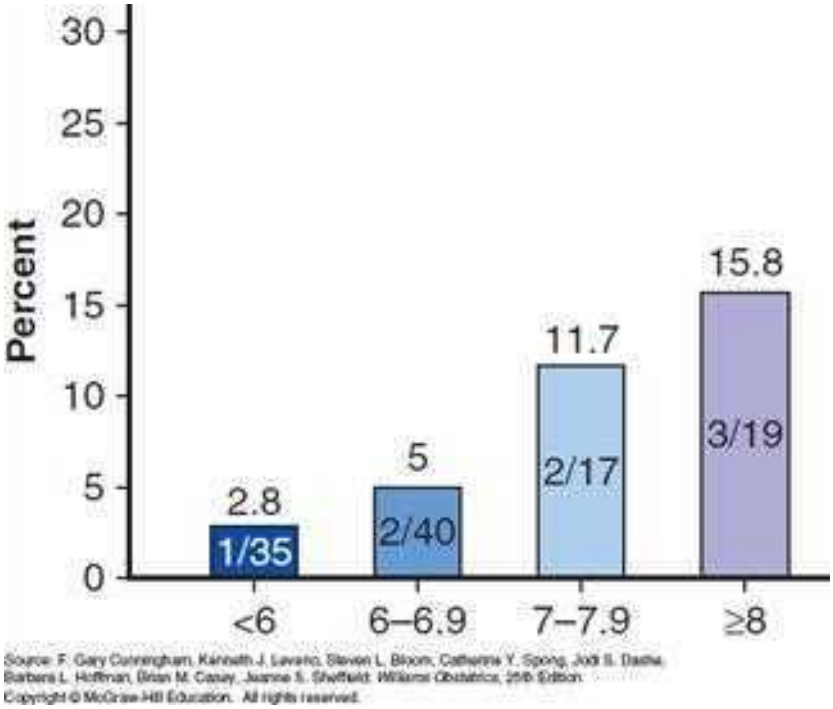
CNS = central nervous system; DM = diabetes mellitus; GDM = gestational diabetes; GI = gastrointestinal.

Data from Jovanovič, 2015.

Poorly controlled diabetes, both preconceptionally and early in pregnancy, is thought to underlie this elevated severe-malformation risk. As shown in Figure 57-2, increased maternal HbA_{1c} levels and major malformations clearly correlate. To explain this, at least three interrelated molecular chain reactions have been linked to maternal hyperglycemia (Reece, 2012). These include alterations in cellular lipid metabolism, excess production of toxic superoxide radicals, and activation of programmed cell death. In their review of molecular mechanisms underlying diabetic embryopathy, Yang and colleagues (2015) suggest that these cellular responses to oxidative stress represent potential therapeutic targets to prevent diabetes-induced embryopathy.

FIGURE 57-2

The frequency of major congenital malformations in newborns of women with pregestational diabetes stratified by hemoglobin A_{1c} levels at first prenatal visit. (Data from Galindo A, Burguillo AG, Azriel S, et al: Outcome of fetuses in women with pregestational diabetes mellitus, J Perinat Med. 2006;34(4):323–331.)

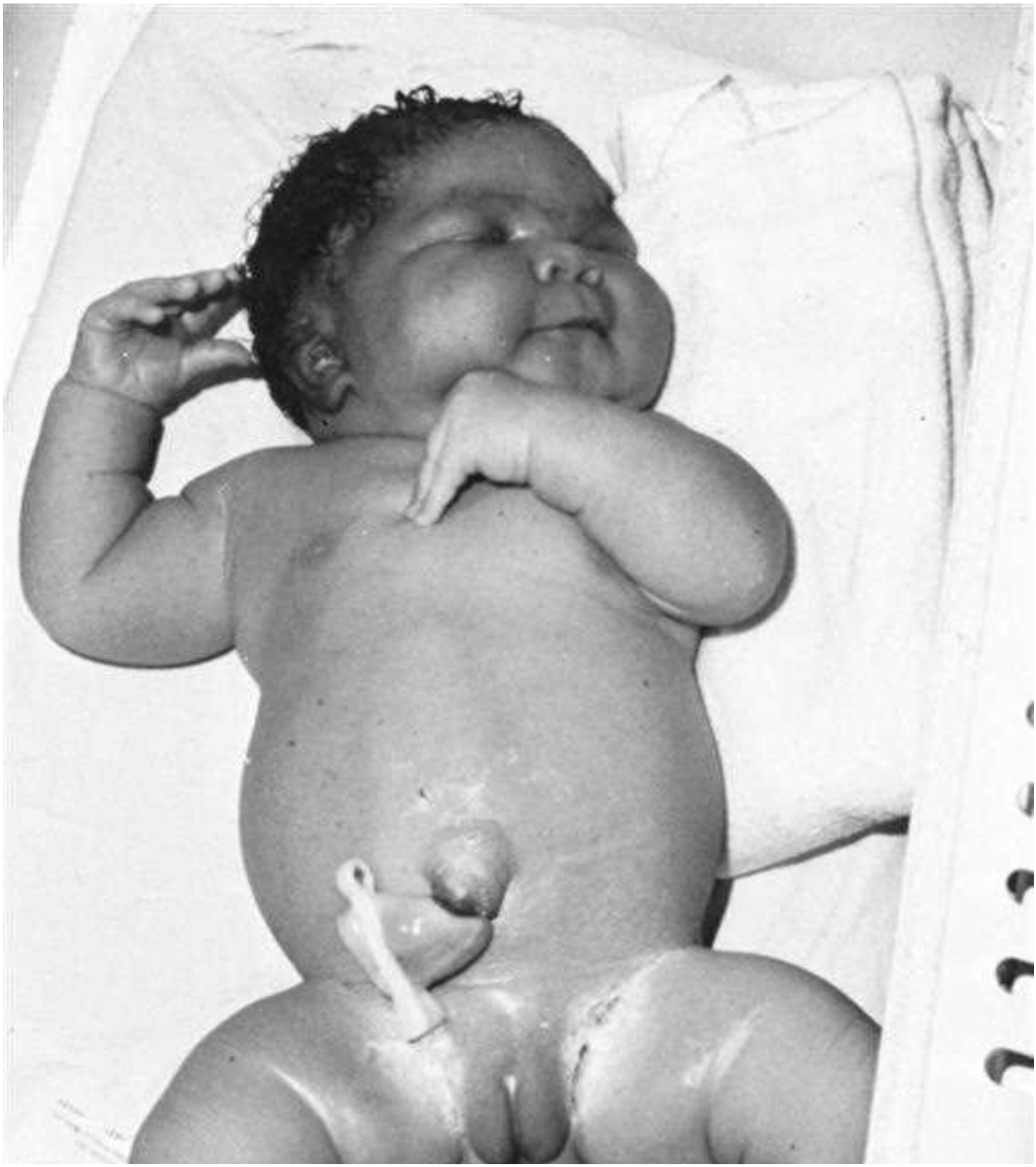


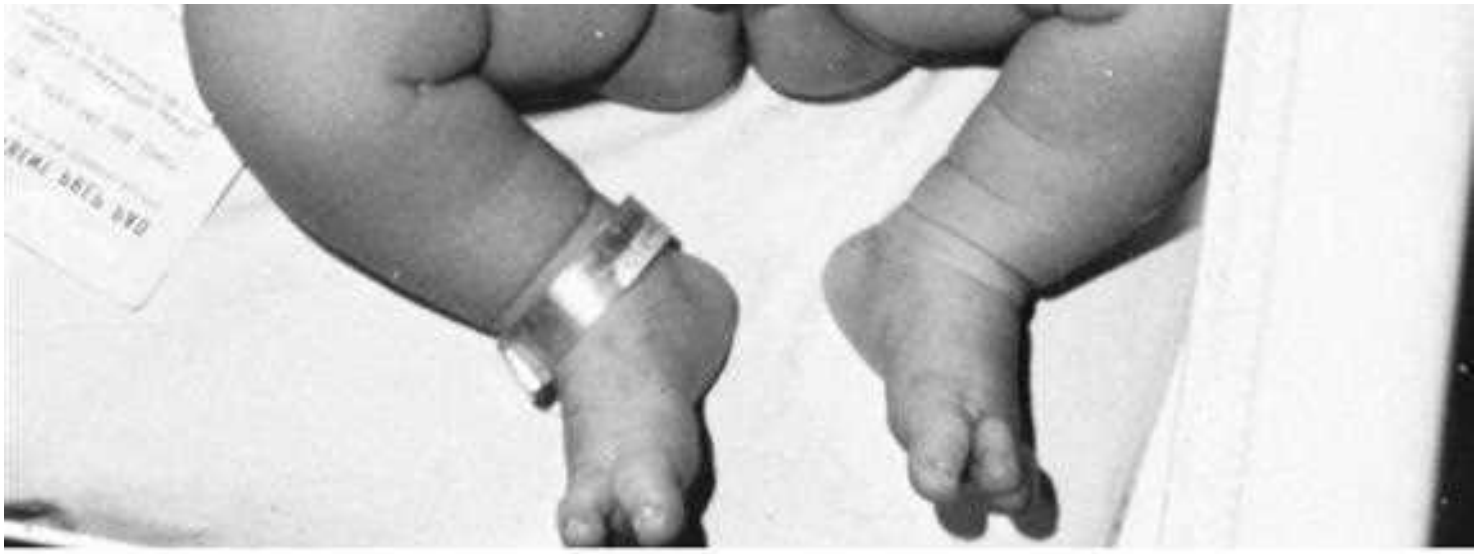
Altered Fetal Growth

Diminished growth may result from congenital malformations or from substrate deprivation due to advanced maternal vascular disease. That said, fetal overgrowth is more typical of pregestational diabetes. Maternal hyperglycemia prompts fetal hyperinsulinemia, and this in turn stimulates excessive somatic growth. Except for the brain, most fetal organs are affected by the macrosomia that characterizes the fetus of a diabetic woman. Newborns such as the one shown in Figure 57-3 are described as being anthropometrically different from other large-for-gestational age (LGA) neonates (Catalano, 2003; Durnwald, 2004). Specifically, those whose mothers are diabetic have excessive fat deposition on the shoulders and trunk, which predisposes to shoulder dystocia or cesarean delivery.

FIGURE 57-3

This 6050-g macrosomic infant was born to a woman with gestational diabetes.

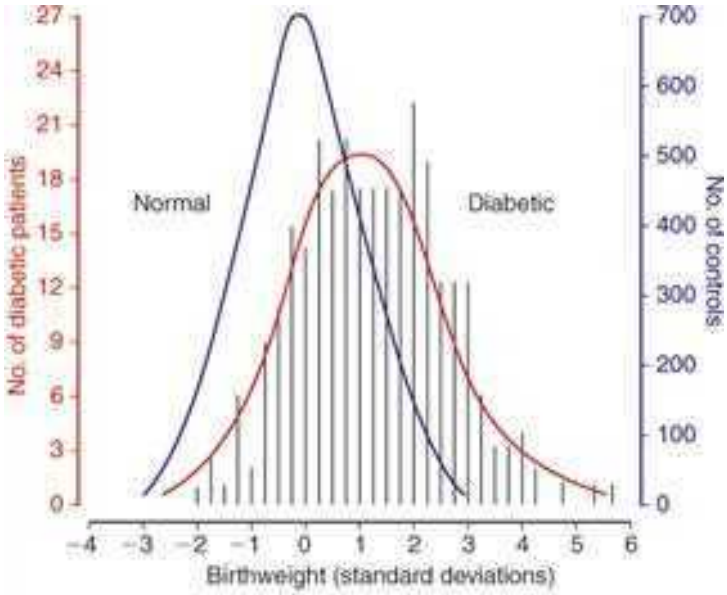




The incidence of macrosomia rises significantly when mean maternal blood glucose concentrations chronically exceed 130 mg/dL (Hay, 2012). Hammoud and coworkers (2013) reported that the macrosomia rates for Nordic women with type 1, type 2, or gestational diabetes were 35 percent, 28 percent, and 24 percent, respectively. As shown in Figure 57-4, the birthweight distribution of neonates of diabetic mothers is skewed toward consistently heavier birthweights.

FIGURE 57-4

Distribution of birthweight standard deviations from the normal mean for gestational age in 280 newborns of diabetic mothers and in 3959 neonates of nondiabetic mothers. (Reproduced with permission from Bradley RJ, Nicolaides KH, Brudenell JM.: Are all infants of diabetic mothers “macrosomic”? BMJ 1988 Dec 17;297(6663):1583–1584.)



In the study by Hammoud and colleagues (2013), fetal growth profiles from 897 sonographic examinations in 244 women with diabetes were compared with 843 examinations in 145 control women. The abdominal circumference grew disproportionately larger in the diabetic groups. Analysis of head circumference/abdominal circumference (HC/AC) ratios shows that this disproportionate growth occurs mainly in diabetic pregnancies that ultimately yield macrosomic newborns. These findings comport with the observation that virtually all neonates of diabetic mothers are growth promoted, and accelerated fetal growth is particularly evident in women with poor glycemic control.

Unexplained Fetal Demise

Worldwide, the risk of fetal death is three to four times higher in women with pregestational diabetes (Gardosi, 2013; Patel, 2015). Stillbirth without an identifiable cause is a phenomenon relatively limited to pregnancies complicated by overt diabetes. These stillbirths are “unexplained” because common factors such as obvious placental insufficiency, placental abruption, fetal-growth restriction, or oligohydramnios are not identified. These fetuses are typically large for gestational age and die before labor, usually late in the third trimester.

These unexplained stillbirths are associated with poor glycemic control. Lauenborg and coworkers (2003) identified suboptimal glycemic control in two thirds of unexplained stillbirths between 1990 and 2000. Also, fetuses of diabetic mothers often have elevated lactic acid levels. Salvesen and colleagues (1992, 1993) analyzed fetal blood samples and reported that mean umbilical venous blood pH was lower in diabetic pregnancies and was significantly related to fetal insulin levels. Such findings support the hypothesis that hyperglycemia-mediated chronic aberrations in oxygen and fetal metabolite transport may underlie these unexplained fetal deaths (Pedersen, 1977).

Aside from hyperglycemia alone, maternal ketoacidosis can cause fetal death. Explicable stillbirths due to placental insufficiency also occur with increased frequency in women with overt diabetes, usually in association with severe preeclampsia. In the prior California study of nearly a half million singleton deliveries, the fetal death risk was sevenfold higher in women with hypertension and pregestational diabetes compared with the threefold increased risk associated with diabetes alone (Yanit, 2012). Stillbirth rates are also greater in women with advanced diabetes and vascular complications.

Hydramnios

Diabetic pregnancies are often complicated by excess amnionic fluid. According to Idris and coworkers (2010), 18 percent of 314 women with pregestational diabetes were identified to have hydramnios, defined as an amnionic fluid index (AFI) >24 cm in the third trimester. And, women with elevated HbA_{1c} values in the third trimester were more likely to have hydramnios. A likely—albeit unproven—explanation is that fetal hyperglycemia causes polyuria (Chap. 11, Etiology). In a study from Parkland Hospital, Dashe and colleagues (2000) found that the AFI parallels the amnionic fluid glucose level among women with diabetes. Further support for this association was provided by Vink and associates (2006), who linked poor maternal glucose control to macrosomia and hydramnios.

Neonatal Effects

Before tests of fetal health and maturity became available, delivery before term was deliberately selected for women with diabetes to avoid unexplained stillbirth. Although this practice has been abandoned, a higher frequency of preterm delivery in women with diabetes persists. Most are indicated deliveries due to advanced diabetes with superimposed preeclampsia. That said, Little and associates (2015) in their analysis of early-term delivery ($37^{0/7}$ to $38^{6/7}$ weeks) found a 13-percent reduction in such deliveries in women with diabetes between 2005 and 2011.

Although modern neonatal care has reduced neonatal death rates due to immaturity, neonatal *morbidity* due to preterm birth continues to be a serious consequence. In one Neonatal Research Network study of 10,781 extremely preterm neonates, those born to diabetic women treated with insulin prior to pregnancy were at greater risk for necrotizing enterocolitis and late-onset sepsis than neonates of mothers without diabetes (Boghossian, 2016).

Respiratory Distress Syndrome

Gestational age rather than overt diabetes is likely the most significant factor associated with respiratory distress syndrome (Chap. 33, Respiratory Distress). Indeed, in one analysis of 19,399 very-low-birthweight neonates delivered between 24 and 33 weeks' gestation, rates of respiratory distress syndrome in newborns of diabetic mothers were not higher compared with rates in neonates of nondiabetic mothers (Bental, 2011).

Hypoglycemia

Newborns of a diabetic mother experience a rapid drop in plasma glucose concentration after delivery. This is attributed to hyperplasia of the fetal β-islet cells induced by chronic maternal hyperglycemia. Low glucose concentrations—defined as <45 mg/dL—are particularly common in newborns of women with unstable glucose concentrations during labor (Persson, 2009). Frequent blood glucose measurements in the newborn and active early feeding practices can mitigate these complications.

Hypocalcemia

Defined as a total serum calcium concentration <8 mg/dL in term newborns, early onset hypocalcemia is one of the potential metabolic derangements in neonates of diabetic mothers. Its cause has not been explained. Theories include aberrations in magnesium–calcium economy, asphyxia, and preterm birth. In a randomized study, 137 pregnant women with type 1 diabetes were managed with strict versus customary glucose control (DeMarini, 1994). Almost a third of neonates in the customary control group developed hypocalcemia compared with only 18 percent of those in the strict-control group.

Hyperbilirubinemia and Polycythemia

The pathogenesis of hyperbilirubinemia in neonates of diabetic mothers is uncertain. A major contributing factor is newborn polycythemia, which raises the bilirubin load (Chap. 33, Polycythemia and Hyperviscosity). Polycythemia is thought to be a fetal response to relative hypoxia. According to Hay (2012), the sources of this fetal hypoxia are hyperglycemia-mediated elevations in maternal affinity for oxygen and fetal oxygen consumption. Together with insulin-like growth factors, this hypoxia leads to elevated fetal erythropoietin levels and red cell production. Fetal renal vein thrombosis is reported to result from polycythemia.

Cardiomyopathy

Newborns of diabetic pregnancies may have hypertrophic cardiomyopathy that primarily affects the interventricular septum (Rolo, 2011). Huang and coworkers (2013) propose that pathological ventricular hypertrophy in neonates born to women with diabetes is due to insulin excess. In severe cases, this cardiomyopathy may lead to obstructive cardiac failure. Russell and coworkers (2008) performed serial echocardiograms on fetuses of 26 women with pregestational diabetes. In the first trimester, fetal diastolic dysfunction was already evident in some. In the third trimester, the fetal interventricular septum and right ventricular wall were thicker in fetuses of diabetic mothers. Most affected newborns are asymptomatic following birth, and hypertrophy usually resolves in the months after delivery.

Long-Term Cognitive Development

Intrauterine metabolic conditions have long been linked to neurodevelopment in offspring. In a study of more than 700,000 Swedish-born men, the intelligence quotient of those whose mothers had diabetes during pregnancy averaged 1 to 2 points lower (Fraser, 2014). DeBoer and associates (2005) demonstrated impaired memory performance in infants of diabetic mothers at age 1 year. Results from the Childhood Autism Risks from Genetics and the Environment (CHARGE) study indicated that autism spectrum disorders or developmental delay were also more common in children of diabetic women (Krakowiak, 2012). Adane and colleagues (2016) confirmed a consistent relationship between maternal diabetes and diminished cognitive and language development in studies of younger children but not older children. Because interpreting effects of the intrauterine environment on neurodevelopment is confounded by postnatal factors, the link between maternal diabetes, glycemic control, and long-term neurocognitive outcome remains unconfirmed.

Inheritance of Diabetes

The risk of developing type 1 diabetes if either parent is affected is 3 to 5 percent. Type 2 diabetes has a much stronger genetic component. If both parents have type 2 diabetes, the risk of developing it approaches 40 percent. Both types of diabetes develop after a complex interplay between genetic predisposition and environmental factors. Type 1 diabetes is prompted by environmental triggers such as infection, diet, or toxins and heralded by the appearance of islet cell autoantibodies in genetically vulnerable individuals (Pociot, 2016; Rewers, 2016). Some but not all studies have shown a reduction in risk for type 1 or type 2 diabetes associated with breastfeeding (Owen, 2006; Rewers, 2016).

Maternal Effects

Diabetes and pregnancy interact significantly such that maternal welfare can be seriously jeopardized. With the possible exception of diabetic retinopathy, however, the long-term course of diabetes is not affected by pregnancy.

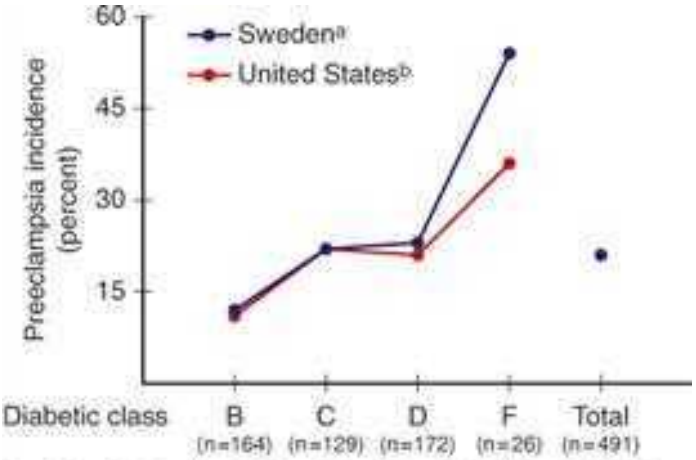
In an analysis of more than 800,000 pregnancies, Jovanovič and colleagues (2015) found that 1125 mothers with type 1 diabetes were at increased risk for hypertension and respiratory complications compared with nondiabetic women. And, 10,126 mothers with type 2 diabetes had an elevated risk for depression, hypertension, infection, and cardiac or respiratory complications compared with pregnant controls. Maternal death is uncommon, but rates in women with diabetes are still higher than those in unaffected gravidas. In one analysis of 972 women with type 1 diabetes, the maternal mortality rate was 0.5 percent, and deaths resulted from diabetic ketoacidosis, hypoglycemia, hypertension, and infection (Leinonen, 2001).

Preeclampsia

Pregnancy-associated hypertension is the complication that most often forces preterm delivery in diabetic women. The incidence of chronic and gestational hypertension—and especially preeclampsia—is remarkably increased (Chap. 40, Incidence and Risk Factors). In a systematic review and metaanalysis of 92 studies including more than 25 million pregnancies, Bartsch and associates (2016) calculated a pooled relative risk of 3.7 for preeclampsia in women with pregestational diabetes. In the study cited earlier by Yanit and colleagues (2012), preeclampsia developed three to four times more often in women with overt diabetes. Moreover, those diabetics with coexistent chronic hypertension were almost 12 times more likely to develop preeclampsia. As shown in Figure 57-5, women with type 1 diabetes in more advanced White classes of overt diabetes, who typically exhibit vascular complications and have preexisting nephropathy, are more likely to develop preeclampsia. This rising risk with duration of diabetes may be related to oxidative stress, which plays a key role in the pathogenesis of diabetic complications and preeclampsia. With this in mind, the Diabetes and Preeclampsia Intervention Trial (DAPIT) randomly assigned 762 women with type 1 diabetes to antioxidant vitamin C and E supplementation or placebo in the first half of pregnancy (McCance, 2010). Preeclampsia rates did not differ except in a few women with a low antioxidant status at baseline.

FIGURE 57-5

Incidence of preeclampsia in 491 type 1 diabetic women in Sweden and the United States. (Data from Hanson[a], 1993; Sibai[b], 2000.)



Diabetic Nephropathy

Diabetes is the leading cause of end-stage renal disease in the United States (Chap. 53, Chronic Kidney Disease). Clinically detectable nephropathy begins with microalbuminuria—30 to 300 mg/24 hours. This may manifest as early as 5 years after diabetes onset. Macroalbuminuria—more than 300 mg/24 hours—develops in patients destined to have end-stage renal disease. Hypertension almost invariably develops during this period, and renal failure

ensues typically in the next 5 to 10 years. The incidence of overt proteinuria is nearly 30 percent in individuals with type 1 diabetes and ranges from 4 to 20 percent in those with type 2 diabetes (Reutens, 2013). Regression is common and, presumably from improved glucose control, the incidence of nephropathy with type 1 diabetes has declined.

Approximately 5 percent of pregnant women with diabetes already have renal involvement. Approximately 40 percent of these will develop preeclampsia (Vidaeff, 2008). In those with microproteinuria, this incidence may not be as high (How, 2004). However, Ambia and associates (2018) reported that the rates of preterm delivery, birthweight <2500 g, and growth restriction were significantly higher in neonates of diabetic women with microproteinuria compared with those of diabetic gravidas without proteinuria.

In general, pregnancy does not appear to worsen diabetic nephropathy. In one prospective study of 43 women with diabetes, diabetic nephropathy did not progress through 12 months after delivery (Young, 2012). Most of these women had only mild renal impairment. Conversely, pregnancy in women with moderate-to-severe renal impairment may have accelerated progression of their disease (Vidaeff, 2008). As in women with glomerulopathies, hypertension or substantial proteinuria before or during pregnancy is a major predictive factor for ultimate progression to renal failure in women with diabetic nephropathy (Chap. 53, Nephrotic Syndromes).

Diabetic Retinopathy

Retinal vasculopathy is a highly specific complication of both type 1 and type 2 diabetes. In the United States, diabetic retinopathy is the most important cause of visual impairment in working-aged adults. The first and most common visible lesions are small microaneurysms followed by blot hemorrhages that form when erythrocytes escape from the aneurysms. These areas leak serous fluid that creates hard exudates. Such features are termed *background* or *nonproliferative retinopathy*. With increasingly severe retinopathy, the abnormal vessels of background eye disease become occluded, leading to retinal ischemia and infarctions that appear as *cotton wool exudates.* These are considered *preproliferative retinopathy.* In response to ischemia, neovascularization begins on the retinal surface and out into the vitreous cavity. Vision is obscured when these vessels bleed. Laser photocoagulation before hemorrhage reduces the rate of visual loss progression and blindness by half. The procedure may be performed during pregnancy when indicated.

Vestgaard and coworkers (2010) reported that almost two thirds of 102 pregnant women with type 1 diabetes examined by 8 weeks' gestation had background retinal changes, proliferative retinopathy, or macular edema. A fourth of these women developed progression of retinopathy in at least one eye during pregnancy. The same group of investigators evaluated 80 type 2 diabetics and identified retinopathy, mostly mild, in 14 percent during early pregnancy. Progression was identified in only 14 percent (Rasmussen, 2010). This complication is believed to be a rare example of a long-term adverse effect of pregnancy.

Other risk factors that have been associated with progression of retinopathy include hypertension, higher levels of insulin-like growth factor-1, placental growth factor, and macular edema identified in early pregnancy (Bargiota, 2011; Huang, 2015; Mathiesen, 2012; Ringholm, 2011; Vestgaard, 2010). The American Academy of Ophthalmology (2016) recommends that pregnant women with preexisting diabetes should routinely be offered retinal assessment after the first prenatal visit. Subsequent eye examinations depend on severity of retinopathy and level of diabetes control. Currently, most agree that laser photocoagulation and good glycemic control during pregnancy minimize the potential for deleterious effects of pregnancy. Ironically, "acute" rigorous metabolic control during pregnancy has been linked to acute worsening of retinopathy. In a study of 201 women with retinopathy, almost 30 percent suffered eye disease progression during pregnancy despite intensive glucose control (McElvy, 2001). That said, Wang and coworkers (1993) observed that although retinopathy worsened during the critical months of rigorous glucose control, long-term progression of eye disease actually slowed. Arun and Taylor (2008) found that only four women required laser photocoagulation during pregnancy, and none required laser in the next 5 years.

Diabetic Neuropathy

Peripheral symmetrical sensorimotor diabetic neuropathy is uncommon in pregnant women. But, a form of this, known as *diabetic gastropathy*, can be troublesome during pregnancy. It causes nausea and vomiting, nutritional problems, and difficulty with glucose control. Women with gastroparesis are advised that this complication is associated with a high risk of morbidity and poor perinatal outcome (Kitzmiller, 2008). Treatment with metoclopramide and D_2-receptor antagonists is sometimes successful. Gastric neurostimulators have also been successfully used during pregnancy (Fuglsang, 2015).

Treatment of *hyperemesis gravidarum* can be challenging, and we routinely provide insulin by continuous infusion for women who are admitted with this condition (Chap. 54, Complications).

Diabetic Ketoacidosis

This serious complication develops in approximately 1 percent of diabetic pregnancies and is most often encountered in women with type 1 diabetes (Hawthorne, 2011). It is increasingly being reported in women with type 2 or even those with gestational diabetes (Bryant, 2017; Sibai, 2014). Diabetic ketoacidosis (DKA) may develop with hyperemesis gravidarum, infection, insulin noncompliance, β-mimetic drugs given for tocolysis, and corticosteroids given to induce fetal lung maturation. DKA results from an insulin deficiency combined with an excess in counter-regulatory hormones such as glucagon. This leads to gluconeogenesis and ketone body formation. The ketone body β-hydroxybutyrate is synthesized at a much greater rate than acetoacetate, which is preferentially detected by commonly used ketosis-detection methods. Therefore, serum or plasma assays for β-hydroxybutyrate more accurately reflect true ketone body levels.

Of gravidas with DKA, fewer than 1 percent die, but perinatal mortality rates from a single episode of DKA may reach 35 percent (Guntupalli, 2015). Noncompliance is a prominent factor, and this and ketoacidosis were historically considered prognostically bad signs in pregnancy (Pedersen, 1974).

Importantly, pregnant women usually develop ketoacidosis at lower blood glucose thresholds than when nonpregnant. In a study from Parkland Hospital, the mean glucose level for pregnant women with DKA was 380 mg/dL, and the mean HbA_{1C} value was 10 percent (Bryant, 2017). Euglycemic ketoacidosis during pregnancy is possible but rare (Sibai, 2014).

One management protocol for diabetic ketoacidosis is shown in Table 57-7. An important cornerstone of management is vigorous rehydration with crystalloid solutions of normal saline or Ringer lactate.

TABLE 57-7

Management of Diabetic Ketoacidosis During Pregnancy

Laboratory Assessment
Obtain arterial blood gases to document degree of acidosis present; measure glucose, ketones, and electrolyte levels at 1- to 2-hour intervals
Insulin
Low-dose, intravenous
Loading dose: 0.2–0.4 U/kg
Maintenance: 2–10 U/hr
Fluids
Isotonic sodium chloride
Total replacement in first 12 hours of 4–6 L
1 L in first hour
500–1000 mL/hr for 2–4 hours
250 mL/hr until 80 percent replaced
Glucose
Begin 5-percent dextrose in normal saline when glucose plasma level reaches 250 mg/dL (14 mmol/L)
Potassium
If initially normal or reduced, an infusion rate up to 15–20 mEq/hr may be required; if elevated, wait until levels decrease into the normal range, then add to intravenous solution in a concentration of 20–30 mEq/L
Bicarbonate
Add one ampule (44 mEq) to 1 L of 0.45 normal saline if pH is <7.1

Data from Bryant, 2017; Landon, 2002; Sibai, 2014.

Infections

The rates of many infections are higher in diabetic pregnancies. Common ones include candidal vulvovaginitis, urinary and respiratory tract infections, and puerperal pelvic sepsis. However, in one study of more than 1250 diabetic gravidas screened before 16 weeks' gestation, rates of bacterial vaginosis or vaginal colonization with *Candida* or *Trichomonas* species were not increased (Marschalek, 2016). But, in their population-based study of almost 200,000 pregnancies, Sheiner and coworkers (2009) found a twofold greater risk of asymptomatic bacteruria in women with diabetes. Similarly, Alvarez and associates (2010) reported positive urine culture results in 25 percent of diabetic women. In a 2-year analysis of pyelonephritis at Parkland Hospital, 5 percent of women with diabetes developed pyelonephritis compared with 1.3 percent of the nondiabetic population (Hill, 2005). Fortunately, these latter infections can be minimized by screening and eradication of asymptomatic bacteriuria (Chap. 53, Asymptomatic Bacteriuria). Finally, Johnston and colleagues (2017) reported that 16.5 percent of women with pregestational diabetes had postoperative wound complications following cesarean delivery.

Management of Diabetes in Pregnancy

Preconceptional Care

Because of the close relationship between pregnancy complications and maternal glycemic control, efforts to achieve glucose targets are typically more aggressive during pregnancy. Management preferably should begin before pregnancy and include specific goals during each trimester.

To minimize early pregnancy loss and congenital malformations in offspring of diabetic mothers, optimal medical care and education are recommended before conception (Chap. 8, Counseling Session). The National Preconception Health and Healthcare Initiative Clinical Workgroup for the CDC established values for optimal glycemic control (Frayne, 2016). This was defined as HbA_{1c} <6.5 percent in women with pregestational diabetes. Unfortunately, nearly half of pregnancies in the United States are unplanned, and diabetic women frequently begin pregnancy with suboptimal glucose control (Finer, 2016; Kim, 2005).

The ADA (2017b) has also defined optimal preconceptional glucose control using insulin. Reflective values are self-monitored preprandial glucose levels of 70 to 100 mg/dL, peak 2-hour postprandial values of 100 to 120 mg/dL, and mean daily glucose concentrations <110 mg/dL. In one prospective population-based study of 933 pregnant women with type 1 diabetes, the risk of congenital malformations was not demonstrably higher with HbA_{1c} levels <6.9 percent compared with the risk in more than 70,000 nondiabetic controls (Jensen, 2010). These investigators also found a substantial fourfold greater risk for malformations at levels >10 percent.

If indicated, evaluation and treatment for diabetic complications such as retinopathy or nephropathy should also be instituted before pregnancy. Finally, folate, 400 µg/d orally, is given periconceptionally and during early pregnancy to decrease the risk of neural-tube defects.

First Trimester

Careful monitoring of glucose control is essential. For this reason, many clinicians hospitalize overtly diabetic women during early pregnancy to initiate an individualized glucose control program and provide education. This also provides an opportunity to assess the extent of diabetic vascular complications and precisely establish gestational age.

Insulin Treatment

The overtly diabetic gravida is best treated with insulin. While oral hypoglycemic agents have been used successfully for gestational diabetes (Diabetic Diet), these agents are not currently recommended for overt diabetes, although this is controversial (American College of Obstetricians and Gynecologists, 2016b). Maternal glycemic control can usually be achieved with multiple daily insulin injections and adjustment of dietary intake. The action profiles of commonly used short- and long-term insulins are shown in Table 57-8.

TABLE 57-8

Action Profiles of Commonly Used Insulins

Insulin Type	Onset	Peak (hr)	Duration (hr)
Short-acting (SC)			
Lispro	<15 min	0.5–1.5	3–4
Glulisine Aspart	<15 min <15 min	0.5–1.5 0.5–1.5	3–4 3–4
Regular	30–60 min	2–3	4–6
Long-acting (SC)			
Detemir	1–4 hr	Minimal[a]	Up to 24
Glargine NPH	1–4 hr 1–4 hr	Minimal[a] 6–10	Up to 24 10–16

[a]Minimal peak activity.

NPH = neutral protamine Hagedorn; SC = subcutaneous.

Data from Powers, 2012.

Subcutaneous insulin infusion by a calibrated pump does not yield better pregnancy outcomes compared with multiple daily injections. But, an infusion pump is a safe alternative in appropriately selected patients (Farrar, 2016; Sibai, 2014). With the advent of sensor-augmented insulin pumps and closed-loop insulin delivery systems, improved glycemic control with either manual or computer-generated insulin adjustments based on continuous glucose monitoring is now possible. One small randomized, crossover study of 16 pregnant women compared these two technologies (Stewart, 2016). Those with automatic closed-loop systems had glucose values within target range for a higher percentage of time and had lower daily median glucose values. Moreover, their rates of hypoglycemic episodes were not increased. Roeder and colleagues (2012) noted with insulin pump use in women with type 1 diabetes that total daily insulin doses declined in the first trimester but later rose more than threefold. Postprandial glucose elevations prompted most of the required daily-dose increases. If a continuous-infusion insulin pump is elected, it is best started before pregnancy to avoid the hypoglycemia and ketoacidosis risk associated with the learning curve (Sibai, 2014).

Monitoring

Self-monitoring of capillary glucose levels using a glucometer is recommended because this involves the woman in her own care. The ADA (2017b) recommends fasting and postprandial glucose monitoring. Glucose goals recommended during pregnancy are shown in Table 57-9. Advances in noninvasive glucose monitoring will undoubtedly render intermittent capillary glucose monitoring obsolete. Subcutaneous continuous glucose monitoring devices have shown that pregnant women with diabetes experience significant periods of daytime hyperglycemia and nocturnal hypoglycemia that are undetected by traditional monitoring (Combs, 2012). Such glucose monitoring systems, coupled with a continuous insulin pump, offer the potential of an “artificial pancreas” to avoid undetected hypo- or hyperglycemia during pregnancy.

TABLE 57-9

Self-Monitored Capillary Blood Glucose Goals

Specimen	Level (mg/dL)
Fasting	≤95
Premeal	≤100
1-hr postprandial	≤140
2-hr postprandial	≤120
0200–0600	≥60
Mean (average)	100
Hemoglobin A_{1c}	≤6%

Diet

Nutritional planning includes appropriate weight gain through carbohydrate and caloric modifications based on height, weight, and degree of glucose intolerance (American Diabetes Association, 2017b; Bantle, 2008). The mix of carbohydrate, protein, and fat is adjusted to meet the metabolic goals and individual patient preferences. A minimum of 175 g/d of carbohydrates ideally is provided. In one analysis of more than 200 obese pregnant women with glucose intolerance, a lower carbohydrate intake, particularly late in pregnancy, was associated with lower fat mass in offspring at birth (Renault, 2015). Allotted carbohydrates are distributed throughout the day in three small- to moderate-sized meals and two to four snacks. Weight loss is not recommended, but modest caloric restriction may be appropriate for overweight or obese women. An ideal dietary composition is 55 percent carbohydrate, 20 percent protein, and 25 percent fat, of which <10 percent is saturated fat.

Hypoglycemia

Diabetes tends to be unstable in the first half of pregnancy, and the incidence of hypoglycemia peaks during the first trimester. Chen and coworkers (2007) identified hypoglycemic events—blood glucose values <40 mg/dL—in 37 of 60 women with type 1 diabetes. A fourth of these were considered severe because the women were unable to treat their own symptoms and required assistance from another person. Caution is recommended when attempting euglycemia in women with recurrent episodes of hypoglycemia.

In a Cochrane database review, Middleton and colleagues (2016) determined that loose glycemic control, defined as fasting glucose values >120 mg/dL, was associated with greater risks for preeclampsia, cesarean delivery, and birthweight above the 90th percentile compared with women with tight or moderate control. Importantly, no obvious benefit were gained from very tight control, defined by fasting values <90 mg/dL, and there were more cases of hypoglycemia. Thus, women with overt diabetes who have glucose values that are viewed by some as “considerably above” this 90 mg/dL threshold can expect good pregnancy outcomes.

Second Trimester

Maternal serum alpha-fetoprotein determination at 16 to 20 weeks’ gestation is used in association with targeted sonographic examination to detect neural-tube defects and other anomalies (Chap. 14, Maternal Serum AFP Elevation: Neural-Tube Defect Screening). These levels may be lower in diabetic pregnancies, and interpretation is altered accordingly. Because the incidence of congenital cardiac anomalies is fivefold in mothers with diabetes, fetal echocardiography is an important part of second-trimester sonographic evaluation (Fouda, 2013). Despite advances in ultrasound technology, however, Dashe and associates (2009) cautioned that detection of fetal anomalies in obese diabetic women is more difficult than in similarly sized women without diabetes.

Regarding second-trimester glucose control, euglycemia with self-monitoring continues to be the goal in management. After the first-trimester instability, a stable period ensues. This is followed by a greater insulin requirement due to the elevated peripheral resistance to insulin described in Chapter 4 (Fat Metabolism).

Third Trimester and Delivery

During the past several decades, the threat of late-pregnancy stillbirth in women with diabetes has prompted recommendations for various fetal surveillance programs beginning in the third trimester. Such protocols include fetal movement counting, periodic fetal heart rate monitoring, intermittent biophysical profile evaluation, and contraction stress testing (Chap. 17, Fetal Movements). None of these techniques has been subjected to prospective

randomized clinical trials, and their primary value seems related to their low false-negative rates. The American College of Obstetricians and Gynecologists (2016b) suggests initiating such testing at 32 to 34 weeks' gestation.

At Parkland Hospital, women with diabetes are seen in a specialized obstetrical clinic every 2 weeks. During these visits, glycemic control records are evaluated and insulin adjusted. Women are routinely instructed to perform fetal kick counts beginning early in the third trimester. At 34 weeks, admission is offered to all insulin-treated women. While in the hospital, they continue daily fetal movement counts and undergo fetal heart rate monitoring three times a week. Delivery is planned for 38 weeks.

Labor induction may be attempted when the fetus is not excessively large and the cervix is considered favorable (Chap. 26, Labor Induction). Little and colleagues (2015) analyzed term singleton births from 2005 to 2011 and showed a higher percentage of diabetic women were delivered each year before 39 weeks compared with the entire cohort—37 versus 29 percent. Cesarean delivery at or near term has frequently been used to avoid traumatic birth of a large fetus in a woman with diabetes. In women with more advanced diabetes, especially those with vascular disease, the reduced likelihood of successful labor induction remote from term has also contributed to an increased cesarean delivery rate. In an analysis of pregnancy outcomes of diabetic women from University of Alabama at Birmingham according to the White classification, the rate of cesarean delivery and preeclampsia escalated with White class (Bennett, 2015). In another study, a HbA_{1c} level >6.4 percent at delivery was independently associated with urgent cesarean delivery. This suggests that tighter glycemic control during the third trimester might reduce late fetal compromise and cesarean delivery for fetal indications (Miailhe, 2013). The cesarean delivery rate for women with overt diabetes has remained at approximately 80 percent for the past 40 years at Parkland Hospital.

Reducing or withholding the dose of long-acting insulin to be given on the day of delivery is recommended. Regular insulin should be used to meet most or all of the insulin needs of the mother during this time, because insulin requirements typically drop markedly after delivery. We have found that continuous insulin infusion by calibrated intravenous pump is most satisfactory (Table 57-10). Throughout labor and after delivery, the woman should be adequately hydrated intravenously and given glucose in sufficient amounts to maintain normoglycemia. Capillary or plasma glucose levels are checked frequently, especially during active labor, and regular insulin is administered accordingly.

TABLE 57-10

Insulin Management During Labor and Delivery

- Usual dose of intermediate-acting insulin is given at bedtime.
- Morning dose of insulin is withheld.
- Intravenous infusion of normal saline is begun.
- Once active labor begins or glucose levels decrease to less than 70 mg/dL, the infusion is changed from saline to 5% dextrose and delivered at a rate of 100–150 cc/h (2.5 mg/kg/min) to achieve a glucose level of approximately 100 mg/dL.
- Glucose levels are checked hourly using a bedside meter allowing for adjustment in the insulin or glucose infusion rate.
- Regular (short-acting) insulin is administered by intravenous infusion at a rate of 1.25 U/h if glucose levels exceed 100 mg/dL.

Data from Coustan DR. Delivery: timing, mode, and management. In: Reece EA, Coustan DR, Gabbe SG, editors. Diabetes in women: adolescence, pregnancy, and menopause. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2004; and Jovanovic L, Peterson CM. Management of the pregnant, insulin-dependent diabetic woman. Diabetes Care 1980;3:63–8.

Puerperium

Often, women may require virtually no insulin for the first 24 hours or so postpartum. Subsequently, insulin requirements may fluctuate markedly during the next few days. Infection must be promptly detected and treated. When appropriate, oral agents can be restarted.

Counseling in the puerperium should include a discussion of birth control. Effective contraception is especially important in women with overt diabetes to allow optimal glucose control before subsequent conception.

GESTATIONAL DIABETES

In the United States in 2010, almost 5 percent of gravidas were affected by gestational diabetes (DeSisto, 2014). Worldwide, its prevalence differs according to race, ethnicity, age, and body composition and by screening and diagnostic criteria. There continue to be several controversies pertaining to the diagnosis and treatment of gestational diabetes. A National Institutes of Health (NIH) Consensus Development Conference (2013) was convened to study this. The American College of Obstetricians and Gynecologists (2017a) has also updated its recommendations. These two authoritative sources provide an analysis of the issues surrounding the diagnosis and bolster the approach to identifying and treating women with gestational diabetes.

The word *gestational* implies that diabetes is induced by pregnancy—ostensibly because of exaggerated physiological changes in glucose metabolism (Chap. 4, Fat Metabolism). Gestational diabetes is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (American College of Obstetricians and Gynecologists, 2017a). This definition applies whether or not insulin is used for treatment and undoubtedly includes some women with previously unrecognized overt diabetes.

Use of the term *gestational diabetes* has been encouraged to communicate the need for enhanced surveillance and to stimulate women to seek further testing postpartum. The most important perinatal correlate is excessive fetal growth, which may result in both maternal and fetal birth trauma. The likelihood of fetal death with appropriately treated gestational diabetes is not different from that in the general population. Importantly, more than half of women with gestational diabetes ultimately develop overt diabetes in the ensuing 20 years. And, as discussed in Types of Diabetes, evidence is mounting for long-range complications that include obesity and diabetes in their offspring.

Screening and Diagnosis

Despite almost 50 years of research, there is still no agreement regarding optimal gestational diabetes screening. The difficulty in achieving consensus is underscored by the controversy following publication of the single-step approach espoused by the International Association of Diabetes and Pregnancy Study Groups Consensus Panel (2010) and shown in Table 57-11. This strategy was greatly influenced by results of the Hypoglycemia and Pregnancy Outcomes (HAPO) Study, described later. Although the ADA (2017a) supports this new scheme, the American College of Obstetricians and Gynecologists (2017a) continues to recommend a two-step approach to screen and diagnose gestational diabetes. Similarly, the NIH Consensus Development Conference in 2013 concluded that evidence is insufficient to adopt a one-step approach.

TABLE 57-11

Threshold Values for Diagnosis of Gestational Diabetes

Plasma Glucose	Glucose Concentration Threshold[a]		Above Threshold (%)
	mmol/L	mg/dL	Cumulative
Fasting	5.1	92	8.3
1-hr OGTT	10.0	180	14.0
2-hr OGTT	8.5	153	16.1[b]

[a]One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of gestational diabetes.

[b]In addition, 1.7% of participants in the initial cohort were unblinded because of fasting plasma glucose levels >5.8 mmol/L (105 mg/dL) or 2-hr OGTT values >11.1 mmol/L (200 mg/dL), bringing the total to 17.8%.

OGTT = oral glucose tolerance test.

Data from International Association of Diabetes and Pregnancy Study Groups, 2010.

The recommended two-step approach begins with either universal or risk-based selective screening using a 50-g, 1-hour oral glucose challenge test. Participants in the Fifth International Workshop Conferences on Gestational Diabetes endorsed use of *selective screening* criteria shown in Table 57-12. Conversely, the American College of Obstetricians and Gynecologists (2017a) recommends *universal screening* of pregnant women using a laboratory-based blood glucose test. It is suggested that attempts to identify the 10 percent of women who should *not* be screened would add unnecessary complexity. Screening should be performed between 24 and 28 weeks' gestation in those women not known to have glucose intolerance earlier in pregnancy. This *50-g screening test* is followed by a *diagnostic 100-g, 3-hour oral glucose tolerance test (OGTT)* if screening results meet or exceed a predetermined plasma glucose concentration.

TABLE 57-12

Risk-Based Recommended Screening Strategy for Detecting GDM[a]

GDM risk assessment: should be ascertained at the first prenatal visit
Low Risk: Blood glucose testing not routinely required if all the following are present:
Member of an ethnic group with a low prevalence of GDM
No known diabetes in first-degree relatives
Age <25 years
Weight normal before pregnancy
Weight normal at birth
No history of abnormal glucose metabolism
No history of poor obstetrical outcome
Average Risk: Perform blood glucose testing at 24 to 28 weeks using either:
Two-step procedure: 50-g oral glucose challenge test (GCT), followed by a diagnostic 100-g OGTT for those meeting the threshold value in the GCT
One-step procedure: diagnostic 100-g OGTT performed on all subjects
High Risk: Perform blood glucose testing as soon as feasible, using the procedures described above, if one or more of these are present:
Severe obesity
Strong family history of type 2 diabetes
Previous history of GDM, impaired glucose metabolism, or glucosuria If GDM is not diagnosed, blood glucose testing should be repeated at 24 to 28 weeks' gestation or at any time symptoms or signs suggest hyperglycemia

[a]Criteria of the Fifth International Workshop-Conference on Gestational Diabetes.

GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test.

Reproduced with permission from Metzger BE, Coustan DR, the Organizing Committee: Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus, Diabetes Care. 1998 Aug; 21 Suppl 2:B161–B167.

For the 50-g screen, the plasma glucose level is measured 1 hour after a 50-g oral glucose load without regard to the time of day or time of last meal. In a recent review, the pooled sensitivity for a threshold of 140 mg/dL ranged from 74 to 83 percent depending on 100-g thresholds used for diagnosis (van Leeuwen, 2012). Sensitivity estimates for a 50-g screen threshold of 135 mg/dL improved only slightly to 78 to 85 percent. Importantly, specificity dropped from a range of 72 to 85 percent for 140 mg/dL to 65 to 81 percent for a threshold of 135 mg/dL. Using a threshold of 130 mg/dL marginally improves sensitivity with a further decline in specificity (Donovan, 2013). That said, in the absence of clear evidence supporting one cutoff value over another, the American College of Obstetricians and Gynecologists (2017a) sanctions using any one of the three 50-g screen thresholds. At Parkland Hospital, we continue to use 140 mg/dL as the screening threshold to prompt the 100-g test.

Justification for screening and treatment of women with gestational diabetes was strengthened by the study by Crowther and coworkers (2005). They assigned 1000 women with gestational diabetes between 24 and 34 weeks' gestation to receive dietary advice with blood glucose monitoring plus insulin therapy—the intervention group—or to undergo routine prenatal care. Women were diagnosed as having gestational diabetes if their blood glucose was >100 mg/dL after an overnight fast and was between 140 and 198 mg/dL 2 hours after ingesting a 75-g glucose solution. Women in the intervention group had a significantly lower risk of a composite adverse outcome that included perinatal death, shoulder dystocia, fetal bone fracture, and fetal nerve palsy. Macrosomia defined by birthweight ≥4000 g complicated 10 percent of deliveries in the intervention group compared with 21 percent in the routine prenatal care group. Cesarean delivery rates were almost identical in the two study groups.

Slightly different results were reported by the Maternal–Fetal Medicine Units Network randomized trial of 958 women (Landon, 2009). Dietary counseling plus glucose monitoring was compared with standard obstetrical care in women with mild gestational diabetes to reduce perinatal morbidity rates. Mild gestational diabetes was identified in women with fasting glucose levels <95 mg/dL. They reported no differences in rates of composite morbidity that included stillbirth; neonatal hypoglycemia, hyperinsulinemia, and hyperbilirubinemia; and birth trauma. Importantly, secondary analyses demonstrated a 50-percent reduction in macrosomia, fewer cesarean deliveries, and a significant decrease in shoulder dystocia rate—1.5 versus 4 percent—in treated versus control women.

Based largely on these two landmark studies, the U.S. Preventive Services Task Force (2014) now recommends universal screening in low-risk women after 24 weeks' gestation. However, the Task Force concluded that evidence is insufficient to assess the balance of benefits versus harms of screening before 24 weeks. For screening, the optimal OGTT to identify gestational diabetes has not been agreed upon. The World Health Organization (2013) and the ADA (2017a) recommend the 75-g, 2-hour OGTT, but acknowledge that the diagnosis can be accomplished using the two-step strategy. In the United States, however, the 100-g, 3-hour OGTT performed after an overnight fast is recommended by the American College of Obstetricians and Gynecologists (2017a). Proposed criteria for interpretation of the diagnostic 100-g OGTT are shown in Table 57-13. In a secondary analysis of the Maternal-Fetal Medicine Units Network treatment trial, Harper and colleagues (2016) showed that women diagnosed with either the National Diabetes Data Group (NDDG) or the Carpenter-Coustan criteria benefited from treatment. However, the number needed to treat to prevent a shoulder dystocia was higher for the Carpenter-Coustan criteria. At Parkland Hospital we continue to use the NDDG criteria for diagnosis. Criteria for the 75-g OGTT recommended are shown in Table 57-11.

TABLE 57-13

Diagnosis of GDM Using Threshold Glucose Values from 100-g Oral Glucose Tolerance Test[a,b]

	NDDG[c]		Carpenter–Coustan[d]	
Time	**(mg/dL)**	**(mmol/L)**	**(mg/dL)**	**(mmol/L)**
Fasting	105	5.8	95	5.3
1-hr	190	10.6	180	10.0
2-hr	165	9.2	155	8.6
3-hr	145	8.0	140	7.8

[a]The test should be performed when the patient is fasting.

[b]Two or more of the venous plasma glucose concentrations listed are met or exceeded for a positive diagnosis.

[c]Serum glucose level.

[d]Serum or plasma glucose level.

NDDG = National Diabetes Data Group.

Data from American Diabetes Association, 2017a; Ferrara, 2002.

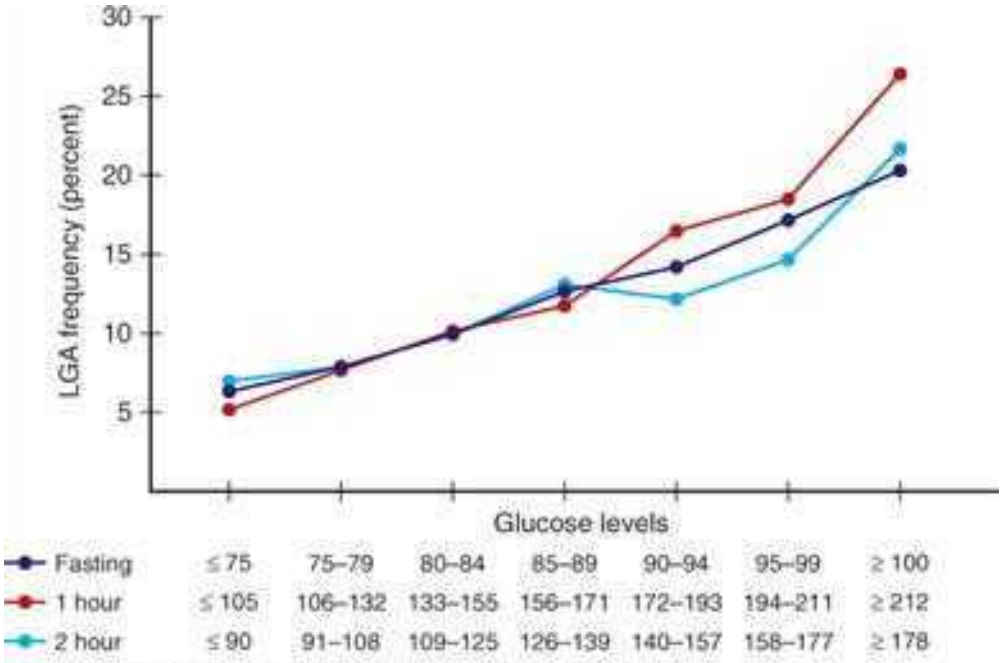
The Hyperglycemia and Adverse Pregnancy Outcome Study

This was a 7-year international epidemiological study of 23,325 pregnant women at 15 centers in nine countries (HAPO Study Cooperative Research Group, 2008). The investigation analyzed the association of various levels of glucose intolerance during the third trimester with adverse infant outcomes in women with gestational diabetes. Between 24 and 32 weeks' gestation, the general population of pregnant women underwent a 75-g OGTT after an overnight fasting. Blood glucose levels were measured fasting and then 1 and 2 hours after glucose ingestion. Caregivers were blinded to results except for women whose glucose levels exceeded values that required treatment and removal from the study. Glucose values at each of these three time posts were stratified into seven categories (Fig. 57-6). These values were then correlated with rates for birthweight >90th percentile (LGA), primary cesarean delivery, neonatal hypoglycemia, and cord-serum C-peptide levels >90th percentile. Odds of each outcome were calculated using the lowest category—for example, fasting plasma glucose ≤75 mg/dL—as the referent group. Their findings in general supported the supposition that increasing plasma glucose levels were associated with increasing adverse outcomes. Ecker and Greene (2008) concluded that it would be difficult to show that treating

lesser degrees of carbohydrate intolerance would provide any meaningful improvements in clinical outcomes. We agree that changes in criteria are not justified until clinical trials prove benefits. This position was also endorsed by the 2013 NIH Consensus Development Conference.

FIGURE 57-6

Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. The frequency of newborn birthweight ≥90th percentile for gestational age plotted against glucose levels fasting and at 1- and 2-hr intervals following a 75-g oral glucose load. LGA = large for gestational age. (Reproduced with permission from HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al: Hyperglycemia and adverse pregnancy outcomes, N Engl J Med. 2008 May 8;358(19):1991–2002.)



International Association of Diabetes and Pregnancy Study Group

The IADPSG sponsored a workshop conference on the diagnosis and classification of gestational diabetes in 2008. After reviewing the results of the HAPO study, a panel developed recommendations for the diagnosis and classification of hyperglycemia during pregnancy. This panel allowed for the diagnosis of overt diabetes during pregnancy as shown in Table 57-4. It also recommended a single-step approach to the diagnosis of gestational diabetes using the 75-g, 2-hour OGTT. Thresholds for fasting, 1-, and 2-hour values based on mean glucose concentrations from the entire HAPO study cohort were considered. These glucose level thresholds were derived using an arbitrary 1.75 odds ratio of outcomes such as LGA birthweight and cord serum C-peptide levels >90th percentile. Only one of these thresholds, shown in Table 57-11, would need to be met or exceeded to make the diagnosis of gestational diabetes.

It is estimated that implementation of these recommendations would raise the prevalence of gestational diabetes in the United States to 17.8 percent! Said another way, the number of women with mild gestational diabetes would grow almost threefold with no evidence of treatment benefit (Cundy, 2012). Feldman and coworkers (2016) evaluated the implementation of the IADPSG paradigm in a before-after analysis that included more than 6000 women. The new strategy was associated with a significant increase in gestational diabetes diagnosis rates but not with reduced macrosomia rates compared with a two-step approach. Remarkably, they identified a higher primary cesarean delivery rate associated with adoption of the IADPSG recommendations. The ADA (2013, 2017a) initially recommended adopting this new approach, however, based on benefits inferred from trials in women identified using a two-step approach described in Screening and Diagnosis, they now concede that data support a two-step strategy as well.

NIH Consensus Development Conference

Prompted by the disparate recommendations, the NIH Consensus Development Conference on Diagnosing Gestational Diabetes Mellitus (2013) was convened. This conference included input from a multidisciplinary planning committee, a systematic evidence review by the Agency for Healthcare Research and Quality Evidence-Based Practice Center, expert testimony, and a nonbiased panel to produce the overall report. The panel concluded that there were potential benefits to worldwide standardization. However, it found insufficient evidence to adopt a one-step diagnostic process such as the one proposed by the IADPSG. Moreover, as mentioned previously, after consideration of these findings, the American College of Obstetricians and Gynecologists (2017a) continues to recommend a two-step screening and diagnostic approach to gestational diabetes diagnosis. The College noted no significant improvements in maternal or perinatal outcomes that would offset the tripling of gestational diabetes incidence that would derive from the one-step approach. We applaud this decision.

Maternal and Fetal Effects

Adverse consequences of gestational diabetes differ from those of pregestational diabetes. Unlike in women with overt diabetes, women with gestational diabetes do not appear to have fetuses with substantially higher rates of anomalies than the general obstetrical population (Sheffield, 2002). In a study of more than 1 million women from the Swedish Medical Birth Registry, major malformation rates were marginally elevated in fetuses of gestational diabetics compared with those of nondiabetic controls—2.3 versus 1.8 percent (Fadl, 2010). The stillbirth rate was not greater in this study. Similarly, the stillbirth rate was not increased in an analysis by Jovanovič and associates (2015) of more than 800,000 pregnancies from 2005 through 2011. In contrast, and not unexpectedly, women with *elevated* fasting glucose levels have elevated rates of unexplained stillbirths similar to those of women with overt diabetes. This increasing risk with progressive maternal hyperglycemia emphasizes the importance of identifying women with evidence of preexisting diabetes early in pregnancy (see Table 57-4). Similar to women with overt diabetes, adverse maternal effects associated with gestational diabetes include a higher frequency of hypertension and cesarean delivery.

Fetal Macrosomia

The primary effect attributed to gestational diabetes is excessive fetal size or macrosomia that is variably defined and discussed further in Chapter 44 (Definition). The perinatal goal is to avoid difficult delivery from macrosomia and concomitant birth trauma associated with shoulder dystocia. In a retrospective analysis of more than 80,000 vaginal deliveries in Chinese women, Cheng and associates (2013) calculated a 76-fold greater risk for shoulder dystocia in newborns weighing ≥4200 g compared with the risk in those weighing <3500 g. Importantly, however, the odds ratio for shoulder dystocia in women with diabetes was <2. Although gestational diabetes is certainly a risk factor, it accounts for only a small number of pregnancies complicated by shoulder dystocia.

The excessive shoulder and trunk fat that commonly characterizes the macrosomic newborn of a diabetic mother theoretically predisposes such neonates to shoulder dystocia or cesarean delivery (Durnwald, 2004; McFarland, 2000). Landon and associates (2011) identified shoulder dystocia in approximately 4 percent of women with mild gestational diabetes compared with <1 percent of women with a 50-g glucose screen result <120 mg/dL. In a prospective study of fetal adipose measurements, however, Buhling and coworkers (2012) demonstrated no differences between measurements in 630 offspring of women with gestational diabetes and 142 without diabetes. The authors attributed this negative finding to successful treatment of gestational diabetes.

Extensive evidence supports that insulin-like growth factors also play a role in fetal-growth regulation (Chap. 44, Normal Birthweight). These proinsulin-like polypeptides are produced by virtually all fetal organs and are potent stimulators of cell differentiation and division. Luo and coworkers (2012) reported that insulin-like growth factor-1 strongly correlated with birthweight. The HAPO study investigators also reported dramatic increases in cord-serum C-peptide levels with rising maternal glucose levels following a 75-g OGTT. C-peptide levels above the 90th percentile were found in almost a third of newborns in the highest glucose categories. Other factors implicated in macrosomia include epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, leptin, and adiponectin (Grissa, 2010; Loukovaara, 2004; Mazaki-Tovi, 2005).

Neonatal Hypoglycemia

Hyperinsulinemia may provoke severe hypoglycemia within minutes of birth, but only three fourths of these episodes occur in the first 6 hours (Harris, 2012). The definition of neonatal hypoglycemia is controversial, with recommended clinical thresholds ranging from 35 to 45 mg/dL. An NIH workshop conference on neonatal hypoglycemia supported using a threshold of 35 mg/dL in term newborns but cautioned that this practice is not strictly evidence based (Hay, 2009). Newborns described by the HAPO study (2008) had an incidence of clinical neonatal hypoglycemia that rose with increasing maternal OGTT result values defined in Figure 57-6. The frequency varied from 1 to 2 percent, but it was as high as 4.6 percent in women with fasting glucose levels ≥100 mg/dL. Similarly, Cho and colleagues (2016), analyzed more than 3000 Korean women who underwent a 50-g OGTT and found that neonates born to women with a screening result ≥200 mg/dL were 84 times more likely to have hypoglycemia than those born to women with a result <140 mg/dL. The risk of neonatal hypoglycemia correlates with umbilical cord C-peptide levels. But, importantly, the risk also rises with birthweight, independent of a maternal diabetes diagnosis (Mitanchez, 2014).

Maternal Obesity

In women with gestational diabetes, maternal body mass index (BMI) is an independent and more substantial risk factor for fetal macrosomia than is glucose intolerance (Ehrenberg, 2004; Mission, 2013). Stuebe and associates (2012) completed a secondary analysis of women with either untreated mild gestational diabetes or normal glucose tolerance testing results. They found that higher BMI levels were associated with rising birthweight, regardless of glucose levels. In one analysis of more than 600,000 pregnant women, gestational diabetes, compared with obesity or gestational weight gain, contributed the least to the population-attributable fraction of LGA neonates (Kim, 2014). The highest fraction of LGA neonates was attributable to maternal obesity plus excessive gestational weight gain. Similarly, Egan and colleagues (2014) found that excessive gestational weight gain is common in women with gestational diabetes and confers an additive risk for fetal macrosomia. Weight distribution also seems to play a role because the risk of gestational diabetes is greater with maternal truncal obesity. Suresh and colleagues (2012) verified that increased maternal abdominal subcutaneous fat thickness as measured by sonography at 18 to 22 weeks' gestation correlated with BMI and was a better predictor of gestational diabetes.

Management

Women with gestational diabetes can be divided into two functional classes using fasting glucose levels. Pharmacological methods are usually recommended if diet modification does not consistently maintain the fasting plasma glucose levels <95 mg/dL or the 2-hour postprandial plasma glucose <120 mg/dL (American College of Obstetricians and Gynecologists, 2017a). Whether pharmacological treatment should be used in women with lesser degrees of fasting hyperglycemia is unclear. There have been no controlled trials to identify ideal glucose targets for fetal risk prevention. On the other hand, the HAPO study (2008) did demonstrate increased fetal risk at glucose levels below the threshold used for diagnosis of diabetes. The Fifth International Workshop Conference recommended that fasting capillary glucose levels be kept ≤95 mg/dL (Metzger, 2007).

In a systematic review, Hartling and colleagues (2013) concluded that treating gestational diabetes resulted in a significantly lower incidence of preeclampsia, shoulder dystocia, and macrosomia. For example, the calculated risk ratio was 0.50 for delivering a newborn >4000 g after treatment. These investigators caution that the attributed risk for these outcomes is low, especially when glucose values are only moderately elevated. Importantly, they were unable to demonstrate an effect on neonatal hypoglycemia or on future metabolic outcomes in the offspring.

Diabetic Diet

Nutritional instructions generally include a carbohydrate-controlled diet sufficient to maintain normoglycemia and avoid ketosis. On average, this includes a daily caloric intake of 30 to 35 kcal/kg. Moreno-Castilla and associates (2013) randomly assigned 152 women with gestational diabetes to either a 40- or a 55-percent daily carbohydrate diet and found no difference in insulin levels and pregnancy outcomes. The American College of Obstetricians and Gynecologists (2017a) suggests that carbohydrate intake be limited to 40 percent of total calories. The remaining calories are apportioned to give 20 percent as protein and 40 percent as fat.

The most appropriate dietary approach for women with gestational diabetes has not been established. One metaanalysis of trials of low-glycemic index diets found that diets higher in complex carbohydrates and dietary fiber reduced the risk of macrosomia and likelihood of insulin use in women with gestational diabetes (Wei, 2016). That said, there clearly are limitations to what can be accomplished with various dietary approaches alone. Most and Langer (2012) found that insulin was effective in reducing the risk of excessive birthweight in offspring of obese women with gestational diabetes. Casey and colleagues (2015b) also found that dietary treatment alone for morbidly obese women with mild gestational diabetes did not reduce neonatal fat mass or LGA birthweights.

Exercise

Few trials have evaluated exercise specifically for women with gestational diabetes. The American College of Obstetricians and Gynecologists (2017a,b) recommends regular physical activity that incorporates aerobic and strength-conditioning exercise during pregnancy and extends this to women with gestational diabetes. Two recent metaanalyses demonstrate that structured exercise programs during pregnancy diminish weight gain during pregnancy and even reduce the risk of developing gestational diabetes (Russo, 2015; Sanabria-Martinez, 2015). Exercise during pregnancy in woman with gestational diabetes also lowers glucose levels (Jovanovic-Peterson, 1989).

Glucose Monitoring

Hawkins and colleagues (2008) compared outcomes in 315 women with diet-treated gestational diabetes who used personal glucose monitors with those of 615 gestational diabetics who were also diet-treated but who underwent intermittent fasting glucose evaluation during weekly obstetrical visits. Women using daily blood-glucose self monitoring had significantly fewer macrosomic newborns. They also gained less weight after diagnosis than women evaluated during clinic visits only. These findings support the common practice of blood-glucose self monitors for women with diet-treated gestational diabetes.

Postprandial surveillance for gestational diabetes has been shown to be superior to preprandial surveillance (DeVeciana, 1995). At Parkland Hospital, we reviewed the impact of changing to postprandial monitoring in women with diet-treated gestational diabetes and demonstrated a significant reduction in maternal weight gain per week—0.63 lb/week to 0.45 lb/week—in women managed with a postprandial monitoring schema. The American College of Obstetricians and Gynecologists (2017a) and the ADA (2017b) recommend glucose assessment four times daily. The first check is performed fasting, and the remainder are done 1 or 2 hours after each meal.

Insulin Treatment

Historically, insulin has been considered standard therapy in women with gestational diabetes when target glucose levels cannot be consistently achieved through nutrition and exercise. It does not cross the placenta, and tight glycemic control can typically be achieved. Insulin therapy is typically added if fasting levels persistently exceed 95 mg/dL in women with gestational diabetes. The American College of Obstetricians and Gynecologists (2017a) also recommends that insulin be considered in women with 1-hour postprandial levels that persistently exceed 140 mg/dL or those with 2-hour levels >120 mg/dL. Importantly, all of these thresholds are extrapolated from recommendations for managing women with overt diabetes.

If insulin is initiated, the starting dose is typically 0.7 to 1.0 units/kg/d and is given in divided doses (American College of Obstetricians and Gynecologists, 2017a). A combination of intermediate-acting and short-acting insulin may be used, and dose adjustments are based on glucose levels at particular times of the day. At Parkland Hospital, the starting daily dose is divided so that two thirds is given in the morning before breakfast and one third in the evening

before dinner. In the morning dose, one third is regular insulin and two thirds are NPH (neutral protamine Hagedorn). For the evening dose, one half is regular insulin and the other half is NPH. Insulin instruction for these women is accomplished either in a specialized outpatient clinic or during a short hospital stay. As shown in Table 57-8, insulin analogues such as insulin aspart and insulin lispro have a more rapid onset of action than regular insulin and theoretically could be helpful in postprandial glucose management. Experience with these analogues with gestational diabetes is limited, and Singh and coworkers (2009) were unable to demonstrate a benefit compared with conventional insulins.

Oral Hypoglycemic Agents

Insulin is the preferred first-line agent for persistent hyperglycemia in women with gestational diabetes. However, both the American College of Obstetricians and Gynecologists (2017a) and the ADA (2017b) acknowledge that several studies support the safety and efficacy of either glyburide (Micronase) or metformin (Glucophage) (Langer, 2000; Nicholson, 2009; Rowan, 2008). Balsells and colleagues (2015) performed metaanalyses of trials comparing both agents to insulin or to each other. In the seven trials comparing glyburide with insulin, glyburide was associated with higher birthweight, more macrosomia, and more frequent neonatal hypoglycemia. In the six trials comparing metformin with insulin, metformin was associated with less maternal weight gain, more preterm birth, and less severe neonatal hypoglycemia. On average from all trials, treatment failures occurred in 6 percent of women treated with glyburide and 34 percent of those treated with metformin. In the two studies comparing oral hypoglycemic agents with each other, metformin treatment was associated with less maternal weight gain, lower birthweight, and less macrosomia. In contrast to trials of each agent compared with insulin, treatment failure rates of both agents in these two studies were equivalent. Importantly, in a randomized trial of glyburide treatment as an adjunct to diet therapy in 395 women with mild gestational diabetes, Casey and coworkers (2015a) did not identify any significant improvements in pregnancy outcomes in women treated with glyburide.

Concerns have emerged regarding potential adverse outcomes among women treated with glyburide. First, like metformin, glyburide crosses the placenta and reaches concentrations in the fetus that are more than two thirds of maternal levels (Caritis, 2013). Additionally, a study of more than 9000 women with gestational diabetes treated with either insulin or glyburide showed a significant rise in rates of neonatal intensive care unit admission, respiratory distress, and neonatal hypoglycemia associated with glyburide use (Castillo, 2015).

Metformin reaches fetal serum concentrations similar to maternal levels. However, in one study of 751 women with gestational diabetes who were randomly assigned to metformin or insulin treatment, short-term perinatal adverse events did not differ between groups (Rowan, 2008). Outcomes included neonatal hypoglycemia, respiratory distress syndrome, phototherapy, birth trauma, 5-minute Apgar score ≤7, and preterm birth. Overall growth of offspring at age 2 years also did not differ (Rowan, 2011). Nevertheless, the fat distribution in children exposed to metformin showed a tendency toward a more favorable pattern. From a smaller randomized metformin trial, at 18 months, offspring exposed to metformin were slightly heavier, but markers of early motor or language development did not differ compared with those in offspring exposed to insulin (Ijäs, 2015).

The Food and Drug Administration has not approved glyburide and metformin use for treatment of gestational diabetes. However, the American College of Obstetricians and Gynecologists (2017a) recognizes both as reasonable choices for second-line glycemic control in women with gestational diabetes. Because long-term outcomes have not been fully studied, the committee recommends appropriate counseling, which includes disclosing the limitations in current safety data.

Obstetrical Management

In general, for women with gestational diabetes who do not require insulin, early delivery or other interventions are seldom required. There is no consensus regarding the value or timing of antepartum fetal testing. It is typically reserved for women with pregestational diabetes because of the greater stillbirth risk. The American College of Obstetricians and Gynecologists (2017a) endorses fetal surveillance in women with gestational diabetes and poor glycemic control. At Parkland Hospital, women with gestational diabetes are routinely instructed to perform daily fetal kick counts in the third trimester (Chap. 17, Clinical Application). Insulin-treated women are offered inpatient admission after 34 weeks' gestation, and antepartum monitoring is performed three times each week.

Women with gestational diabetes and adequate glycemic control are managed expectantly. Elective labor induction to prevent shoulder dystocia compared with spontaneous labor remains controversial. Alberico and colleagues (2017) recently described their truncated randomized trial of 425 women with gestational diabetes that compared labor induction between 38 and 39 weeks' and expectant management until 41 weeks' gestation. Although underpowered, this GINEXMAL Trial demonstrated no clinically meaningful difference in the cesarean delivery rate between the induction and expectant management groups—12.6 versus 11.8 percent. However, with early labor induction, neonatal hyperbilirubinemia rates were significantly higher, and ironically, there was a nonsignificant threefold greater shoulder dystocia rate. In a retrospective cohort study of 8392 Canadian women with gestational diabetes, Melamed and coworkers (2016) found that routine delivery at 38 or 39 weeks was associated with a lower rate of cesarean delivery but with an elevated rate of neonatal intensive care unit admission. The American College of Obstetricians and Gynecologists (2017a) recommends that routine labor induction in women with diet-treated gestational diabetes should not occur before 39 weeks' gestation. At Parkland Hospital, women with diet-treated gestational diabetes are not electively induced for this indication. However, those treated with insulin are delivered at 38 weeks' gestation.

Elective cesarean delivery to avoid brachial plexus injuries in overgrown fetuses is another important issue. The American College of Obstetricians and Gynecologists (2017a) has concluded that data are insufficient to determine whether cesarean delivery in women with *gestational* diabetes whose fetuses

have a sonographically estimated weight ≥4500 g should be performed to avoid risk of birth trauma. From their systematic review, Garabedian and coworkers (2010) estimated that as many as 588 cesarean deliveries in women with gestational diabetes and an estimated fetal weight of ≥4500 g would be necessary to avoid one case of permanent brachial plexus palsy. Scifres and colleagues (2015), in their retrospective analysis of 903 women with gestational diabetes who underwent sonographic evaluation within 1 month of delivery, demonstrated that sonographic estimates of fetal weight typically overdiagnosed fetuses as being LGA. Only 22 percent of women estimated to have an LGA fetus actually delivered an overgrown newborn. Still, the American College of Obstetricians and Gynecologists (2016a) acknowledges that prophylactic cesarean delivery may be considered in diabetic women with an estimated fetal weight ≥4500 g.

Postpartum Evaluation

Recommendations for postpartum evaluation are based on the 50-percent likelihood of women with gestational diabetes developing overt diabetes within 20 years (O'Sullivan, 1982). The Fifth International Workshop Conference on Gestational Diabetes recommended that women diagnosed with gestational diabetes undergo postpartum evaluation with a 75-g OGTT (Metzger, 2007). These recommendations are shown in Table 57-14 along with the classification scheme of the ADA (2017b). Eggleston and colleagues (2016) reviewed insurance claim data from 2000 to 2013 and found that only 24 percent of women with a pregnancy complicated by gestational diabetes underwent postpartum screening within a year, and less than half of those underwent a 75-g OGTT. The American College of Obstetricians and Gynecologists (2017a) recommends either a fasting glucose or the 75-g, 2-hour OGTT at 4 to 12 weeks postpartum for the diagnosis of overt diabetes. The ADA (2017a) recommends testing at least every 3 years in women with a history of gestational diabetes but normal postpartum glucose screening.

TABLE 57-14

Fifth International Workshop-Conference: Metabolic Assessments Recommended after Pregnancy with Gestational Diabetes

Time	**Test**	**Purpose**
Postdelivery (1–3 d)	Fasting or random plasma glucose	Detect persistent, overt diabetes
Early postpartum (6–12 wk)	75-g, 2-hr OGTT	Postpartum classification of glucose metabolism
1-yr postpartum	75-g, 2-hr OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Triannually	75-g, 2-hr OGTT	Assess glucose metabolism
Prepregnancy	75-g, 2-hr OGTT	Classify glucose metabolism
Classification of the American Diabetes Association (2013)		
Normal Values	**Impaired Fasting Glucose or Impaired Glucose Tolerance**	**Diabetes Mellitus**
Fasting <100 mg/dL	100–125 mg/dL	≥126 mg/dL
2 hr <140 mg/dL	2 hr ≥140–199 mg/dL	2 hr ≥200 mg/dL
Hemoglobin A_{1c}<5.7%	5.7–6.4%	≥6.5%

OGTT = oral glucose tolerance test.

Data from American Diabetes Association, 2013, 2017a; Metzger, 2007.

Women with a history of gestational diabetes are also at risk for cardiovascular complications associated with dyslipidemia, hypertension, and abdominal obesity—the *metabolic syndrome* (Chap. 48, Metabolic Syndrome). In a study of 47,909 parous women, Kessous and coworkers (2013) evaluated subsequent hospitalizations due to cardiovascular morbidity. They found that almost 5000 women with gestational diabetes were 2.6 times more likely to be hospitalized for cardiovascular morbidity. Another study evaluated 483 women between 5 and 10 years after being diagnosed with mild gestational diabetes (Varner, 2017). Investigators found no increased risk for developing metabolic syndrome associated with additional pregnancies. However, risk for subsequent diabetes rose almost fourfold if gestational diabetes complicated at least one subsequent pregnancy.

Recurrent Gestational Diabetes

In a metaanalysis of published reports from 1973 through 2014, the pooled gestational diabetes recurrence rate was 48 percent (Schwartz, 2015). Rates in primiparas were lower (40 percent) than in multiparas (73 percent). The same group of investigators identified maternal BMI, insulin use, fetal macrosomia, and weight gain between pregnancies as additional risk factors for gestational diabetes recurrence (Schwartz, 2016). Thus, lifestyle behavioral changes that include weight control and exercise between pregnancies would seem likely to prevent gestational diabetes recurrence. Guelfi and colleagues (2016) were unable to demonstrate a lower recurrence rate in women randomized to an exercise program that started before 14 weeks' gestation in a subsequent pregnancy. Conversely, Ehrlich and colleagues (2011) found that prepregnancy loss of at least two BMI units was associated with a lower subsequent risk of gestational diabetes in women who were overweight or obese in the first pregnancy.

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CHAPTER 58: Endocrine Disorders

In a small number of cases the thyroid gland increases markedly in size, though we are ignorant as to its significance.

—J. Whitridge Williams (1903)

INTRODUCTION

In 1903, little was known of many endocrine disorders. Still, endocrinopathies seem particularly closely related to pregnancy because of its gestational proclivity for prodigious hormone secretion. This is best illustrated by placental lactogen in diabetes, the most common endocrinopathy encountered in pregnancy (Chap. 57, Types of Diabetes). Pregnancy is also interrelated with some endocrinopathies that are at least partially due to autoimmune dysregulation. Clinical manifestations of this result from complex interplay among genetic, environmental, and endogenous factors that activate the immune system against targeted cells within endocrine organs. An extraordinary example of these interactions comes from studies that implicate maternal organ engraftment by fetal cells that were transferred during pregnancy. These cells later provoke antibody production, tissue destruction, and autoimmune endocrinopathies.

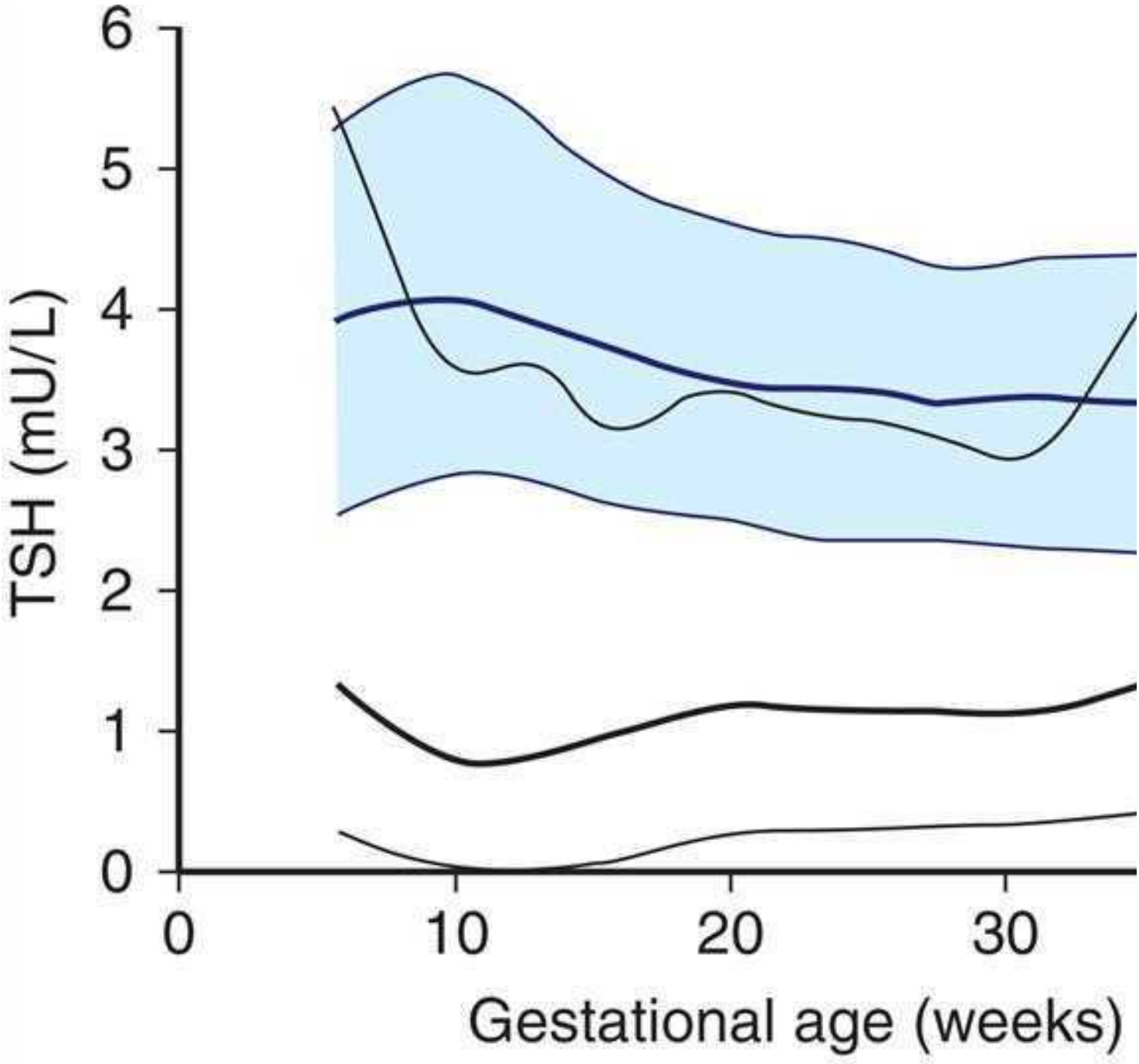
THYROID DISORDERS

Taken in aggregate, disorders of the thyroid gland are common in young women and thus frequently encountered in pregnancy. Maternal and fetal thyroid function are intimately related, and drugs that affect the maternal thyroid also affect the fetal gland. Moreover, thyroid autoantibodies have been associated with increased rates of early pregnancy wastage. Also, uncontrolled thyrotoxicosis and untreated hypothyroidism are both associated with adverse pregnancy outcomes. Finally, evidence suggests that the severity of some autoimmune thyroid disorders may be ameliorated during pregnancy, only to be exacerbated postpartum.

Thyroid Physiology and Pregnancy

Maternal thyroid changes are substantial, and normally altered gland structure and function are sometimes confused with thyroid abnormalities. These alterations are discussed in detail in Chapter 4 (Thyroid Gland), and normal serum hormone level values are found in the Appendix (Serum and Blood Constituents). First, maternal serum concentrations of thyroid binding globulin are increased concomitantly with total or bound thyroid hormone levels (Fig. 4-16). Second, *thyrotropin,* also called *thyroid-stimulating hormone (TSH),* currently plays a central role in screening and diagnosis of many thyroid disorders. Notably, TSH receptors are cross stimulated, albeit weakly, by massive quantities of human chorionic gonadotropin (hCG) secreted by placental trophoblast. Because TSH does not cross the placenta, it has no direct fetal effects. During the first 12 weeks of gestation, when maternal hCG serum levels are maximal, thyroid hormone secretion is stimulated. The resulting greater serum free thyroxine (T_4) levels act to suppress hypothalamic *thyrotropin-releasing hormone (TRH)* and in turn limit pituitary TSH secretion (Fig. 58-1). Accordingly, TRH is undetectable in maternal serum. Conversely, in fetal serum, beginning at midpregnancy, TRH becomes detectable, but levels are static and do not increase.

FIGURE 58-1
Gestational age specific values for serum thyroid stimulating hormone (TSH) levels (*black lines*) and free thyroxine (T_4) levels (*blue lines*). Data were derived from 17,298 women tested during pregnancy. For each color, the dark solid lines represent the 50th percentile, whereas the upper and lower light lines represent the 2.5th and 97.5th percentiles, respectively. (Data from Casey, 2005; Dashe, 2005.)



Throughout pregnancy, maternal thyroxine is transferred to the fetus (American College of Obstetricians and Gynecologists, 2017). Maternal thyroxine is important for normal fetal brain development, especially before the onset of fetal thyroid gland function (Bernal, 2007; Korevaar, 2016). And, even though the fetal gland begins concentrating iodine and synthesizing thyroid hormone after 12 weeks' gestation, maternal thyroxine contribution remains important. In fact, maternal sources account for 30 percent of thyroxine in fetal serum at term (Thorpe-Beeston, 1991). Still, developmental risks associated with maternal hypothyroidism after midpregnancy remain poorly understood (Morreale de Escobar, 2004; Sarkhail, 2016).

Autoimmunity and Thyroid Disease

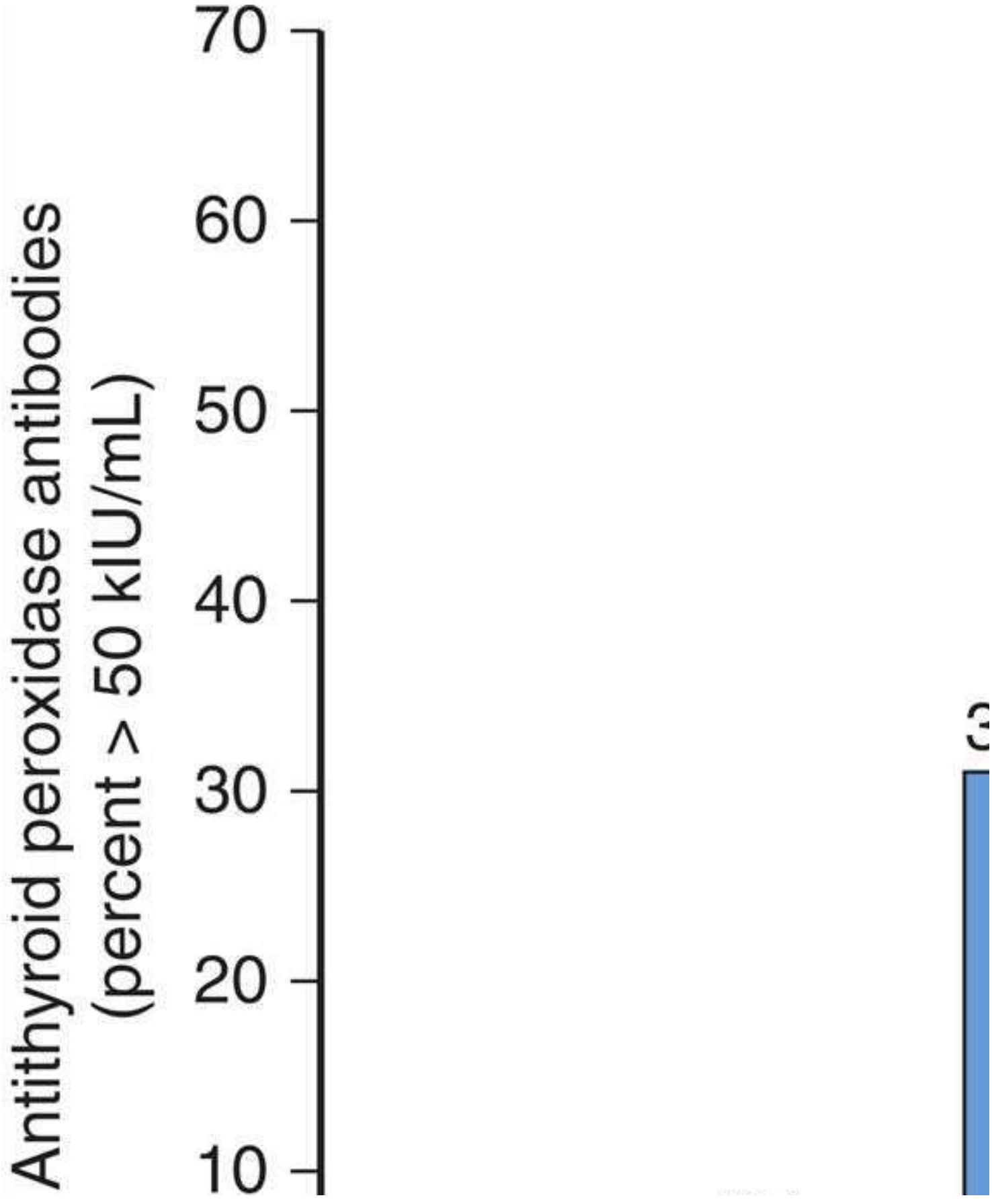
Most thyroid disorders are inextricably linked to autoantibodies against nearly 200 thyrocyte components. These antibodies variably stimulate thyroid function, block function, or cause thyroid inflammation that may lead to follicular cell destruction. Often, these effects overlap or even coexist.

Thyroid-stimulating autoantibodies, also called *thyroid-stimulating immunoglobulins (TSIs)*, bind to the TSH receptor and activate it, causing thyroid hyperfunction and growth. Although these antibodies are identified in most patients with classic Graves disease, simultaneous production of *thyroid-stimulating blocking antibodies* may blunt this effect (Jameson, 2015). *Thyroid peroxidase (TPO)* is a thyroid gland enzyme that normally functions in the production of thyroid hormones. *Thyroid peroxidase antibodies*, previously called *thyroid microsomal autoantibodies,* are directed against TPO and, as shown in Figure 58-2, have been identified in 5 to 15 percent of all pregnant women (Abbassi-Ghanavati, 2010; Sarkhail, 2016). These antibodies have been associated in some studies with early pregnancy loss and preterm birth (Negro, 2006; Korevaar, 2013; Plowden, 2017; Thangaratinam, 2011). In another study with more than 1000 TPO antibody-positive

pregnant women, the risk for preterm birth was not elevated, however, the risk for placental abruption was greater (Abbassi-Ghanavati, 2010). These women are also at high risk for postpartum thyroid dysfunction and at lifelong risk for permanent thyroid failure (Andersen, 2016; Jameson, 2015).

FIGURE 58-2

Incidence in percent of antithyroid peroxidase antibodies in 16,407 women who are normal or euthyroid, in 233 with isolated maternal hypothyroxinemia (IMH), in 598 with subclinical hypothyroidism (SCH), and in 134 with overt hypothyroidism. (Data from Casey, 2007).



Fetal Microchimerism

Autoimmune thyroid disease is much more common in women than in men. One intriguing explanation for this disparity is fetal-to-maternal cell trafficking (Greer, 2011). Fetal cells are known to enter maternal circulation during pregnancy. When fetal lymphocytes enter maternal circulation, they can live for more than 20 years. Stem cell interchange can lead to engraftment in several maternal tissues and is termed *fetal microchimerism.* In some cases, this may involve the thyroid gland (Bianchi, 2003; Boddy, 2015; Khosrotehrani, 2004). A high prevalence of Y-chromosome-positive cells has been identified using fluorescence in situ hybridization (FISH) in the thyroid glands of women with Hashimoto thyroiditis—60 percent, or with Graves disease—40 percent (Renné, 2004). In another study of women giving birth to a male fetus, Lepez and colleagues (2011) identified significantly more circulating male mononuclear cells in those with Hashimoto thyroiditis. Ironically, such microchimerism may have a protective role for autoimmune thyroid disorders (Cirello, 2015).

Hyperthyroidism

The incidence of thyrotoxicosis or hyperthyroidism in pregnancy is varied and complicates between 2 and 17 per 1000 births when gestational-age appropriate TSH threshold values are used (Table 58-1). Because normal pregnancy simulates some clinical findings similar to thyroxine excess, clinically mild thyrotoxicosis may be difficult to diagnose. Suggestive findings include tachycardia that exceeds that usually seen with normal pregnancy, thyromegaly, exophthalmos, and failure to gain weight despite adequate food intake. Laboratory testing is confirmatory. TSH levels are markedly depressed, while serum free T_4 (fT_4) levels are elevated (Jameson, 2015). Rarely, hyperthyroidism is caused by abnormally high serum triiodothyronine (T_3) levels—so-called *T_3-toxicosis.*

TABLE 58-1

Incidence of Overt Hyperthyroidism in Pregnancy

Study	Country	Incidence
Wang (2011)[a]	China	1%
Vaidya (2007)[a]	United Kingdom	0.7%
Lazarus (2007)[b]	United Kingdom	1.7%
Casey (2006)[c]	United States	0.4%
Andersen (2016)[c,d]	Denmark	0.4–0.7%

[a]Screened in the first trimester.

[b]Screened at 9–15 weeks.

[c]Screened before 20 weeks.

[d]Diagnosed in early versus later pregnancy.

Thyrotoxicosis and Pregnancy

The overwhelming cause of thyrotoxicosis in pregnancy is Graves disease, an organ-specific autoimmune process associated with thyroid-stimulating TSH-receptor antibodies as previously discussed (De Leo, 2016). Because these antibodies are specific to Graves hyperthyroidism, such assays have been proposed for diagnosis,

management, and prognosis in pregnancies complicated by hyperthyroidism (Barbesino, 2013). At Parkland Hospital, these receptor antibody assays are generally reserved for cases in which fetal thyrotoxicosis is suspected. With Graves disease, during the course of pregnancy, hyperthyroid symptoms may initially worsen because of hCG stimulation but then subsequently diminish with drops in receptor antibody titers in the second half of pregnancy (Mestman, 2012; Sarkhail, 2016). Amino and coworkers (2003) have found that levels of blocking antibodies also decline during pregnancy.

Treatment

Thyrotoxicosis during pregnancy can nearly always be controlled by thionamide drugs. *Propylthiouracil (PTU)* has been historically preferred because it partially inhibits the conversion of T_4 to T_3 and crosses the placenta less readily than *methimazole*. The latter has also been associated with a rare methimazole embryopathy, characterized by *esophageal* or *choanal atresia* as well as *aplasia cutis*, a congenital skin defect. Yoshihara and associates (2012, 2015) analyzed outcomes in Japanese women with first-trimester hyperthyroidism and found a twofold increased risk of major fetal malformations in pregnancies exposed to methimazole compared with either PTU or potassium iodide. Specifically, seven of nine cases with aplasia cutis and the only case of esophageal atresia were in the group of methimazole-exposed fetuses. There have also been reports of a PTU-associated embryopathy (Andersen, 2014).

In 2009, the Food and Drug Administration issued a safety alert on PTU-associated hepatotoxicity. This warning prompted the American Thyroid Association and the American Association of Clinical Endocrinologists (2011) to recommend PTU therapy during the first trimester followed by methimazole beginning in the second trimester. The obvious disadvantage is that this might lead to poorly controlled thyroid function. Accordingly, at Parkland Hospital, we continue to prescribe PTU treatment throughout pregnancy.

Transient leukopenia can be documented in up to 10 percent of women taking antithyroid drugs, but this does not require therapy cessation (American College of Obstetricians and Gynecologists, 2017). In approximately 0.3 percent, however, *agranulocytosis* develops suddenly and mandates drug discontinuance (Thomas, 2013). It is not dose related, and because of its acute onset, serial leukocyte counts during therapy are not helpful. *Thus, if fever or sore throat develops, women are instructed to discontinue medication immediately and report for a complete blood count.*

Therapy may have other side effects. First, as noted, hepatotoxicity is a possibility and develops in approximately 0.1 percent of treated women. Serial measurement of hepatic enzyme levels does not prevent fulminant PTU-related hepatotoxicity. Second, approximately 20 percent of patients treated with PTU develop *antineutrophil cytoplasmic antibodies (ANCA).* Despite this, only a small percentage of these subsequently develops serious vasculitis (Kimura, 2013). Finally, although thionamides have the potential to cause fetal complications, these are uncommon. In some cases, thionamides may even be therapeutic for the fetus, because TSH-receptor antibodies cross the placenta and can stimulate the fetal thyroid gland to cause thyrotoxicosis and goiter.

The initial thionamide dose is empirical. For nonpregnant patients, the American Thyroid Association recommends that methimazole be used at an initial higher daily dose of 10 to 20 mg orally followed by a lower maintenance dose of 5 to 10 mg. If PTU is selected, a dose of 50 to 150 mg orally three times daily may be initiated depending on clinical severity (Bahn, 2011). At Parkland Hospital, we usually initially give 300 or 450 mg of PTU daily in three divided doses for pregnant women. Occasionally, daily doses of 600 mg or higher are necessary. As discussed, we generally do not transition women to methimazole during the second trimester. The goal is treatment with the lowest possible thionamide dose to maintain thyroid hormone levels slightly above or in the high normal range, while TSH levels remains suppressed (Bahn, 2011). Serum free T_4 concentrations are measured every 4 to 6 weeks.

Subtotal thyroidectomy can be performed after thyrotoxicosis is medically controlled. This seldom is done during pregnancy but may be appropriate for the very few women who cannot adhere to medical treatment or in whom drug therapy proves toxic (Stagnaro-Green, 2012a). Surgery is best accomplished in the second trimester. Potential drawbacks of thyroidectomy include inadvertent resection of parathyroid glands and injury to the recurrent laryngeal nerve.

Thyroid ablation with therapeutic radioactive iodine is contraindicated during pregnancy. The necessary doses may also cause fetal thyroid gland destruction. Thus, when radioactive iodine is given unintentionally, many clinicians recommend abortion. Any exposed fetus must be carefully evaluated, and the incidence of fetal hypothyroidism depends on gestational age and radioiodine dose (Berlin, 2001). There is no evidence that radioiodine given before pregnancy causes fetal anomalies if enough time has passed to allow radiation effects to dissipate and if the woman is euthyroid (Ayala, 1998). The International Commission on Radiological Protection has recommended that women avoid pregnancy for 6 months after radioablative therapy (Brent, 2008). Moreover, during lactation, the breast also concentrates a substantial amount of iodine. This may pose neonatal risk due to ^{131}I-containing milk ingestion and maternal risk from significant breast irradiation. To limit the latter, a delay of 3 months after breastfeeding cessation will more reliably ensure complete breast involution.

Pregnancy Outcome

Women with thyrotoxicosis have pregnancy outcomes that largely depend on whether metabolic control is achieved. For example, excess thyroxine may cause miscarriage or preterm birth (Andersen, 2014; Sheehan, 2015). In untreated women or in those who remain hyperthyroid despite therapy, incidences of preeclampsia, heart failure, and adverse perinatal outcomes are higher (Table 58-2). A prospective cohort study from China showed that women with clinical hyperthyroidism had a 12-fold greater risk of delivering an infant with hearing loss (Su, 2011).

TABLE 58-2

Pregnancy Outcomes in Women with Overt Thyrotoxicosis

	Treated and Euthyroid[a] n = 380	Uncontrolled Thyrotoxicosis[a] n = 90
Maternal Outcome		
Preeclampsia	40 (10%)	15 (17%)
Heart failure	1	7 (8%)
Death	0	1
Perinatal Outcome		
Preterm delivery	51 (16%)	29 (32%)
Growth restriction	37 (11%)	15 (17%)
Stillbirth	0/59	6/33 (18%)
Thyrotoxicosis	1	2
Hypothyroidism	4	0
Goiter	2	0

[a]Data presented as n (%).

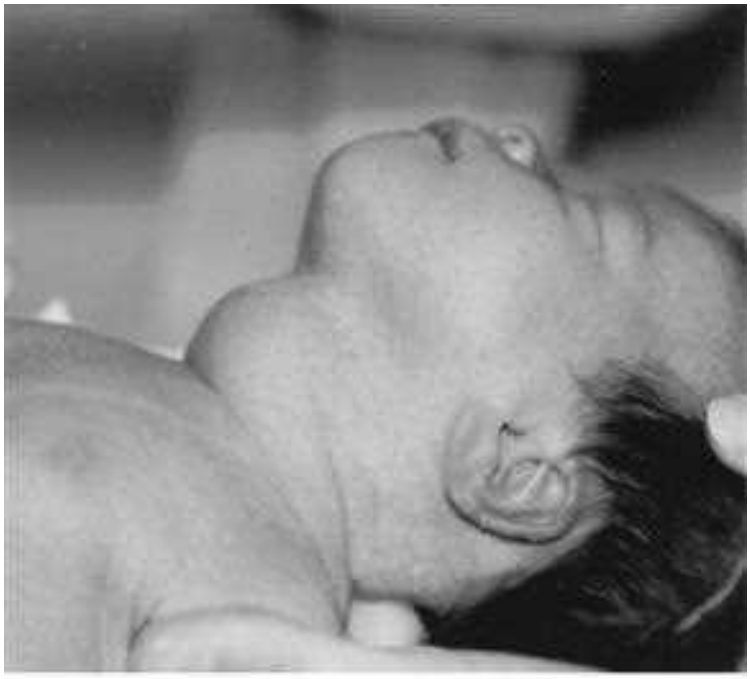
Data from Davis, 1989; Kriplani, 1994; Luewan, 2011; Medici, 2014; Millar, 1994.

Fetal and Neonatal Effects

In most cases, the perinate is euthyroid. In some, however, hyper- or hypothyroidism can develop with or without a goiter (Fig. 58-3). Clinical hyperthyroidism develops in up to 1 percent of neonates born to women with Graves disease (Barbesino, 2013; Fitzpatrick, 2010). If fetal thyroid disease is suspected, nomograms are available for sonographically measured thyroid volume (Gietka-Czernel, 2012).

FIGURE 58-3

Term hypothyroid neonate delivered of a woman with a 3-year history of thyrotoxicosis that recurred at 26 weeks' gestation. The mother was given methimazole 30 mg orally daily and was euthyroid at delivery.



The fetus or neonate who was exposed to excessive maternal thyroxine may have any of several clinical presentations. First, *goitrous thyrotoxicosis* is caused by placental transfer of thyroid-stimulating immunoglobulins. Nonimmune hydrops and fetal demise have been reported with fetal thyrotoxicosis (Nachum, 2003; Stulberg, 2000). The best predictor of perinatal thyrotoxicosis is presence of thyroid-stimulating TSH-receptor antibodies in women with Graves disease (Nathan, 2014). This is especially true if their levels are more than threefold higher than the upper normal limit (Barbesino, 2013). In a study of 72 pregnant women with Graves disease, Luton and associates (2005) reported that none of the fetuses in 31 low-risk mothers had a goiter, and all were euthyroid at delivery. Low risk was defined as no requirement for antithyroid medications during the third trimester or an absence of antithyroid antibodies. Conversely, in a group of 41 women who either were taking antithyroid medication at delivery or had thyroid receptor antibodies, 11 fetuses—27 percent—had sonographic evidence of a goiter at 32 weeks' gestation. Seven of these 11 fetuses were determined to be hypothyroid, and the remaining fetuses were hyperthyroid. In response to these results, the American Thyroid Association and American Association of Clinical Endocrinologists (2011) recommend routine evaluation of TSH-receptor antibodies between 22 and 26 weeks' gestation in women with Graves disease. The American College of Obstetricians and Gynecologists (2017), however, does not recommend such testing. If the fetus is thyrotoxic, maternal thionamide drugs are adjusted even though maternal thyroid function may be within the targeted range (Mestman, 2012). Although usually short-lived, neonatal thyrotoxicosis may require short-course antithyroid drug treatment (Levy-Shraga, 2014; Nathan, 2014).

A second presentation is *goitrous hypothyroidism* caused by fetal exposure to maternally administered thionamides (see Fig. 58-3). Although there are theoretical neurological implications, reports of adverse fetal effects seem to have been exaggerated. Available data indicate that thionamides carry an extremely small risk for causing neonatal hypothyroidism (Momotani, 1997; O'Doherty, 1999). For example, in at least 239 treated thyrotoxic women shown in Table 58-1, evidence of hypothyroidism was found in only four newborns. Furthermore, at least four long-term studies report no abnormal intellectual and physical development of these children (Mestman, 1998). If maternal hypothyroidism developed, the fetus can be treated by a reduced maternal antithyroid medication dose and injections of intraamnionic thyroxine if necessary.

A third presentation, *nongoitrous hypothyroidism,* may develop from transplacental passage of maternal TSH-receptor blocking antibodies (Fitzpatrick, 2010; Gallagher, 2001). And finally, *fetal thyrotoxicosis* after maternal thyroid gland ablation, usually with ^{131}I radioiodine, may result from transplacental thyroid-stimulating antibodies. In one report of early fetal exposure to radioiodine, neonatal thyroid studies indicated transient hyperthyroidism from maternal transfer of stimulating antibodies (Tran, 2010).

Fetal Diagnosis

Evaluation of fetal thyroid function is somewhat controversial. Although the fetal thyroid volume can be measured sonographically in women taking thionamide drugs or in those with thyroid-stimulating antibodies, most investigators do not currently recommend this routinely (Cohen, 2003; Luton, 2005). Kilpatrick (2003) recommends umbilical cord blood sampling and fetal antibody testing only if the mother has previously undergone radioiodine ablation. Because fetal hyper- or hypothyroidism may cause hydrops, growth restriction, goiter, or tachycardia, fetal blood sampling may be appropriate if these are identified (Brand, 2005). The Endocrine Society clinical practice guidelines recommend umbilical cord blood sampling only when the diagnosis of fetal thyroid disease cannot be reasonably ascertained based on clinical and sonographic data (Garber, 2012). Diagnosis and treatment are considered further in Chapter 16 (Surgical Therapy).

Thyroid Storm and Heart Failure

Both of these are acute and life-threatening in pregnancy. Thyroid storm is a hypermetabolic state and is rare in pregnancy. In contrast, pulmonary hypertension and heart failure from cardiomyopathy caused by the profound myocardial effects of thyroxine are common in pregnant women (Sheffield, 2004). As shown in Table 58-2, heart failure developed in 8 percent of 90 women with uncontrolled thyrotoxicosis. In these women, cardiomyopathy is characterized by a high-output state, which may lead to a dilated cardiomyopathy (Fadel, 2000; Klein, 1998). The pregnant woman with thyrotoxicosis has minimal cardiac reserve, and decompensation is

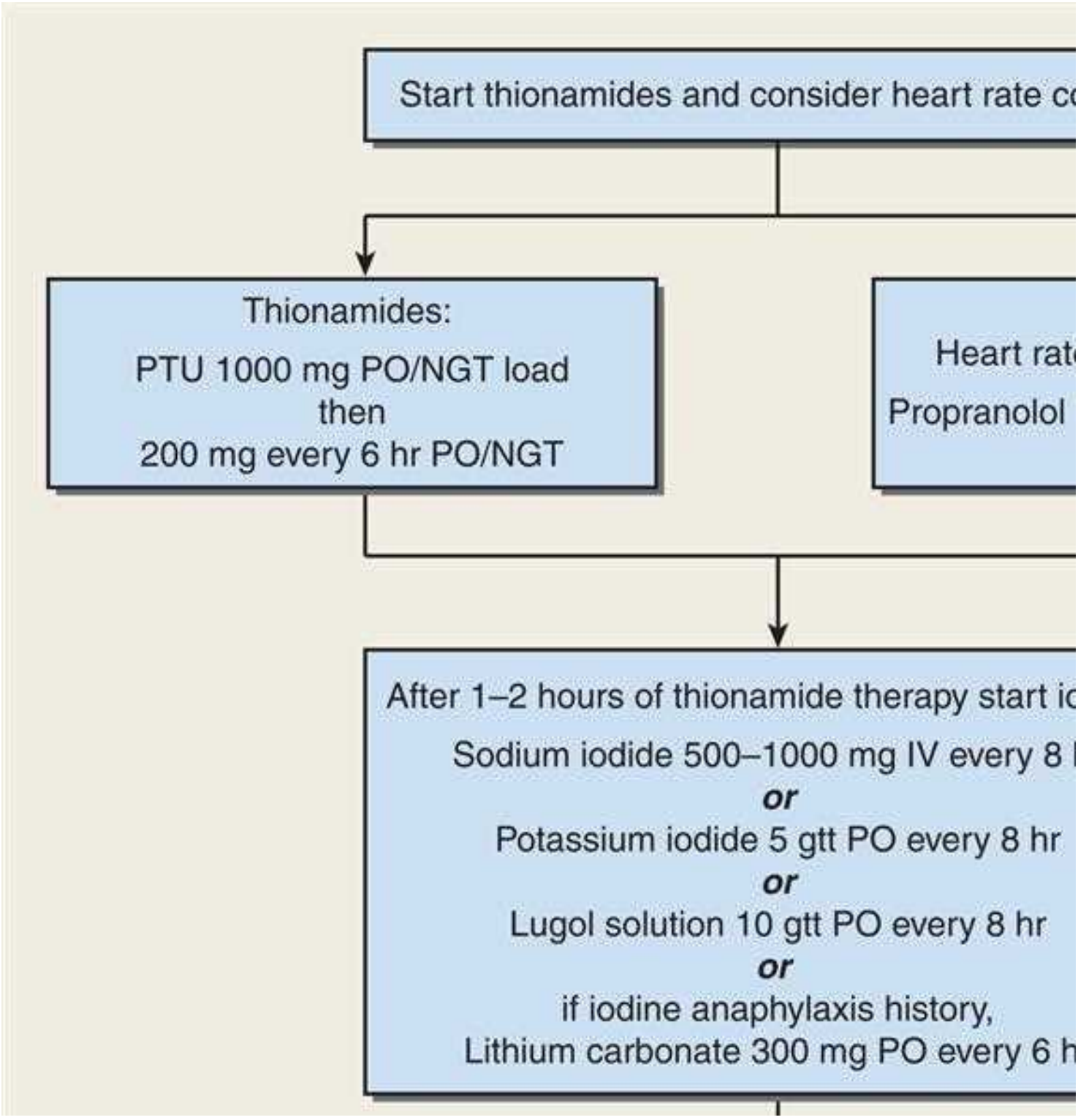
usually precipitated by preeclampsia, anemia, sepsis, or a combination of these. Fortunately, thyroxine-induced cardiomyopathy and pulmonary hypertension are frequently reversible (Sheffield, 2004; Siu, 2007; Vydt, 2006).

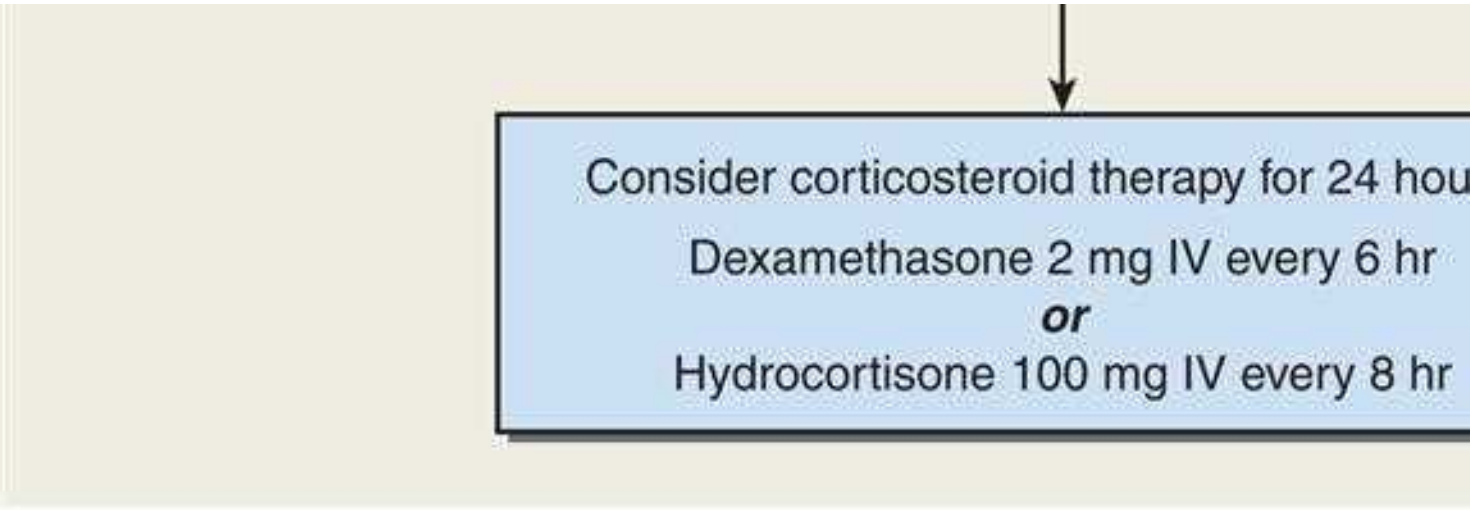
Management

Treatment is similar for thyroid storm and heart failure and should be carried out in an intensive care area that may include special-care units within labor and delivery (American College of Obstetricians and Gynecologists, 2017). Shown in Figure 58-4 is our stepwise approach to medical management of thyroid storm or thyrotoxic heart failure. An hour or two after initial thionamide administration, iodide is given to inhibit thyroidal release of T_3 and T_4. It can be given intravenously as sodium iodide or orally as either saturated solution of potassium iodide (SSKI) or Lugol solution. With a history of iodine-induced anaphylaxis, lithium carbonate, 300 mg every 6 hours, is given instead. Most authorities recommend dexamethasone, 2 mg intravenously every 6 hours for four doses, to further block peripheral conversion of T_4 to T_3. If a β-blocker drug is given to control tachycardia, its effect on heart failure must be considered. Propranolol, labetalol, and esmolol have all been used successfully. Coexisting severe preeclampsia, infection, or anemia should be aggressively managed before delivery is considered.

FIGURE 58-4

One management method for thyroid storm or thyrotoxic heart failure. gtt = drops; IV = intravenous; NGT = nasogastric tube; PO = orally; PTU = propylthiouracil.





Hyperemesis Gravidarum and Gestational Transient Thyrotoxicosis

Transient biochemical features of hyperthyroidism may be observed in 2 to 15 percent of women in early pregnancy (Fitzpatrick, 2010). Many women with hyperemesis gravidarum have abnormally high serum thyroxine levels and low TSH levels (Chap. 54, Management). This results from TSH-receptor stimulation from massive—but normal for pregnancy— concentrations of hCG. This transient condition is also termed *gestational transient thyrotoxicosis.* Even if associated with hyperemesis, antithyroid drugs are not warranted (American College of Obstetricians and Gynecologists, 2017). The degree of hCG level elevation does not correlate with thyroxine and TSH values, which become more normal by midpregnancy (Nathan, 2014; Yoshihara, 2015).

Thyrotoxicosis and Gestational Trophoblastic Disease

The prevalence of increased thyroxine levels in women with a molar pregnancy ranges between 25 and 65 percent (Hershman, 2004). As discussed, abnormally high hCG levels lead to overstimulation of the TSH receptor. Because these tumors are now usually diagnosed early, clinically apparent hyperthyroidism has become less common. With molar evacuation, serum free T_4 levels usually normalize rapidly in parallel with declining hCG concentrations. This is discussed further in Chapter 20 (Diagnosis).

Subclinical Hyperthyroidism

Third-generation TSH assays with an analytical sensitivity of 0.002 mU/mL permit identification of subclinical thyroid disorders. These biochemically defined extremes usually represent normal biological variations but may herald the earliest stages of thyroid dysfunction. *Subclinical hyperthyroidism* is characterized by an abnormally low serum TSH concentration in concert with normal thyroxine hormone levels (Surks, 2004). Long-term effects of persistent subclinical thyrotoxicosis include osteoporosis, cardiovascular morbidity, and progression to overt thyrotoxicosis or thyroid failure. Casey and Leveno (2006) reported that subclinical hyperthyroidism was found in 1.7 percent of pregnant women. Importantly, subclinical hyperthyroidism was not associated with adverse pregnancy outcomes. In separate retrospective analyses of almost 25,000 women who underwent thyroid screening throughout pregnancy, Wilson and colleagues (2012) and Tudela and coworkers (2012) also found no relationship between subclinical hyperthyroidism and preeclampsia or gestational diabetes.

Treatment of subclinical hyperthyroidism is unwarranted in pregnancy because antithyroid drugs may affect the fetus. These women may benefit from periodic surveillance, and approximately half eventually have normal TSH concentrations.

Hypothyroidism

Overt or symptomatic hypothyroidism, as shown in Table 58-3, has been reported to complicate between 2 and 12 per 1000 pregnancies. It is characterized by insidious nonspecific clinical findings that include fatigue, constipation, cold intolerance, muscle cramps, and weight gain. A pathologically enlarged thyroid gland depends on the etiology of hypothyroidism and is more likely in women in areas of endemic iodine deficiency or those with Hashimoto thyroiditis. Other findings include edema, dry skin, hair loss, and prolonged relaxation phase of deep tendon reflexes. *Clinical* or *overt hypothyroidism* is confirmed when an abnormally high serum TSH level is accompanied by an abnormally low thyroxine level. *Subclinical hypothyroidism,* discussed later, is defined by an elevated serum TSH level and *normal* serum thyroxine concentration (Jameson, 2015). Sometimes included in the spectrum of subclinical thyroid disease are asymptomatic individuals with high levels of anti-TPO or antithyroglobulin antibodies. Autoimmune euthyroid disease represents a new investigative frontier in screening and treatment of thyroid dysfunction during pregnancy.

TABLE 58-3

Frequency of Overt Hypothyroidism in Pregnancy

Study	Country	Incidence
Wang (2011)[a]	China	0.3%
Cleary-Goldman (2008)[a]	United States	0.3%
Vaidya (2007)[a]	United Kingdom	1.0%
Casey (2005)[b]	United States	0.2%
Andersen (2016)[d]	Denmark	1.2%

[a]Screened during first trimester.

[b]Screened before 20 weeks.

[c]Includes those treated before pregnancy.

[d]Diagnosed in early versus later pregnancy.

Overt Hypothyroidism and Pregnancy

The most common cause of hypothyroidism in pregnancy is Hashimoto thyroiditis, characterized by glandular destruction from autoantibodies, particularly anti-TPO antibodies. Another cause is postablative Graves disease. Clinical identification of hypothyroidism is especially difficult during pregnancy because many of the signs or symptoms are also common to pregnancy itself. Thyroid analyte testing should be performed on symptomatic women or those with a history of thyroid disease (American College of Obstetricians and Gynecologists, 2017). S*evere hypothyroidism* during pregnancy is uncommon, probably because it is often associated with infertility and higher spontaneous abortion rates (De Groot, 2012). Even women with treated hypothyroidism undergoing in vitro fertilization have a significantly lower chance of achieving pregnancy (Scoccia, 2012).

Treatment

The American Thyroid Association and American Association of Clinical Endocrinologists (2011) recommend replacement therapy for overt hypothyroidism beginning with levothyroxine in doses of 1 to 2 µg/kg/d or approximately 100 µg daily. Women who are athyreotic after thyroidectomy or radioiodine therapy may require higher doses. Surveillance is with TSH levels measured at 4- to 6-week intervals, and the thyroxine dose is adjusted by 25- to 50-µg increments until TSH values become normal. Pregnancy is associated with an increased thyroxine requirement in approximately a third of supplemented women (Abalovich, 2010; Alexander, 2004). The increased demand in pregnancy is believed to be related to augmented estrogen production (Arafah, 2001).

Greater thyroxine requirements begin as early as 5 weeks' gestation. In a randomized trial that provided an increased levothyroxine dose at pregnancy confirmation in 60 mothers, Yassa and coworkers (2010) found that a 29- to 43-percent increase in the weekly dose maintained serum TSH values <5.0 mU/L during the first trimester in all women. Importantly, however, this increase caused TSH suppression in more than a third of women. Significant hypothyroidism may develop early in women without thyroid reserve, such as those with a previous thyroidectomy, those with prior radioiodine ablation, or those undergoing assisted reproductive techniques (Alexander, 2004; Loh, 2009). Anticipatory 25-percent increases in thyroxine replacement at pregnancy confirmation will reduce this likelihood. All other women with hypothyroidism should instead undergo TSH testing at initiation of prenatal care.

Pregnancy Outcome with Overt Hypothyroidism

Observational studies, although limited, indicate that excessive adverse perinatal outcomes are associated with overt thyroxine deficiency (Table 58-4). Preterm birth rates, for example, are higher (Sheehan, 2015). With appropriate replacement therapy, however, rates of adverse effects are not increased in most reports (Bryant, 2015; Matalon, 2006; Tan, 2006). In one dissenting study, however, risks for some pregnancy complications were greater even in women taking replacement therapy (Wikner, 2008). Most experts agree that adequate hormone replacement during pregnancy minimizes the risk of adverse outcomes and most complications.

TABLE 58-4

Pregnancy Complications in 440 Women with Hypothyroidism

	Hypothyroidism (%)	
Complications	**Overt (n = 112)**	**Subclinical (n = 328)**
Preeclampsia	32	8
Placental abruption	8	1
Cardiac dysfunction	3	2
Birthweight <2000 g[a,b]	33	32
Stillbirths[c]	9	3[c]

[a]Preterm or term deliveries were the only outcomes reported by Abalovich, 2002.

[b]Low birthweight and stillbirth were outcomes reported by Su, 2011.

[c]One infant died from syphilis.

Data from Abalovich, 2002; Davis, 1988; Leung, 1993; Männistö, 2009; Su, 2011.

Fetal and Neonatal Effects

Undoubtedly, maternal and fetal thyroid abnormalities are related. In both, thyroid function is dependent on adequate iodide intake, and its deficiency early in pregnancy can cause both maternal and fetal hypothyroidism. And, as discussed, maternal TSH-receptor-blocking antibodies can cross the placenta and cause fetal thyroid dysfunction. Rovelli and colleagues (2010) evaluated 129 neonates born to women with autoimmune thyroiditis. They found that 28 percent had an elevated TSH level on the third or fourth day of life, and 47 percent of these had TPO antibodies on day 15. Still, autoantibodies were undetectable at 6 months of age. It seems paradoxical that despite these transient laboratory findings in the *neonate*, TPO and antithyroglobulin antibodies have little or no effect on *fetal* thyroid function (Fisher, 1997). Indeed, prevalence of fetal hypothyroidism in women with Hashimoto thyroiditis is estimated to be only 1 in 180,000 newborns (Brown, 1996).

Subclinical Hypothyroidism

Although common in women, the incidence of subclinical hypothyroidism varies depending on age, race, dietary iodine intake, and serum TSH thresholds used to establish the diagnosis (Jameson, 2015). In two large studies totaling more than 25,000 pregnant women screened in the first half of pregnancy, subclinical hypothyroidism was identified in 2.3 percent (Casey, 2005; Cleary-Goldman, 2008). The rate of progression to overt thyroid failure is affected by TSH level, age, other disorders such as diabetes, and presence and concentration of antithyroid antibodies.

Diez and Iglesias (2004) prospectively followed 93 nonpregnant women with subclinical hypothyroidism for 5 years and reported that in a third, TSH values became normal. In the other two thirds, those women whose TSH levels were 10 to 15 mU/L developed overt disease at a rate of 19 per 100 patient years. Those women whose TSH levels were <10 mU/L developed overt hypothyroidism at a rate of 2 per 100 patient years.

Regarding screening for subclinical hypothyroidism in nonpregnant individuals, the U.S. Preventative Services Task Force also reports that nearly all patients who develop overt hypothyroidism within 5 years have an initial TSH level >10 mU/L (Helfand, 2004; Karmisholt, 2008).

For gravidas, in a 20-year follow-up study of 5805 women who were screened in early pregnancy, only 3 percent developed thyroid disease. Of the 224 women identified with subclinical hypothyroidism during pregnancy, 17 percent developed thyroid disease in the next 20 years, and most of these had either TPO or thyroglobulin antibodies during pregnancy (Männistö, 2010). Thus, the likelihood of progression to overt hypothyroidism *during* pregnancy in otherwise healthy women with subclinical hypothyroidism seems remote.

Subclinical Hypothyroidism and Pregnancy

Earlier studies were suggestive that subclinical hypothyroidism might be associated with adverse pregnancy outcomes. In 1999, interest was heightened by two studies indicating that undiagnosed maternal thyroid hypofunction may impair fetal neuropsychological development. In one study, Pop and associates (1999) described 22 women with free T_4 levels <10th percentile whose offspring were at higher risk for impaired psychomotor development. In the other study, Haddow and coworkers (1999) retrospectively evaluated children born to 48 untreated women whose serum TSH values were >98th percentile. Some had diminished school performance, reading recognition, and intelligent quotient (IQ) scores. Although described as "subclinically hypothyroid," these women had an abnormally low mean serum free thyroxine level, and thus, many had *overt* hypothyroidism.

To further evaluate any adverse effects, Casey and colleagues (2005) identified subclinical hypothyroidism in 2.3 percent of 17,298 women screened at Parkland Hospital before midpregnancy. These women had small but significantly higher incidences of preterm birth, placental abruption, and neonates admitted to the intensive care nursery compared with euthyroid women. In another study of 10,990 similar women, however, Cleary-Goldman and associates (2008) did not find such associations.

Other studies subsequently confirmed a link between subclinical thyroid function and adverse outcomes (Chen, 2017; Maraka, 2016). One included 24,883 women screened throughout pregnancy and showed an almost twofold greater risk of severe preeclampsia (Wilson, 2012). In an analysis of the same cohort, a consistent relationship was shown between rising TSH levels and the risk for gestational diabetes (Tudela, 2012). Finally, Nelson and colleagues (2014) found an elevated risk for diabetes and stillbirth.

Lazarus and colleagues (2012) reported the findings of the international multicenter Controlled Antenatal Thyroid Screening (CATS) study. This study evaluated prenatal thyroid screening and randomized treatment of both subclinical hypothyroidism and isolated maternal hypothyroxinemia. They reported that offspring IQ scores at age 3 years were not superior in the treated pregnancies.

Despite these findings, the unanswered question concerned whether treatment of subclinical hypothyroidism would mitigate any or all of these reported adverse outcomes. To address this, the Maternal-Fetal Medicine Units Network screened more than 97,000 pregnant women for thyroid disorders and reported that 3.3 percent had subclinical hypothyroidism. These 677 women were randomly assigned to thyroxine replacement therapy or placebo. As reported by Casey and colleagues (2017), and shown in Table 58-5, maternal adverse pregnancy outcomes or cognitive development in the offspring at 5 years did not differ between groups. Annual developmental testing scores and behavioral and attention-deficit hyperactivity disorder results also did not differ.

TABLE 58-5

Pregnancy and Perinatal Outcomes According to Diagnosis and Treatment Group of Thyroid Disorders[a]

	Subclinical Hypothyroidism		Isolated Hypothyroxinemia	
Outcome	**Thyroxine**	**Placebo**	**Thyroxine**	**Placebo**
Maternal				
EGA at delivery (weeks)	39.1 ± 2.5	38.9 ± 3.1	39.0 ± 2.4	38.8 ± 3.1
Preterm birth <34 weeks	9.1%	10.9%	3.8%	2.7%
Placental abruption	0.3%	1.5%	1.1%	0.8%
Preeclampsia	6.5%	5.9%	3.4%	4.2%
Diabetes	7.4%	6.5%	8.0%	9.2%
Perinatal and Childhood				
Stillbirth	12/1000	21/1000	8/1000	19/1000
Neonatal death	0	3/1000	4/1000	4/1000
NICU admission	8.6%	6.2%	11.8%	11.9%
Birthweight <10th centile	9.8%	8.1%	8.8%	7.8%
IQ median (25th, 75th percentile)	97 (85,105)	94 (85,107)	94 (83,101)	91 (82,101)

[a]For all comparisons, $p > 0.05$.

EGA = estimated gestational age; IQ = intelligence quotient; NICU = neonatal intensive care unit.

Data from Casey, 2017.

Screening in Pregnancy

Because of the findings in the studies from 1999 cited above, some professional organizations began to recommend routine prenatal screening and treatment for subclinical hypothyroidism. Consequent to the Lazarus study, however, clinical practice guidelines from the Endocrine Society, the American Thyroid Association, and the American Association of Clinical Endocrinologists uniformly recommended screening only those at greater risk during pregnancy (De Groot, 2012; Garber, 2012). This has been and still is the recommendation of the American College of Obstetricians and Gynecologists (2017). The findings of Casey and colleagues (2017) further buttress these recommendations.

Isolated Maternal Hypothyroxinemia

Women with low serum free T_4 values but a normal-range TSH level are considered to have *isolated maternal hypothyroxinemia*. Its incidence in two large trials was 1.3 to 2.1 percent (Casey, 2007; Cleary-Goldman, 2008). As shown in Figure 58-2, unlike in subclinical hypothyroidism, these women had a low prevalence of antithyroid antibodies.

Evolution of the knowledge of this thyroid disorder was similar to that seen with subclinical hypothyroidism. Initial studies reported that offspring of women with isolated hypothyroxinemia had neurodevelopmental difficulties (Kooistra, 2006; Pop, 1999, 2003). In another study, Casey and colleagues (2007) found no higher risks for other adverse perinatal outcomes compared with those of euthyroid women. Also, the aforementioned CATS study did not find improved neurodevelopmental outcomes in women with isolated hypothyroxinemia who were then treated with thyroxine (Lazarus, 2012).

The randomized trial conducted by the Maternal-Fetal Medicine Units Network also provided data to settle this question. Casey and colleagues (2017) noted no higher rates of adverse outcomes between groups and found that early thyroxine treatment offered no benefits (see Table 58-5).

Euthyroid Autoimmune Thyroid Disease

Autoantibodies to TPO and thyroglobulin have been identified in 6 to 20 percent of reproductive-aged women (Thangaratinam, 2011). Most who test positive for such antibodies, however, are euthyroid. That said, such women carry a two- to fivefold increased risk for early pregnancy loss (Stagnaro-Green, 2004; Thangaratinam, 2011). The presence of thyroid antibodies has also been associated with preterm birth (Stagnaro-Green, 2009). In a randomized treatment trial of 115 euthyroid women with TPO antibodies, Negro and coworkers (2006) reported that treatment with levothyroxine astoundingly reduced the preterm birth rate from 22 to 7 percent. Contrarily, Abbassi-Ghanavati and associates (2010) evaluated pregnancy outcomes in more than 1000 untreated women with TPO antibodies and did not find an increased risk for preterm birth compared with the risk in 16,000 euthyroid women without antibodies. These investigators, however, did find a threefold greater risk of placental abruption in these women.

As with nonpregnant subjects with TPO antibodies, these women are also at increased risk for progression of thyroid disease and postpartum thyroiditis (Jameson, 2015; Stagnaro-Green, 2012a). Currently, universal screening for the thyroid autoantibodies is not recommended by any professional organization (De Groot, 2012; Stagnaro-Green, 2011a, 2012a).

Iodine Deficiency

Decreasing iodide fortification of table salt and bread products in the United States during the past 25 years has led to occasional iodide deficiency (Caldwell, 2005; Hollowell, 1998). Importantly, the most recent National Health and Nutrition Examination Survey indicated that, overall, the United States population remains iodine sufficient (Caldwell, 2011). Even so, experts agree that iodine nutrition in vulnerable populations, such as pregnant women, requires continued monitoring. In 2011, the Office of Dietary Supplements of the National Institutes of Health sponsored a workshop to prioritize iodine research. Participants emphasized the decline in median urinary iodine levels to 125 µg/L in pregnant women and the serious potential effects on developing fetuses (Swanson, 2012).

Dietary iodine requirements are higher during pregnancy due to augmented thyroid hormone production, increased renal losses, and fetal iodine requirements. Adequate iodine is requisite for fetal neurological development beginning soon after conception, and abnormalities are dependent on the degree of deficiency. The World Health Organization (WHO) has estimated that 38 million children are born every year at risk of lifelong brain damage associated with iodine deficiency (Alipui, 2008).

Although it is doubtful that *mild deficiency* causes intellectual impairment, supplementation does prevent fetal goiter (Stagnaro-Green, 2012b). *Severe deficiency*, on the other hand, is frequently associated with damage typically encountered with *endemic cretinism* (Delange, 2001). It is presumed that *moderate deficiency* has intermediate and variable effects. Berbel and associates (2009) began daily supplementation in more than 300 pregnant women with moderate deficiency at three time periods—4 to 6 weeks, 12 to 14 weeks, and after delivery. They found improved neurobehavioral development scores in offspring of women supplemented with 200 µg potassium iodide very early in pregnancy. Similarly, Velasco and coworkers (2009) found improved Bayley Psychomotor Development scores in offspring of women supplemented with 300 µg of iodine daily in the first trimester. In contrast, Murcia and colleagues (2011) identified lower psychomotor scores in 1-year-old infants whose mothers reported daily supplementation of more than 150 µg. To address this, randomized controlled trial of iodine supplementation in mildly to moderately iodine-deficient pregnant women in India and Thailand is nearing completion (Pearce, 2016).

Regarding daily iodine intake, the Institute of Medicine (2001) recommends 220 µg/d during pregnancy and 290 µg/d during lactation (Chap. 9, Minerals). The Endocrine Society recommends an average iodine intake of 150 µg/d in reproductive-aged women, and this should be increased to 250 µg during pregnancy and breastfeeding (De Groot, 2012). The American Thyroid Association has recommended that 150 µg of iodine be added to prenatal vitamins to achieve this average daily intake (Becker, 2006). According to Leung and coworkers (2011), however, only 51 percent of the prenatal multivitamins in the United States contain iodine. It has even been suggested that because most cases of maternal hypothyroxinemia worldwide are related to relative iodine deficiency, supplementation may obviate the need to consider thyroxine treatment in such women (Gyamfi, 2009). However, without evidence of benefit, it is hard to justify the cost of iodine supplementation of large numbers of pregnant women in areas with mild iodine deficiency (Pearce, 2016). Importantly, experts caution against oversupplementation. Teng and associates (2006) contend that excessive iodine intake—defined as >300 µg/d—may lead to subclinical hypothyroidism and autoimmune thyroiditis. The Endocrine Society, in accordance with the WHO, advises against exceeding twice the daily recommended intake of iodine, or 500 µg/d (De Groot, 2012; Leung, 2011).

Congenital Hypothyroidism

Universal newborn screening for neonatal hypothyroidism was introduced in 1974 and is now required by law in all states (Chap. 32, Routine Newborn Care). This develops in approximately 1 in 3000 newborns and is one of the most preventable causes of mental retardation (LaFranchi, 2011). Developmental disorders of the

thyroid gland such as agenesis and hypoplasia account for 80 to 90 percent of these cases. The remainder is caused by hereditary defects in thyroid hormone production (Moreno, 2008).

Early and aggressive thyroxine replacement is critical for newborns with congenital hypothyroidism. Still, some neonates identified by screening programs who were treated promptly will exhibit cognitive deficits into adolescence (Song, 2001). Therefore, in addition to timing of treatment, the severity of congenital hypothyroidism is an important factor in long-term cognitive outcomes. Olivieri and colleagues (2002) reported that 8 percent of 1420 newborns with congenital hypothyroidism also had other major congenital malformations.

Postpartum Thyroiditis

Transient autoimmune thyroiditis is consistently found in approximately 5 to 10 percent of women during the first year after childbirth (Nathan, 2014; Stagnaro-Green, 2011b, 2012a). Postpartum thyroid dysfunction with an onset within 12 months includes hyperthyroidism, hypothyroidism, or both. The propensity for thyroiditis antedates pregnancy and is directly related to increasing serum levels of thyroid autoantibodies. Up to 50 percent of women who are thyroid-antibody positive in the first trimester will develop postpartum thyroiditis (Stagnaro-Green, 2012a). In a Dutch study of 82 women with type 1 diabetes, postpartum thyroiditis developed in 16 percent and was threefold higher than in the general population (Gallas, 2002). Importantly, 46 percent of those identified with overt postpartum thyroiditis had TPO antibodies in the first trimester.

Clinical Manifestations

In clinical practice, postpartum thyroiditis is diagnosed infrequently because it typically develops months after delivery and causes vague and nonspecific symptoms (Stagnaro-Green, 2004). The clinical presentation varies, and classically two clinical phases that may develop in succession are recognized. The first and earliest is *destruction-induced thyrotoxicosis* with symptoms from excessive release of hormone from glandular disruption. The onset is abrupt, and a small, painless goiter is common. Although there may be many symptoms, only fatigue and palpitations are more frequent in thyrotoxic women compared with normal controls. This thyrotoxic phase usually lasts only a few months. Thionamides are ineffective, and if symptoms are severe, a β-blocking agent may be given. The second and usually later phase between 4 and 8 months postpartum is *hypothyroidism* from thyroiditis. Thyromegaly and other symptoms are common and more prominent than during the thyrotoxic phase. Thyroxine replacement at doses of 25 to 75 µg/d is typically given for 6 to 12 months.

Stagnaro-Green and associates (2011b) reported postpartum surveillance results in 4562 Italian gravidas who had been screened for thyroid disease in pregnancy. Serum TSH and anti-TPO antibody levels were measured again at 6 and 12 months. Overall, two thirds of 169 women (3.9 percent) with postpartum thyroiditis were identified to have hypothyroidism only. The other third were diagnosed with hyperthyroidism. Only 14 percent of all women demonstrated the “classic” biphasic progression described above. These findings are consistent with data compiled from 20 other studies between 1982 and 2008 (Stagnaro-Green, 2012a).

Importantly, women who experience either type of postpartum thyroiditis have a 20- to 30-percent risk of eventually developing permanent hypothyroidism, and the annual progression rate is 3.6 percent (Nathan, 2014). Women at greater risk for developing hypothyroidism are those with higher titers of thyroid antibodies and higher TSH levels during the initial hypothyroid phase. Others may develop subclinical disease, but half of those with thyroiditis who are positive for TPO antibodies develop permanent hypothyroidism by 6 to 7 years (Stagnaro-Green, 2012a).

An association between postpartum thyroiditis and postpartum depression has been proposed but remains unresolved. Lucas and coworkers (2001) found a 1.7-percent incidence of postpartum depression at 6 months in women with thyroiditis as well as in controls. Pederson and colleagues (2007) found a significant correlation between abnormal scores on the Edinburgh Postnatal Depression Scale and total thyroxine values in the low normal range during pregnancy in 31 women. Similarly unsettled is the link between depression and thyroid antibodies. Kuijpens and associates (2001) reported that TPO antibodies were a marker for postpartum depression in euthyroid women. In a randomized trial, however, Harris and coworkers (2002) reported no difference in postpartum depression in 342 women with TPO antibodies who were given either levothyroxine or placebo.

Nodular Thyroid Disease

Thyroid nodules can be found in 1 to 2 percent of reproductive-aged women (Fitzpatrick, 2010). Management of a palpable thyroid nodule during pregnancy depends on gestational age and mass size. Small nodules detected by sensitive sonographic methods are more common during pregnancy in some populations. Kung and associates (2002) used high-resolution sonography and found that 15 percent of Chinese women had nodules larger than 2 mm in diameter. Almost half were multiple, and the nodules usually enlarged modestly across pregnancy and did not regress postpartum. Biopsy of those >5 mm^3 that persisted at 3 months usually showed nodular hyperplasia, and none were malignant. In most studies, 90 to 95 percent of solitary nodules are benign (Burch, 2016).

Evaluation of thyroid nodules during pregnancy should be similar to that for nonpregnant patients. As discussed in Chapter 46 (Radiographic Contrast Agents), *radioiodine scanning* in pregnancy is usually not recommended (American College of Obstetricians and Gynecologists, 2017). *Sonographic* examination reliably detects nodules >5 mm, and their solid or cystic structure also is determined. According to the American Association of Clinical Endocrinologists, sonographic characteristics associated with malignancy include hypoechogenic pattern, irregular margins, and microcalcifications (Gharib, 2005). *Fine-needle aspiration (FNA)* is an excellent assessment method, and histological tumor markers and immunostaining are reliable to evaluate for malignancy (Hegedüs, 2004). If the FNA biopsy shows a follicular lesion, surgery may be deferred until after delivery.

Evaluation of thyroid cancer involves a multidisciplinary approach (Fagin, 2016). Most thyroid carcinomas are well differentiated and pursue an indolent course. Messuti and coworkers (2014) provided evidence that persistence or recurrence of these tumors may be more common in pregnant women. When thyroid malignancy is diagnosed during the first or second trimester, thyroidectomy may be performed before the third trimester (Chap. 63, Thyroid Cancer). In women without evidence of an aggressive thyroid cancer or in those diagnosed in the third trimester, surgical treatment can be deferred to the immediate puerperium (Gharib, 2010).

PARATHYROID DISEASE

The function of *parathyroid hormone (PTH)* is to maintain extracellular fluid calcium concentration. This 84-amino acid hormone acts directly on bone and kidney and indirectly on small intestine through its effects on synthesis of vitamin D (1,25-$(OH)_2$D) to increase serum calcium (Potts, 2015). Secretion is regulated by serum ionized calcium concentration through a negative feedback system. *Calcitonin* is a potent parathyroid hormone that acts as a physiological parathyroid hormone antagonist. The interrelationships between these hormones, calcium metabolism, and *PTH-related protein* produced by fetal tissue are discussed in Chapter 4 (Parathyroid Glands).

Of fetal demands, calcium requirements reach 300 mg/d in late pregnancy and 30 g for the entire gestation. These needs and greater renal calcium loss from augmented glomerular filtration substantively raise maternal calcium demands. Pregnancy is associated with a twofold rise in serum concentrations of 1,25-dihydroxyvitamin D, which increases gastrointestinal calcium absorption. The effectuating hormone is probably of placental and decidual origin because maternal PTH levels are low normal or decreased during pregnancy (Cooper, 2011; Molitch, 2000). Total serum calcium levels decline with serum albumin concentrations, but ionized calcium levels remain unchanged. Vargas Zapata and colleagues (2004) have suggested a role for insulin-like growth factor-1 (IGF-1) in maternal calcium homeostasis and bone turnover.

Hyperparathyroidism

Hypercalcemia is caused by hyperparathyroidism or cancer in 90 percent of cases (Potts, 2015). Because many automated laboratory systems include serum calcium measurement, hyperparathyroidism has changed from being a condition defined by symptoms to one that is discovered on routine screening (Pallan, 2012). It has a reported prevalence of 2 to 3 per 1000 women, but some have estimated the rate to be as high as 14 per 1000 when asymptomatic cases are included. Almost 80 percent are caused by a solitary adenoma, and another 15 percent by hyperfunctioning of all four glands. In the remainder, a malignancy as the cause of increased serum calcium levels is usually obvious. Of note, PTH produced by tumors is not identical to the natural hormone and may not be detected by routine assays.

In most patients, the serum calcium level is elevated to within only 1 to 1.5 mg/dL above the upper normal limit. This may help to explain why only 20 percent of those who have abnormally elevated levels are symptomatic (Bilezikian, 2004). In a fourth, however, symptoms become apparent when the serum calcium level continues to rise. *Hypercalcemic crisis* manifests as stupor, nausea, vomiting, weakness, fatigue, and dehydration.

All women with symptomatic hyperparathyroidism should be surgically treated (Potts, 2015). Indications for parathyroidectomy include a serum calcium level 1.0 mg/dL above the upper normal range, a calculated creatinine clearance <60 mL/min, reduced bone density, or age >50 years (Bilezikian, 2009). Those not meeting these criteria should undergo annual serum calcium and creatinine level measurement and bone density assessment every 1 to 2 years (Pallan, 2012).

Hyperparathyroidism in Pregnancy

In their review, Schnatz and Thaxton (2005) found fewer than 200 reported cases of hyperparathyroidism complicating pregnancy. As in nonpregnant patients, parathyroid adenoma is the most common etiology. Ectopic parathyroid hormone production and rare cases of parathyroid carcinoma have been reported in pregnancy (Montoro, 2000; Saad, 2014). Symptoms include hyperemesis, generalized weakness, renal calculi, and psychiatric disorders. Occasionally, pancreatitis is the presenting disorder (Cooper, 2011; Hirsch, 2015).

Pregnancy theoretically improves hyperparathyroidism because of significant calcium shunting to the fetus and augmented renal excretion (Power, 1999). When the “protective effects” of pregnancy are withdrawn, however, postpartum hypercalcemic crisis is a significant danger. This life-threatening complication can be seen with serum calcium levels greater than 14 mg/dL and is characterized by nausea, vomiting, tremors, dehydration, and mental status changes (Malekar-Raikar, 2011).

Early reports described excessive stillbirths and preterm deliveries in pregnancies complicated by hyperparathyroidism. More recent reports, however, described lower rates of stillbirth, neonatal death, and neonatal tetany (Kovacs, 2011). Other fetal complications include miscarriage, fetal-growth restriction, and low birthweight (Chamarthi, 2011). Schnatz (2005) reported a 25-percent incidence of preeclampsia.

Management in Pregnancy

Surgical removal of a symptomatic parathyroid adenoma is preferable. This should prevent fetal and neonatal morbidities and postpartum parathyroid crises (Kovacs, 2011). Elective neck exploration during pregnancy is usually well tolerated, even in the third trimester (Hirsch, 2015; Schnatz, 2005; Stringer, 2017). In at least two cases, a mediastinal adenoma was removed at midpregnancy (Rooney, 1998; Saad, 2014).

Medical management may be appropriate in asymptomatic pregnant women with mild hypercalcemia (Hirsch, 2015). If so, patients are carefully monitored in the puerperium for hypercalcemic crisis. Initial medical management might include *calcitonin* to decrease skeletal calcium release, or oral phosphate, 1 to 1.5 g daily in divided doses, to bind excess calcium. For women with dangerously elevated serum calcium levels or those who are mentally obtunded with *hypercalcemic crisis*, emergency treatment is instituted. Diuresis with intravenous normal saline is begun so that urine flow exceeds 150 mL/hr. *Furosemide* is given in conventional doses to block tubular calcium reabsorption. Importantly, hypokalemia and hypomagnesemia should be prevented. Adjunctive therapy includes *mithramycin,* which inhibits bone resorption.

Neonatal Effects

Normally, cord blood calcium levels are higher than maternal levels (Chap. 7, Placental Role in Embryofetal Development). With maternal hyperparathyroidism, abnormally elevated maternal and thus fetal levels further suppress fetal parathyroid function. Because of this, newborn calcium levels rapidly drop after birth, and 15 to 25 percent of these neonates develop severe hypocalcemia with or without tetany (Molitch, 2000). Neonatal hypoparathyroidism caused by maternal hyperparathyroidism is usually transient and is treated with calcium and 1,25-dihydroxyvitamin D_3 (calcitriol). The latter will not be effective in preterm infants,

however, because the intestinal vitamin D receptor is not sufficiently expressed (Kovacs, 2011). Neonatal tetany or seizures should stimulate an evaluation for maternal hyperparathyroidism (Beattie, 2000; Ip, 2003).

Hypoparathyroidism

The most common cause of hypocalcemia is hypoparathyroidism that usually follows parathyroid or thyroid surgery. Hypoparathyroidism is estimated to follow up to 7 percent of total thyroidectomies (Shoback, 2008). It is characterized by facial muscle spasms, muscle cramps, and paresthesias of the lips, tongue, fingers, and feet. This can progress to tetany and seizures (Potts, 2015). Chronically, hypocalcemic pregnant women may also have a fetus with skeletal demineralization resulting in multiple bone fractures in the neonatal period (Alikasifoglu, 2005).

Maternal treatment includes calcitriol, dihydrotachysterol, or large vitamin D doses of 50,000 to 150,000 U/d; calcium gluconate or calcium lactate in doses of 3 to 5 g/d; and a low-phosphate diet. Fetal risks from large doses of vitamin D have not been established. During treatment, the therapeutic challenge in women with known hypoparathyroidism is management of blood calcium levels. It is possible that the greater calcium absorption typical of pregnancy will result in lower calcium requirements or that the fetal demand for calcium will result in greater need. The goal during pregnancy is to maintain a corrected calcium level in the low normal range.

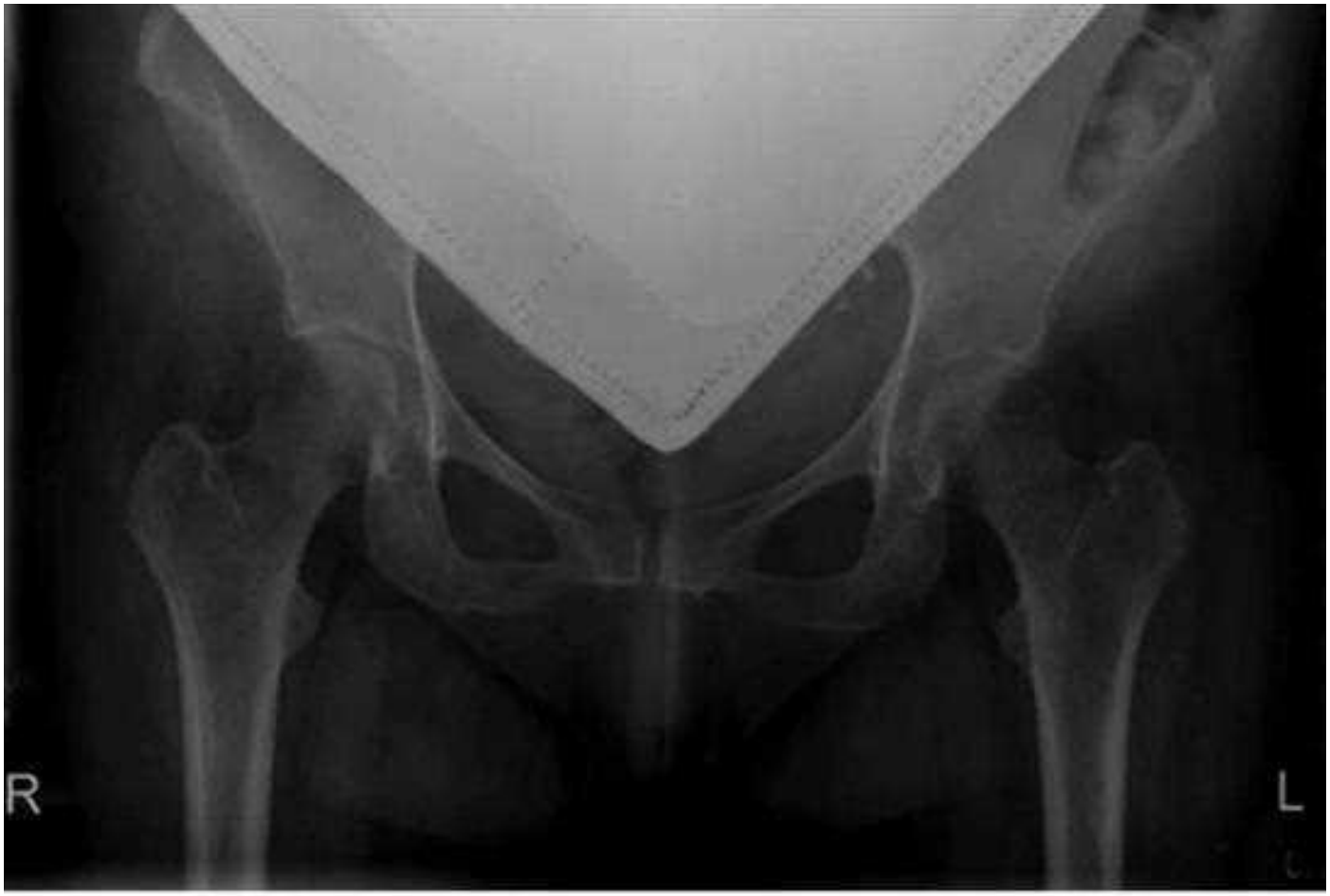
Pregnancy-Associated Osteoporosis

In most gravidas, even with their remarkably increased calcium requirements, it is uncertain whether pregnancy causes osteopenia (Kaur, 2003; To, 2003). In one study of 200 pregnant women in which bone mass was measured, Kraemer and colleagues (2011) demonstrated a decline in bone density during pregnancy. Women who breastfed, carried twin pregnancies, or had a low body mass index were at higher risk of bone loss. From their review, Thomas and Weisman (2006) cite a 3- to 4-percent average reduction in bone mineral density during pregnancy. Lactation also represents a period of negative calcium balance that is corrected through maternal skeletal resorption. Feigenberg and coworkers (2008) found cortical bone mass reductions using ultrasound in young primiparas in the puerperium compared with nulligravid controls. Rarely, some women develop idiopathic osteoporosis while pregnant or lactating (Hellmeyer, 2007).

The most common symptom of osteoporosis is back pain in late pregnancy or postpartum. Other symptoms are hip pain, either unilateral or bilateral, and difficulty in weight bearing until the woman is nearly immobilized (Maliha, 2012). In more than half of women, no apparent reason for osteopenia is found. Some known causes include heparin (unfractionated only), prolonged bed rest, and corticosteroid therapy (Cunningham, 2005; Galambosi, 2016). In a few cases, overt hyperparathyroidism or thyrotoxicosis eventually develops.

Treatment is problematic and includes calcium and vitamin D supplementation and standard pain management. Shown in Figure 58-5 is a hip radiograph from a woman treated at Parkland Hospital during the third trimester for transient osteoporosis of pregnancy. For women with pregnancy-associated osteopenia, long-term surveillance indicates that although bone density improves, these women and their offspring may have chronic osteopenia (Carbone, 1995). Related, prenatal supplementation of normal women with cholecalciferol, 1000 IU/d, did not increase offspring bone mineral content, although it did ensure maternal vitamin D repletion (Cooper, 2016).

FIGURE 58-5
Anteroposterior plain hip radiograph of a 25-year-old woman at 26 weeks' gestation. She complained of left hip and knee pain and progressive weakness. Transient osteoporosis of the left femur responded over 3 months to physical therapy combined with vitamin D and calcium supplementation.



ADRENAL GLAND DISORDERS

Pregnancy has profound effects on adrenal cortical secretion and its control or stimulation. These interrelationships were reviewed by Lekarev and New (2011) and are discussed in detail in Chapter 4 (Parathyroid Glands).

Pheochromocytoma

Pheochromocytomas are chromaffin tumors that secrete catecholamines and usually are located in the adrenal medulla, although 10 percent are located in sympathetic ganglia. They are called the *10-percent tumor* because approximately 10 percent are bilateral, 10 percent are extraadrenal, and 10 percent are malignant. These tumors can be associated with medullary thyroid carcinoma and hyperparathyroidism in some of the autosomally dominant or recessive *multiple endocrine neoplasia syndromes*, as well as in neurofibromatosis and von Hippel-Lindau disease (Neumann, 2015).

These tumors complicate approximately 1 per 50,000 pregnancies (Quartermaine, 2017). Notably, they are found in 0.1 percent of hypertensive patients (Abdelmannan, 2011). However, they are more commonly found at autopsy but with infrequent clinical recognition. Symptoms are usually paroxysmal and manifest as hypertensive crisis, seizure disorders, or anxiety attacks. Hypertension is sustained in 60 percent of patients, but half of these also have paroxysmal crises. Other symptoms during paroxysmal attacks are headaches, profuse sweating, palpitations, chest pain, nausea and vomiting, and pallor or flushing.

The standard screening test is quantification of metanephrines and catecholamine metabolites in a 24-hour urine specimen (Neumann, 2015). Diagnosis is established by measurement of a 24-hour urine collection with at least two of three assays for free catecholamines, metanephrines, or vanillylmandelic acid (VMA). Determination of plasma catecholamine levels is the most sensitive test. In nonpregnant patients, adrenal localization is usually successful with either computed tomography (CT) or magnetic resonance (MR) imaging. For most cases, preferred treatment is laparoscopic adrenalectomy (Neumann, 2015).

Pheochromocytoma Complicating Pregnancy

These tumors are rare but result in dangerous pregnancy complications. Geelhoed (1983) provided an earlier review of 89 cases in which 43 mothers died. Maternal death was much more common if the tumor was not diagnosed antepartum—58 versus 18 percent. As seen in Table 58-6, maternal mortality rates are now lower but still formidable. In their review of 77 cases, Biggar and Lennard (2013) reported that antepartum diagnosis is the most important determinant of maternal mortality risk. That said, Salazar-Vega and colleagues (2014) described good outcomes in women diagnosed after delivery.

TABLE 58-6

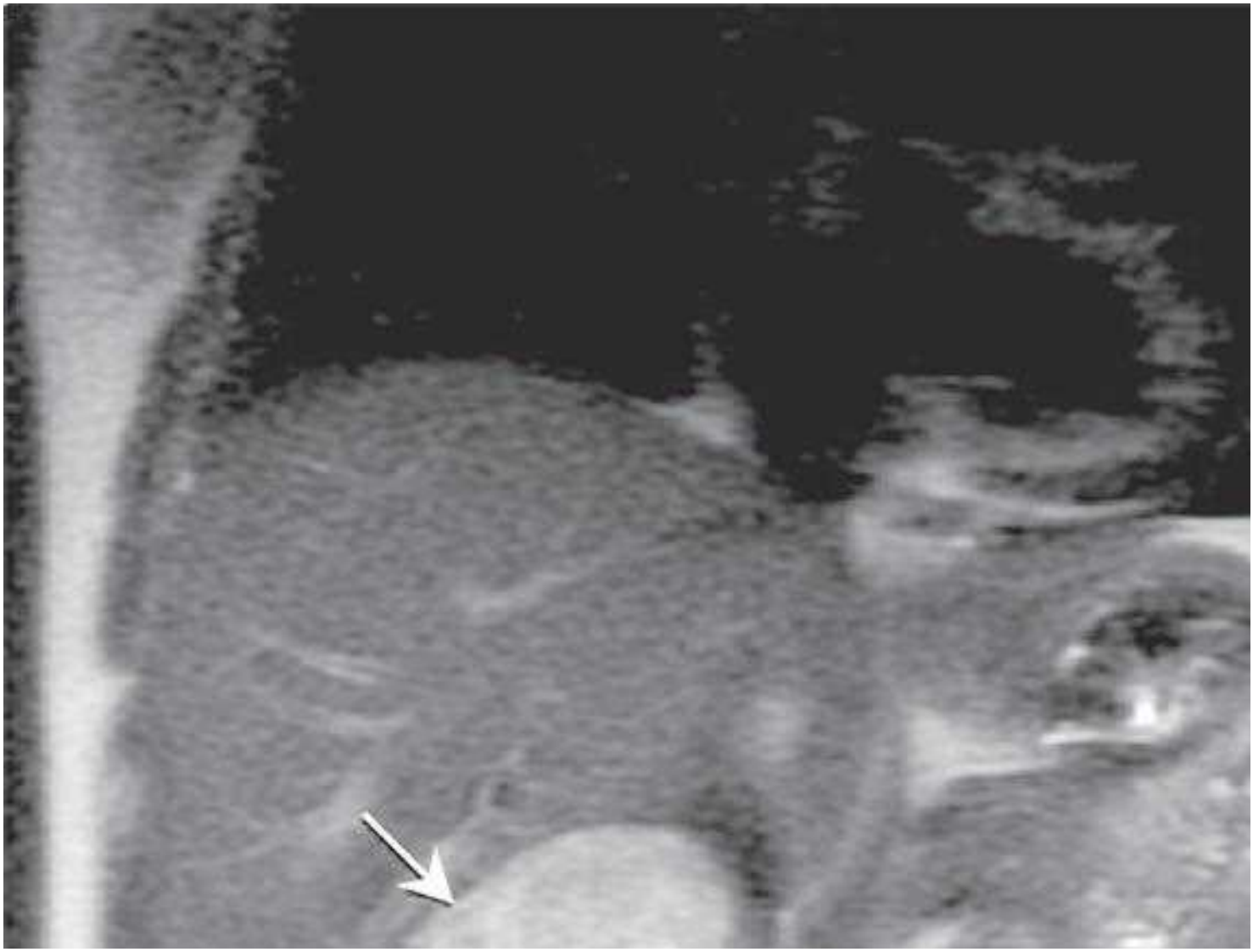
Outcomes of Pregnancies Complicated by Pheochromocytoma and Reported in Four Contiguous Epochs

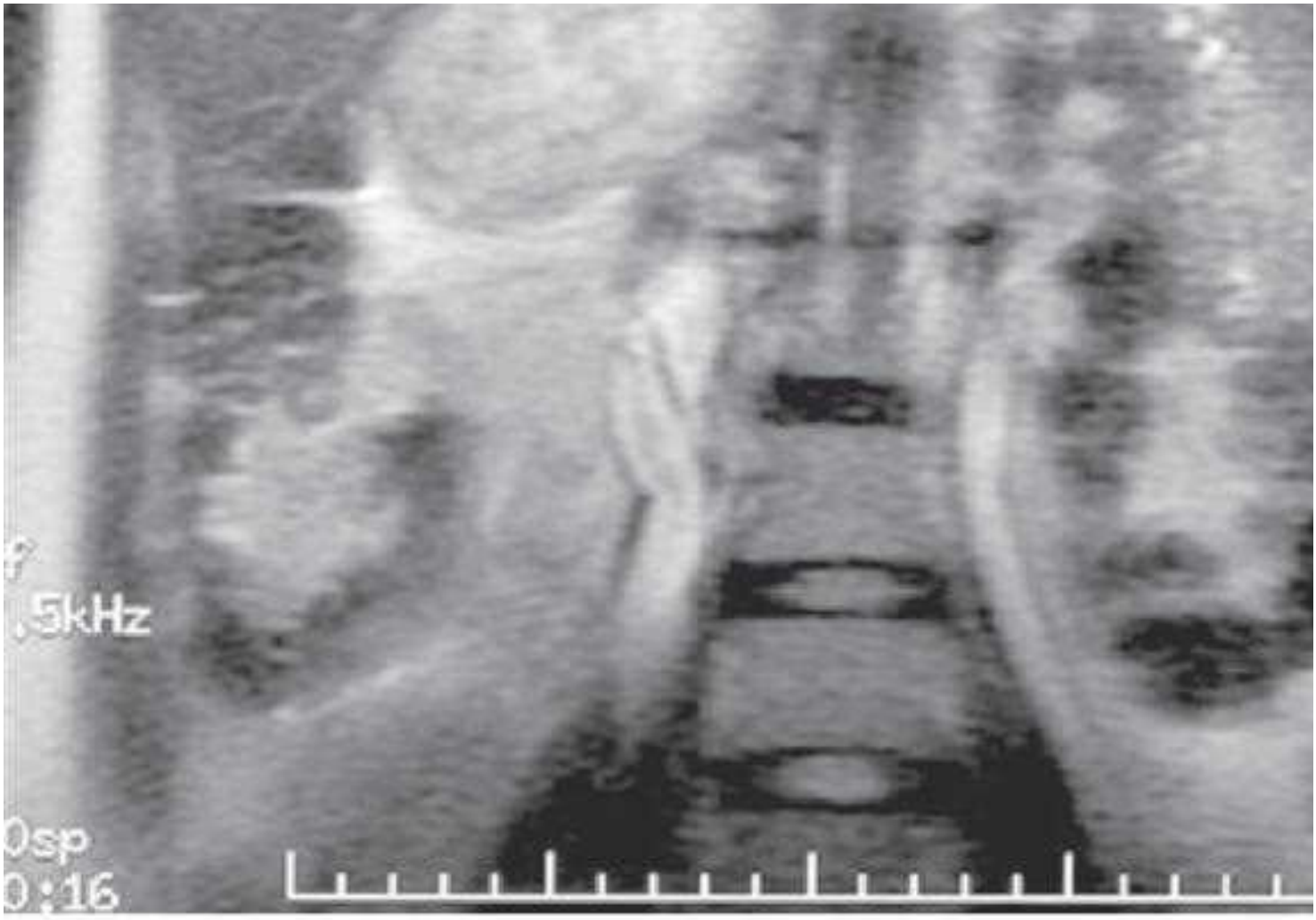
	Incidence (%)			
Factor	**1980–87 Harper (1989) n = 48**	**1988–97 Ahlawat (1999) n = 42**	**1998–2008 Sarathi (2010) n = 60**	**2000–2001 Biggar (2013) n = 78**
Diagnosis				
Antepartum	51	83	70	73
Postpartum	36	14	23	28
Autopsy	12	2	7	
Maternal death	16	4	12	8
Fetal wastage	26	11	17	17

Diagnosis of pheochromocytoma in pregnancy is similar to that for nonpregnant patients. MR imaging is the preferred technique because it almost always locates adrenal and extraadrenal pheochromocytomas (Fig. 58-6). In many cases, the principal challenge is to differentiate preeclampsia from the hypertensive crisis caused by pheochromocytoma. Grimbert and colleagues (1999) diagnosed two pheochromocytomas during 56 pregnancies in 30 women with von Hippel-Lindau disease.

FIGURE 58-6

Coronal magnetic resonance image taken in a 32-week pregnant woman shows a right-sided pheochromocytoma (*arrow*) and its position relative to the liver above it.





Management

Immediate control of hypertension and symptoms with an α-adrenergic blocker such as *phenoxybenzamine* is imperative. The dose is 10 to 30 mg, two to four times daily. After α-blockade is achieved, β-blockers may be given for tachycardia. In many cases, surgical exploration and tumor removal are performed during pregnancy, preferably during the second trimester (Biggar, 2013; Dong, 2014). Successful laparoscopic removal of adrenal tumors has become the norm (Miller, 2012; Zuluaga-Gómez, 2012). If diagnosed later in pregnancy, either planned cesarean delivery with tumor excision or postpartum resection is appropriate.

Recurrent tumors are troublesome, and even with good blood pressure control, dangerous peripartum hypertension may develop. We have cared for three women in whom recurrent pheochromocytoma was identified during pregnancy. Hypertension was managed with phenoxybenzamine in all three. Two newborns were healthy, but a third was stillborn in a mother with a massive tumor burden who was receiving phenoxybenzamine, 100 mg daily. In all three women, tumor was resected postpartum.

Cushing Syndrome

This syndrome is rare and the female:male ratio is 3:1 (Arit, 2015). Most cases are iatrogenic from long-term corticosteroid treatment. *Cushing disease* refers to bilateral adrenal hyperplasia stimulated by corticotropin-producing pituitary adenomas. Corticotropin is also called adrenocorticotropic hormone (ACTH). Most adenomas are microadenomas measuring <1 cm, and half measure <5 mm. Rarely, abnormal secretion of hypothalamic corticotropin-releasing factor may cause corticotropic hyperplasia. Such hyperplasia may also be caused by nonendocrine tumors that produce polypeptides similar to either corticotropin-releasing factor or corticotropin. Less than a fourth of cases of Cushing syndrome are corticotropin independent, and most of these are caused by an adrenal adenoma. Tumors are usually bilateral, and half are malignant. Occasionally, associated androgen excess may lead to severe virilization.

The typical cushingoid body habitus is caused by adipose tissue deposition that characteristically results in *moon facies,* a *buffalo hump,* and *truncal obesity.* Fatigability and weakness, hypertension, hirsutism, and amenorrhea are each encountered in 75 to 85 percent of nonpregnant patients (Hatipoglu, 2012). Personality changes, easy bruisability, and cutaneous striae are common. Up to 60 percent may have impaired glucose tolerance. Diagnosis can be difficult and is suggested by elevated plasma cortisol levels that cannot be suppressed by dexamethasone or by elevated 24-hour urine free cortisol excretion (Arit, 2015; Loriaux, 2017). Neither test is totally accurate, and each is more difficult to interpret in obese patients. Serum corticotropin levels and CT and MR imaging are used to localize pituitary and adrenal tumors or hyperplasia.

Cushing Syndrome and Pregnancy

Because most women have corticotropin-dependent Cushing syndrome, associated androgen excess may cause anovulation, and pregnancy is rare. In their review, Lekarev and New (2011) identified fewer than 140 reported cases of Cushing syndrome in pregnancy. These differ compared with nonpregnant women in that half are caused by corticotropin-independent adrenal adenomas (Kamoun, 2014; Lacroix, 2015). Approximately 30 percent of cases are from a pituitary adenoma, and 10 percent from adrenal carcinomas. All reports stress difficulties in diagnosis because of pregnancy-induced increases in plasma cortisol, corticotropin, and corticotropin-releasing factor levels. Measurement of 24-hour urinary free cortisol excretion is recommended, with consideration for the normal elevation seen in pregnancy.

Pregnancy outcomes in women with Cushing syndrome are listed in Table 58-7. Heart failure is common during pregnancy and is a major cause of maternal mortality (Buescher, 1992). Hypercortisolism in pregnancy may also cause poor wound healing, osteoporotic fracture, and psychiatric complications (Kamoun, 2014).

TABLE 58-7

Maternal and Perinatal Complications in Pregnancies Complicated by Cushing Syndrome

Complication	Incidence (%)
Maternal	
Hypertension	68
Diabetes	25
Preeclampsia	15
Osteoporosis/fracture	5
Psychiatric disorders	4
Cardiac failure	3
Mortality	2
Perinatal	
Fetal-growth restriction	21
Preterm delivery	43
Stillbirth	6
Neonatal death	2

Data from Lindsay, 2005.

Long-term medical therapy for Cushing syndrome usually is ineffective, and definitive therapy is resection of the pituitary or adrenal adenoma or bilateral adrenalectomy for hyperplasia (Lacroix, 2015; Motivala, 2011). During pregnancy, management of hypertension in mild cases may suffice until delivery. In their review, Lindsay and associates (2005) described primary medical therapy in 20 women with Cushing syndrome. Most were successfully treated with *metyrapone* as an interim treatment until definitive surgery after delivery. A few cases were treated with oral *ketoconazole*. However, because this drug also blocks testicular steroidogenesis, treatment during pregnancy with a male fetus is worrisome. *Mifepristone,* the norethindrone derivative used for abortion and labor induction, has shown promise for treating Cushing disease but should not be used in pregnancy for obvious reasons. If necessary, pituitary adenomas can be treated by transsphenoidal resection (Boscaro, 2001; Lindsay, 2005). Unilateral adrenalectomy has been safely performed in the early third trimester and can also be curative (Abdelmannan, 2011).

Adrenal Insufficiency—Addison Disease

Primary adrenocortical insufficiency is rare because more than 90 percent of total gland volume must be destroyed for symptoms to develop. *Autoimmune adrenalitis* is the most common cause in the developed world, but tuberculosis is a more frequent etiology in resource-poor countries (Arit, 2015; Kamoun, 2014). The incidence has been cited as being as high as 1 in 3000 births in Norway (Lekarev, 2011). In the United States, the prevalence was 1 per 10,000 to 20,000 pregnancies (Schneiderman, 2017). There is an increased incidence of concurrent Hashimoto thyroiditis, primary ovarian insufficiency, type 1 diabetes, and Graves disease. These *polyglandular autoimmune syndromes* also include pernicious anemia, vitiligo, alopecia, nontropical sprue, and myasthenia gravis.

Untreated adrenal hypofunction frequently causes infertility, but with replacement therapy, ovulation is restored. If untreated, symptoms often include weakness, fatigue, nausea and vomiting, and weight loss. Because serum cortisol levels are increased during pregnancy, the finding of a low value should prompt a cosyntropin test to document the lack of response to infused corticotropin (Salvatori, 2005).

In a large Swedish cohort study, 1188 women with Addison disease were compared with more than 11,000 age-matched controls who delivered between 1973 and 2006 (Björnsdottir, 2010). Women diagnosed with adrenal insufficiency within 3 years of delivery were significantly more likely to deliver preterm, to deliver a low-birthweight newborn, and to undergo cesarean delivery. Others have reported similar adverse outcomes (Quartermaine, 2017). Most pregnant women with Addison disease are already taking glucocorticoid and mineralocorticoid replacement drugs. These should be continued and women observed for evidence of either inadequate or excessive corticosteroid replacement (Lebbe, 2013). During labor, delivery, and postpartum, or after a surgical procedure, corticosteroid replacement must be increased appreciably to approximate the normal adrenal response—the so-called *stress dose*. Hydrocortisone, 100 mg, is usually given intravenously every 8 hours for 48 hours. It is important that shock from causes other than adrenocortical insufficiency—for example, hemorrhage or sepsis—be recognized and treated promptly.

Primary Aldosteronism

Hyperaldosteronism is caused by an adrenal adenoma—Conn syndrome—in approximately 75 percent of cases. Idiopathic bilateral adrenal hyperplasia makes up the remainder, except for rare cases of adrenal carcinoma (Abdelmannan, 2011; Eschler, 2015). Findings include hypertension, hypokalemia, and muscle weakness. High serum or urine levels of aldosterone confirm the diagnosis.

In normal pregnancy, as discussed in Chapter 4 (Musculoskeletal System), progesterone blocks aldosterone action, and thus there are very high aldosterone levels (Appendix, Serum and Blood Constituents). Accordingly, the diagnosis of hyperaldosteronism during pregnancy can be difficult. Since renin levels are suppressed in pregnant women with hyperaldosteronism, a plasma aldosterone-to-renin activity ratio may be helpful for diagnosis (Kamoun, 2014). Hypertension worsens as pregnancy progresses, and medical management includes potassium supplementation and antihypertensive therapy. In many cases, hypertension responds to *spironolactone,* but β-blockers or calcium-channel blockers may be preferred because of the potential fetal antiandrogenic effects of spironolactone. Mascetti and coworkers (2011) reported successful use of *amiloride* in a pregnant woman. Use of *eplerenone*, a selective aldosterone-receptor antagonist, has also been reported (Cabassi, 2012). Laparoscopic tumor resection is curative (Eschler, 2015; Miller, 2012).

PITUITARY DISORDERS

The pituitary enlarges impressively during pregnancy, predominately from lactotrophic cellular hyperplasia induced by estrogen stimulation (Chap. 4, Gastrointestinal Tract). Several pituitary disorders can also complicate pregnancy.

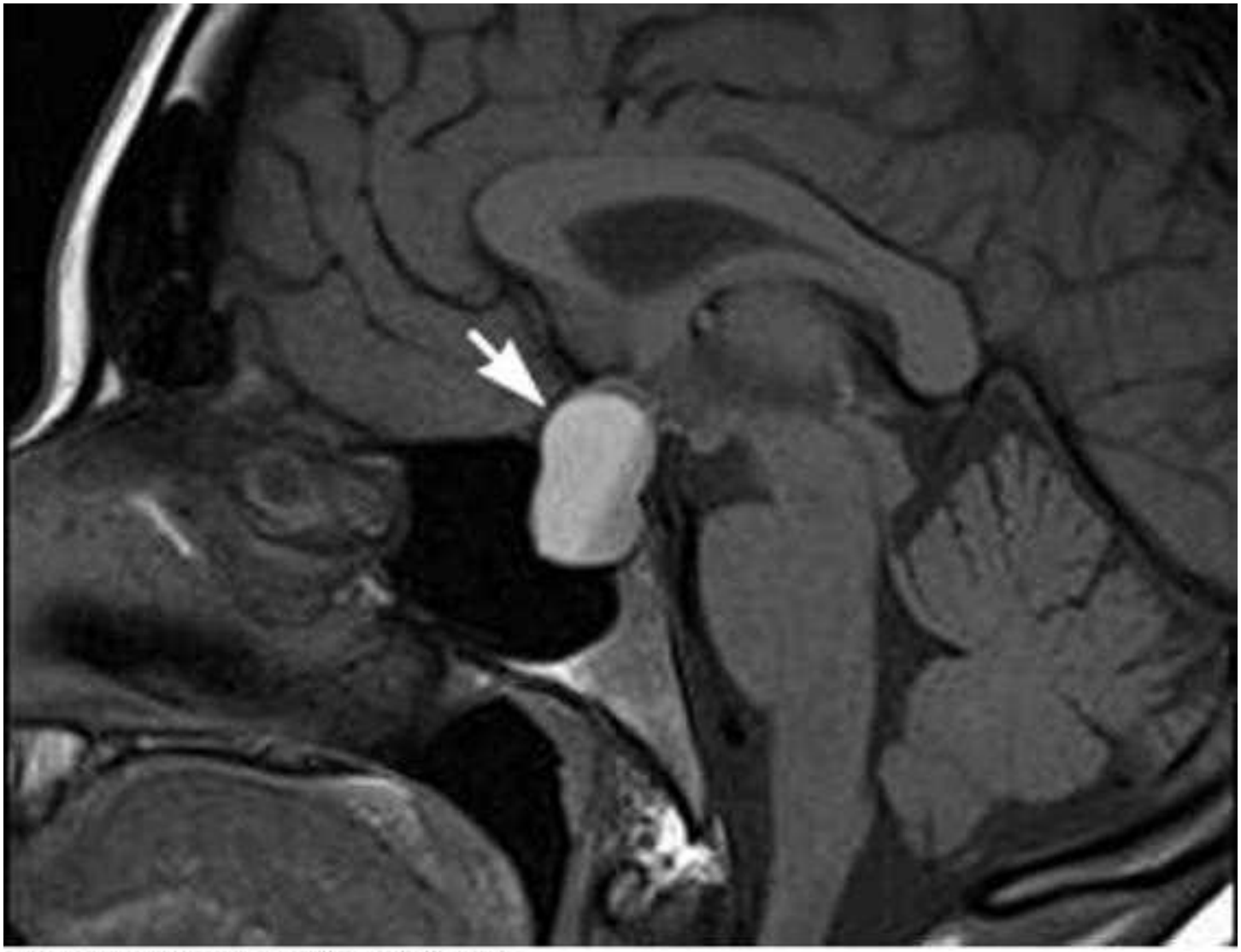
Prolactinomas

These adenomas are found often in nonpregnant women since the advent of widely available serum prolactin assays. Serum levels <25 pg/mL are considered normal in nonpregnant women (Motivala, 2011). Adenoma symptoms and findings include amenorrhea, galactorrhea, and hyperprolactinemia. Tumors are classified arbitrarily by their size measured by CT or MR imaging. A microadenoma is ≤10 mm, and a macroadenoma is >10 mm. Treatment for microadenomas is usually with bromocriptine, a dopamine agonist and powerful prolactin inhibitor, which frequently restores ovulation. For suprasellar macroadenomas, most recommend surgical resection before pregnancy is attempted (Araujo, 2015).

In a pooled analysis of more than 750 pregnant women with prolactinomas, only 2.4 percent with *microadenomas* developed symptomatic enlargement during pregnancy (Molitch, 2015). Symptomatic enlargement of *macroadenomas,* however, is more frequent and was found in 21 percent of 238 pregnant women. Schlechte (2007) also reported that 15 to 35 percent of suprasellar macroadenomas have tumor enlargement that causes visual disturbances, headaches, and diabetes insipidus. Nonfunctioning adenomas can also cause symptoms of pituitary expansion in pregnancy (Lambert, 2017).

Pregnant women with microadenomas should be queried regularly for headaches and visual symptoms. Those with macroadenomas are followed more closely and have visual field testing during each trimester. CT or MR imaging is recommended only if symptoms develop (Fig. 58-7). Serial serum prolactin levels serve little use because of normal rises during pregnancy (Appendix, Serum and Blood Constituents). Symptomatic tumor enlargement should be treated immediately with a dopamine antagonist. The safety of bromocriptine in pregnancy is well established. The safety profile is less well known for cabergoline, which is increasingly used in nonpregnant women because it is better tolerated and more effective. Cabergoline is generally considered safe for use in pregnancy (Araujo, 2015; Auriemma, 2013). Lebbe and colleagues (2010) described 100 pregnancies exposed to cabergoline and found no adverse effects. Similar findings were reported in 85 exposed Japanese pregnant women (Ono, 2010). Surgery is recommended for women with no response.

FIGURE 58-7
Magnetic resonance imaging of a pituitary adenoma: Sagittal T1-weighed image demonstrates a hyperintense sellar and suprasellar mass (*arrow*). Note the layering of complex fluid within the mass, which was found during surgery to be hemorrhage. (Used with permission from Dr. April Baily.)



Acromegaly

This is caused by excessive growth hormone, usually from an acidophilic or a chromophobic pituitary adenoma. In normal pregnancy, pituitary growth hormone levels decrease as placental epitopes are secreted. Diagnosis is confirmed by elevated IGF-1 serum levels (Katznelson, 2014). Fewer than 100 cases of acromegaly have been reported during pregnancy (Cheng, 2012; Dias, 2013; Motivala, 2011). Pregnancy is probably rare in women with acromegaly because half are hyperprolactinemic and anovulatory. During pregnancy, affected women are at marginally greater risk for gestational diabetes and hypertension (Caron, 2010; Dias, 2013).

Management is similar to that for prolactinomas, with close monitoring for symptoms of tumor enlargement. Dopamine agonist therapy is less effective than for prolactinomas. And, transsphenoidal resection, generally considered first-line treatment outside of pregnancy, may be necessary for symptomatic tumor enlargement during pregnancy (Motivala, 2011). Guven and associates (2006) reported a case of pituitary apoplexy necessitating emergent transsphenoidal adenoma resection and cesarean delivery at 34 weeks. Successful treatment of pregnant women with the somatostatin-receptor ligand *octreotide* and with the GH analogue *pegvisomant* has also been reported (Dias, 2013; Fleseriu, 2015).

Diabetes Insipidus

The vasopressin deficiency evident in diabetes insipidus is usually due to agenesis or destruction of the neurohypophysis (Robertson, 2015). True diabetes insipidus is a rare complication of pregnancy.

Diabetes insipidus therapy is intranasal administration of a synthetic analogue of vasopressin, *desmopressin,* which is 1-deamino- 8-d-arginine vasopressin (DDAVP). Ray (1998) reviewed 53 cases in which DDAVP was used during pregnancy with no adverse sequelae. Most women require increased doses during pregnancy because of an increased metabolic clearance rate stimulated by placental vasopressinase (Lindheimer, 1994). By this same mechanism, *subclinical diabetes insipidus* may become symptomatic or cases of *transient diabetes insipidus* may be encountered during pregnancy (Bellastella, 2012; Robertson, 2015). The prevalence of vasopressinase-induced diabetes insipidus is estimated at 2 to 4 per 100,000 pregnancies (Wallia, 2013).

In our experiences, as described in Chapter 55 (Acute Viral Hepatitis), transient secondary diabetes insipidus is more likely encountered with *acute fatty liver of pregnancy* (Nelson, 2013). This probably is due to altered vasopressinase clearance because of hepatic dysfunction.

Sheehan Syndrome

Sheehan (1937) reported that pituitary ischemia and necrosis associated with obstetrical blood loss could result in hypopituitarism. With modern methods of hemorrhagic shock treatment, Sheehan syndrome is now seldom encountered (Feinberg, 2005; Pappachan, 2015; Robalo, 2012). Affected women may have persistent hypotension, tachycardia, hypoglycemia, and lactation failure. Because deficiencies of some or all pituitary-responsive hormones may develop after the initial insult, Sheehan syndrome can be heterogenous and may not be identified for years (Tessnow, 2010). In one cohort study of 60 women from Costa Rica with Sheehan syndrome, the average time to diagnosis was 13 years (Gei-Guardia, 2011). Because adrenal insufficiency is the most life-threatening complication, adrenal function should be immediately assessed in any woman suspected of having Sheehan syndrome. After glucocorticoid replacement, subsequent analyses and replacement of thyroid, gonadal, and growth hormones is considered.

Lymphocytic Hypophysitis

This rare autoimmune pituitary disorder is characterized by massive infiltration by lymphocytes and plasma cells with parenchymal destruction of the gland. Many cases are temporally linked to pregnancy (Foyouzi, 2011; Honegger, 2015; Melmed, 2015). There are varying degrees of hypopituitarism or symptoms of mass effect, including headaches and visual field defects. A sellar mass is seen with CT or MR imaging. A mass accompanied by a modestly elevated serum prolactin level—usually <100 pg/mL—suggests lymphocytic hypophysitis. In contrast, levels >200 pg/mL are encountered with a prolactinoma. The etiology is unknown, but nearly 30 percent have a history of coexisting autoimmune diseases including Hashimoto thyroiditis, Addison disease, type 1 diabetes, or pernicious anemia. Treatment is with glucocorticoids and pituitary hormone replacement. The disease may be self-limited, and a careful withdrawal of hormone replacement is attempted after inflammation subsides (Foyouzi, 2011; Melmed, 2015).

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CHAPTER 59: Connective Tissue Disorders

FIGURE 59-1

Owing to the great vascularity incident to pregnancy, the various pelvic joints always show a somewhat increased motility. In rare instances, particularly when the pelvis is contracted in the lower portion, spontaneous rupture of the symphysis pubis or one or both sacro-iliac joints has been observed.

—J. Whitridge Williams (1903)

INTRODUCTION

The principal concerns in the 1st edition of *Williams Obstetrics* with disorders of the joints were the obstructed pelvis caused by rickets. There is no mention of the arthritides complicating pregnancy. And of course, immune-mediated disease had not yet been elucidated.

Connective tissue disorders, which are also termed collagen vascular disorders, have two basic underlying causes. First are the *immune-complex diseases* in which connective tissue damage is caused by deposition of immune complexes. Because these are manifest by sterile inflammation—predominately of the skin, joints, blood vessels, and kidneys—they are referred to as rheumatic diseases. Many of these immune-complex diseases are more prevalent in women, for example, systemic lupus erythematosus (SLE) and rheumatoid arthritis. Second are the *inherited disorders* of bone, skin, cartilage, blood vessels, and basement membranes. Some examples include Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome.

IMMUNE-MEDIATED CONNECTIVE TISSUE DISEASES

These disorders can be separated into those associated with and those without autoantibody formation. The *rheumatoid factor (RF)* is an autoantibody found in many autoimmune inflammatory conditions such as SLE, rheumatoid arthritis, systemic sclerosis (scleroderma), mixed connective tissue disease, dermatomyositis, polymyositis, and various vasculitis syndromes. The *RF-seronegative spondyloarthropathies* are strongly associated with expression of the human leukocyte antigen B27 (HLA-B27) antigen and include ankylosing spondylitis, psoriatic arthritis, Reiter disease, and other arthritis syndromes.

Pregnancy may mitigate activity in some of these syndromes as a result of the immunosuppression that also allows successful engraftment of fetal and placental tissues. These changes are discussed in detail in Chapters 4 (Iron Metabolism) and 5 (Amnion). One example is pregnancy-induced predominance of T2 helper

cells compared with cytokine-producing T1 helper cells (Keeling, 2009). Pregnancy hormones also alter immune cells. Namely, estrogens upregulate and androgens downregulate T-cell response, and progesterone is immunosuppressive (Cutolo, 2006; Häupl, 2008a; Robinson, 2012).

In contrast, immune-mediated disease may contribute to obstetrical complications. One longitudinal cohort study found that unrecognized autoimmune systemic rheumatic disorders are associated with significant risk for preeclampsia and fetal-growth restriction (Spinillo, 2016). In this study, the prevalence of unrecognized rheumatic arthritis was 0.4 percent, and was 0.3 percent each for SLE, Sjögren syndrome, and antiphospholipid syndrome.

Last, some immune-mediated diseases may either be caused or activated as a result of prior pregnancies. To explain, fetal cells and free fetal DNA are detectable in maternal blood beginning early in pregnancy (Simpson, 2013; Sitar, 2005; Waldorf, 2008). *Fetal cell microchimerism* is the persistence of fetal cells in the maternal circulation and in organs following pregnancy. These fetal cells may become engrafted in maternal tissues and stimulate autoantibodies. This raises the possibility that fetal cell microchimerism leads to the predilection for autoimmune disorders among women (Adams, 2004). Evidence for this includes fetal stem cells engrafted in tissues in women with autoimmune thyroiditis and systemic sclerosis (Jimenez, 2005; Srivatsa, 2001). Such microchimerism has also been described in women with SLE and those with rheumatoid arthritis-associated HLA alleles (da Silva, 2016; Lee, 2010; Rak, 2009a). Conversely, engrafted maternal cells may provoke autoimmune conditions in a woman's offspring (Ye, 2012; Stevens, 2016).

SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus is a heterogeneous autoimmune disease with a complex pathogenesis that results in interactions between susceptibility genes and environmental factors (Hahn, 2015). Immune system abnormalities include overactive B lymphocytes that are responsible for autoantibody production. These result in tissue and cellular damage when autoantibodies or immune complexes are directed at one or more cellular nuclear components (Tsokos, 2011). In addition, immunosuppression is impaired, including regulatory T-cell function (Tower, 2013). Some autoantibodies produced in patients with SLE are shown in Table 59-1.

TABLE 59-1

Some Autoantibodies Produced in Patients with Systemic Lupus Erythematosus (SLE)

Antibody	Prevalence (%)	Clinical Associations
Antinuclear (ANA)	84–98	Best screening test, multiple antibodies; a second negative test makes SLE unlikely
Anti-dsDNA	62–70	High titers SLE-specific; may correlate with disease activity, nephritis, and vasculitis
Anti-Sm (Smith)	25–38	Specific for SLE
Anti-RNP	33–40	Not SLE-specific, high titers associated with rheumatic syndromes
Anti-Ro (SS-A)	30–49	Not SLE-specific; associated with sicca syndrome, predisposes to cutaneous lupus, neonatal lupus with heart block, reduced risk of nephritis
Anti-La (SS-B)	10–35	Associated with anti-Ro
Antihistone	70	Common in drug-induced lupus
Antiphospholipid	21–50	Lupus anticoagulant and anticardiolipin antibodies associated with thrombosis, fetal loss, thrombocytopenia, valvular heart disease; false-positive test for syphilis
Antierythrocyte	60	Direct Coombs test, may develop hemolysis
Antiplatelet	30	Thrombocytopenia in 15%; poor clinical test

dsDNA = double-stranded DNA; RNP = ribonucleoprotein.

Data from Arbuckle, 2003; Hahn, 2015.

Almost 90 percent of SLE cases are in women, and its prevalence in those of childbearing age approximates 1 in 500 (Lockshin, 2000). Accordingly, the disease is encountered relatively frequently during pregnancy. The 10-year survival rate is 70 to 90 percent (Tsokos, 2011). Infection, lupus flares, end-organ failure, hypertension, stroke, and cardiovascular disease account for most deaths.

Genetic influences are implicated by a higher concordance with monozygotic compared with dizygotic twins —25 versus 2 percent, respectively. Moreover, frequency in patients with one affected family member is 10 percent. The relative risk of disease rises if there is inheritance of the “autoimmunity gene” on chromosome 16 that predisposes to SLE, rheumatoid arthritis, Crohn disease, and psoriasis. Susceptibility genes such as *HLA-A1, -B8, -DR3, -DRB1*, and -*TET3* explain only a portion of the genetic heritability (Tsokos, 2011; Yang, 2013). Interestingly, even maternal exposure to fetal genes elevates susceptibility to SLE development. A case-control study found that a child’s HLA-DRB1 genotype increases the risk of SLE in the mother (Cruz, 2016). Furthermore, neonatal lupus erythematosus has been reported in an infant conceived via oocyte donor to a mother with autoimmune disease with circulating anti-Ro and anti-La antibodies (Chiou, 2016).

Clinical Manifestations and Diagnosis

Lupus is notoriously variable in its presentation, course, and outcome (Table 59-2). Findings may be confined initially to one organ system, and others become involved later. Or, the disease may first be multisystem. Frequent findings are malaise, fever, arthritis, rash, pleuropericarditis, photosensitivity, anemia, and cognitive dysfunction. At least half of patients have renal involvement. SLE is also associated with declines in attention, memory, and reasoning (Hahn, 2015; Kozora, 2008).

TABLE 59-2

Some Clinical Manifestations of Systemic Lupus Erythematosus

Organ System	Clinical Manifestations	Percent
Systemic	Fatigue, malaise, fever, weight loss	95
Musculoskeletal	Arthralgias, myalgias, polyarthritis, myopathy	95
Hematological	Anemia, hemolysis, leukopenia, thrombocytopenia, lupus anticoagulant, splenomegaly	85
Cutaneous	Malar (butterfly) rash, discoid rash, photosensitivity, oral ulcers, alopecia, skin rashes	80
Neurological	Cognitive dysfunction, mood disorder, headache, seizures, stroke	60
Cardiopulmonary	Pleuritis, pericarditis, myocarditis, endocarditis, pneumonitis, pulmonary hypertension	60
Renal	Proteinuria, nephrotic syndrome, renal failure	30–50
Gastrointestinal	Nausea, pain, diarrhea, abnormal liver enzyme levels	40
Vascular	Thrombosis: venous (10%), arterial (5%)	15
Ocular	Conjunctivitis, sicca syndrome	15

Modified from Kasper, 2015.

Identification of antinuclear antibodies (ANA) is the best screening test, however, a positive result is not specific for SLE. For example, low titers are found in normal individuals, other autoimmune diseases, acute viral infections, and chronic inflammatory processes. Several drugs can also cause a positive reaction. Antibodies to double-stranded DNA (dsDNA) and to Smith (Sm) antigens are relatively specific for SLE, whereas other antibodies are not (see Table 59-1). Although hundreds of autoantibodies have been described in SLE, only a few have been shown to participate in tissue injury (Sherer, 2004; Tsokos, 2011). Currently, microarray profiles are being developed for more accurate SLE diagnosis (Putterman, 2016).

Anemia develops frequently, and there may be leukopenia and thrombocytopenia. Proteinuria and casts are found in the half of patients with glomerular lesions. Lupus nephritis can also cause renal insufficiency, which is more common if there are antiphospholipid antibodies (Moroni, 2004). Other laboratory findings

include false-positive syphilis serology, prolonged partial thromboplastin time, and higher RF levels. Elevated serum d-dimer concentrations often follow a flare or infection, but unexplained persistent elevations are associated with a high risk for thrombosis (Wu, 2008).

The diagnostic criteria for SLE are listed in Table 59-3. If any four or more of these 11 criteria are present, serially or simultaneously, the diagnosis of lupus is made. Importantly, numerous drugs can induce a lupus-like syndrome. These include proton-pump inhibitors, thiazide diuretics, antifungals, chemotherapeutics, statins, and antiepileptics. Drug-induced lupus is rarely associated with glomerulonephritis and usually regresses when the medication is discontinued (Laurinaviciene, 2017).

TABLE 59-3

Clinical Criteria for Classification of Systemic Lupus Erythematosus

Clinical Manifestations
Skin
Oral ulcers
Alopecia
Synovitis
Renal: proteinuria, casts, biopsy
Neurological: seizures, psychosis, myelitis, neuropathies, confusional state
Hemolytic anemia
Leukopenia or lymphopenia
Thrombocytopenia
Immunological Manifestations
ANA
Anti-dsDNA
Anti-Sm
Antiphospholipid
Hypocomplementemia
Direct Coombs

ANA = antinuclear antibodies; dsDNA = double-stranded DNA; Sm = Smith.

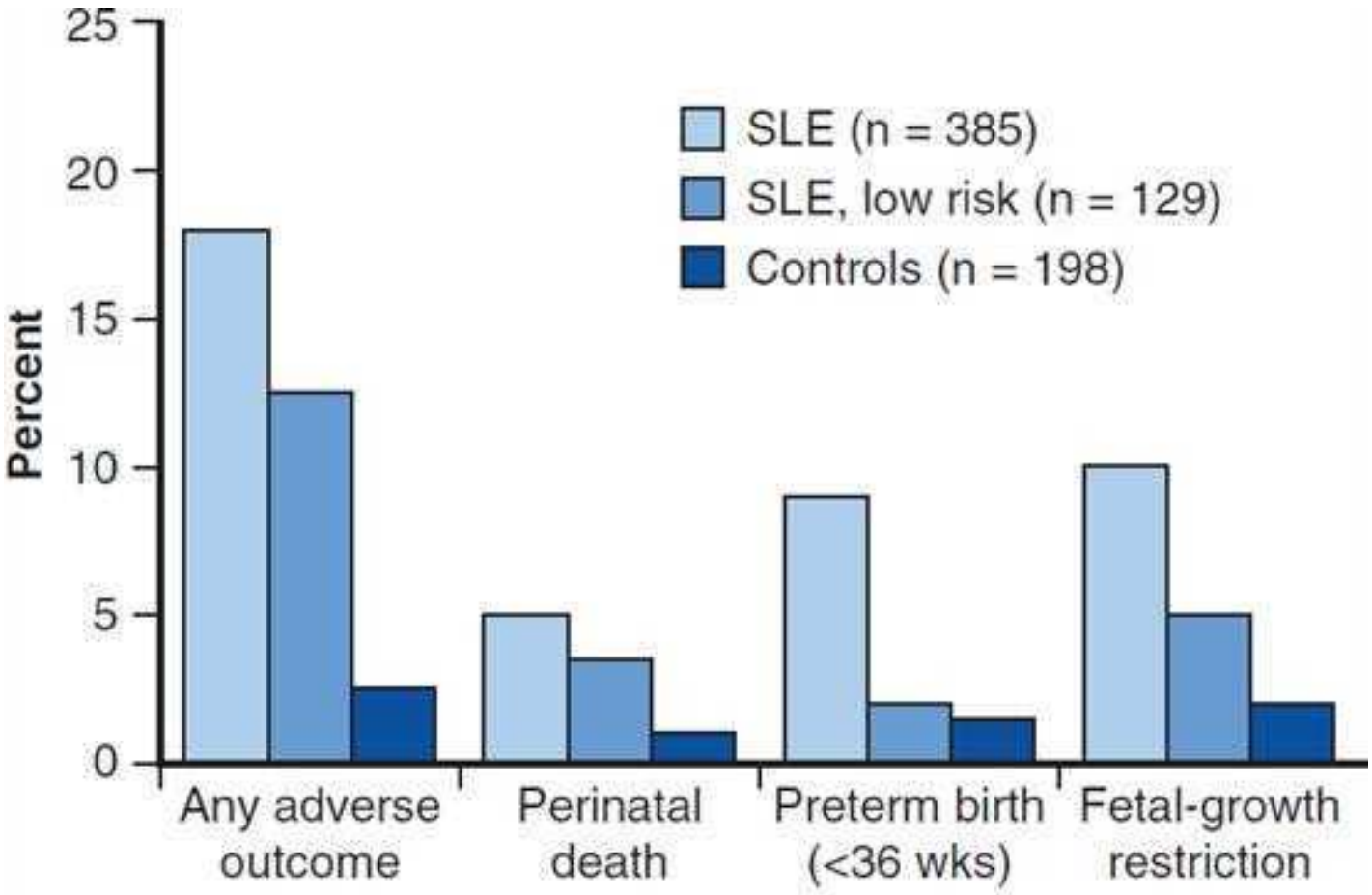
Data from Hahn, 2015; Hochberg, 1997.

Lupus and Pregnancy

Of nearly 16.7 million pregnancies from 2000 to 2003 in the United States, 13,555 were complicated by lupus—an incidence of approximately 1 in 1250 pregnancies (Clowse, 2008). During pregnancy, lupus improves in a third of women, remains unchanged in a third, and worsens in the remaining third. Thus, in any given pregnancy, the clinical condition can worsen or *flare* without warning (Hahn, 2015; Khamashta, 1997).

Petri (1998) reported a 7-percent risk of major morbidity during pregnancy. In a cohort of 13,555 women with SLE during pregnancy, the maternal mortality and severe morbidity rate was 325 per 100,000 (Clowse, 2008). In a review of 13 studies with 17 maternal deaths attributable to SLE and lupus nephritis, all occurred in those with active disease (Ritchie, 2012). Results of a prospective cohort study of 385 women are shown in Figure 59-1.

FIGURE 59-1
Frequency of adverse pregnancy outcomes. All women with systemic lupus erythematosus (SLE) in the PROMISSE study are compared with a subset of low-risk SLE patients and with control patients without SLE. (Data from Buyon, 2015.)



During the past several decades, pregnancy outcomes in women with SLE have improved remarkably. For most women with inactive or mild/moderate SLE, pregnancy outcomes are relatively favorable. Women who have confined cutaneous lupus do not usually have adverse outcomes (Hamed, 2013). However, newly

diagnosed SLE during pregnancy tends to be severe (Zhao, 2013). In general, pregnancy outcome is best in women for whom: (1) lupus activity has been quiescent for at least 6 months before conception; (2) there is no lupus nephritis manifest by proteinuria or renal dysfunction; (3) antiphospholipid syndrome or lupus anticoagulant is absent; and (4) superimposed preeclampsia does not develop (Peart, 2014; Stojan, 2012; Wei, 2017; Yang, 2014).

Lupus Nephritis

Active nephritis is associated with adverse pregnancy outcomes, although these have improved remarkably and especially if disease remains in remission (Moroni, 2002, 2005; Stojan, 2012). Of complications, women with renal disease have a high incidence of gestational hypertension and preeclampsia. Of 80 gravidas with SLE reported by Lockshin (1989), 63 percent of women with preexisting renal disease developed preeclampsia compared with only 14 percent of those without underlying renal disease. In a review of 309 pregnancies complicated by lupus nephritis, 30 percent suffered a flare, and 40 percent of these had associated renal insufficiency (Moroni, 2005). The maternal mortality rate was 1.3 percent. These findings were corroborated in a subsequent prospective study (Moroni, 2016b). In addition, a third of the 113 pregnancies were delivered preterm (Imbasciati, 2009; Moroni, 2016a). Wagner and coworkers (2009) compared outcomes of 58 women with 90 pregnancies and found that active nephritis was linked with a significantly higher incidence of maternal complications—57 versus 11 percent.

Most recommend continuation during pregnancy of immunosuppressive therapy for nephritis. New-onset nephritis or severe renal flare is treated aggressively with intravenous corticosteroids and consideration of immunosuppressive drugs or intravenous immunoglobulin (Lazzaroni, 2016).

Lupus versus Preeclampsia-Eclampsia

Chronic hypertension complicates up to 30 percent of pregnancies in women with SLE (Egerman, 2005). Also, as mentioned, preeclampsia is common, and superimposed preeclampsia is encountered even more often, and earlier, in those with nephritis or antiphospholipid antibodies (Bertsias, 2008). Preeclampsia and lupus nephritis share features of hypertension, proteinuria, edema, and renal function deterioration. However, the management is distinct, as lupus nephritis is treated with immunosuppression, and severe preeclampsia/eclampsia requires delivery (Lazzaroni, 2016). It may be difficult, if not impossible, to differentiate lupus flare with nephropathy from severe preeclampsia if the kidney is the only involved organ (Petri, 2007). Central nervous system involvement with lupus may culminate in convulsions similar to those of eclampsia. One proposed schema for differentiating the two is shown in Table 59-4. Management for preeclampsia-eclampsia is described in Chapter 40 (Preeclampsia).

TABLE 59-4

Some Distinctions between Lupus Flare and Preeclampsia Syndrome

Factor	Lupus	Preeclampsia
Clinical findings	Fatigue, headache, extra-renal signs (rash, serositis, arthritis)	Headaches, confusion, visual changes, convulsions
Blood pressure	Normal or high	High
Anemia	Hemolytic	Absent
Proteinuria	Present	Present
Creatinine	Normal or high	Normal or high
Transaminases	Normal	Normal or high
Complement	Decreased	Normal

Data from Andreoli, 2012.

Management During Pregnancy

Lupus management consists primarily of monitoring fetal well-being and maternal clinical and laboratory status (Lateef, 2012). Pregnancy-induced thrombocytopenia and proteinuria resemble SLE disease activity, and the identification of a lupus flare is confounded by the increased facial and palmar erythema of normal pregnancy (Lockshin, 2003).

For SLE activity monitoring, various laboratory techniques have been recommended, but interpretation may be challenging. The sedimentation rate may be misleading because of pregnancy-induced hyperfibrinogenemia. Serum complement levels are also normally increased in pregnancy (Appendix, Serum and Blood Constituents). And, although falling or low levels of complement components C_3, C_4, and CH_{50} are more likely to be associated with active disease, higher levels provide no assurance against disease activation. Our experiences and those of others suggest that clinical manifestations of disease and complement levels correlate poorly (Lockshin, 1995; Varner, 1983).

Serial hematological studies may detect changes in disease activity. Hemolysis is characterized by a positive Coombs test, anemia, reticulocytosis, and unconjugated hyperbilirubinemia. Thrombocytopenia, leukopenia, or both may develop. According to Lockshin and Druzin (1995), chronic thrombocytopenia in

early pregnancy may be due to antiphospholipid antibodies. Later, thrombocytopenia may indicate preeclampsia.

Urine is tested frequently to detect new-onset or worsening proteinuria. The fetus is closely observed for adverse effects such as growth restriction and oligohydramnios. Many recommend screening for anti-SS-A (anti-Ro) and anti-SS-B (anti-La) antibodies, because of associated fetal complications described subsequently. Antepartum, the fetus is surveilled as outlined by the American College of Obstetricians and Gynecologists (2016a) and described in Chapter 17 (Fetal Movements). Unless hypertension or evidence of fetal compromise or growth restriction develops, pregnancy is allowed to progress to term. Peripartum corticosteroids in “stress doses” are given to women who are taking these drugs or who recently have done so.

Pharmacological Treatment

There is no cure for SLE, and complete remissions are rare. Approximately a fourth of pregnant women have mild disease, which is not life threatening, but may be disabling because of pain and fatigue. Arthralgia and serositis can be managed by nonsteroidal antiinflammatory drugs (NSAIDs). However, chronic or large intermittent dosing is avoided due to related oligohydramnios or ductus arteriosus closure (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Low-dose aspirin can be used throughout gestation. Severe disease is managed with corticosteroids such as prednisone, 1 to 2 mg/kg/d orally. After the disease is controlled, this dose is tapered to a daily morning dose of 10 to 15 mg. Corticosteroid therapy can lead to gestational diabetes.

Immunosuppressive agents such as azathioprine are beneficial for active disease. These are usually reserved for lupus nephritis or disease that is corticosteroid resistant. Azathioprine has a good safety record during pregnancy (Fischer-Betz, 2013; Petri, 2007). Its recommended daily oral dose is 2 to 3 mg/kg. Teratogenic medications to be avoided include mycophenolate mofetil, methotrexate, and cyclophosphamide (Götestam Skorpen, 2016). However, cyclophosphamide can be considered in the second or third trimester for severe disease (Lazzaroni, 2016). In some situations, mycophenolate is the only treatment that achieves disease stability. In these cases, counseling is essential regarding fetal risks described in Chapter 12 (Immunosuppressant Medications) (Bramham, 2012).

Antimalarials reduced dermatitis, arthritis, and fatigue (Hahn, 2015). Although these agents cross the placenta, hydroxychloroquine is not associated with congenital malformations. Because of the long half-life of antimalarials and because discontinuing therapy can precipitate a lupus flare, most recommend their continuation during pregnancy (Borden, 2001).

When severe disease supervenes—usually a lupus flare—high-dose glucocorticoid therapy is given. Petri (2007) recommends pulse therapy consisting of methylprednisolone, 1000 mg given intravenously over 90 minutes daily for 3 days, then a return to maintenance doses if possible.

In nonpregnant subjects, antihypertensive therapy often includes an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker. For pregnancy, these should be changed to safer fetal options such as calcium-channel blockers, alpha methyldopa, or labetalol (Cabiddu, 2016).

Perinatal Mortality and Morbidity

Adverse perinatal outcome rates are significantly elevated in pregnancies complicated by SLE. Among these are preterm delivery, fetal-growth restriction, stillbirth, and neonatal lupus syndrome (Madazli, 2014; Phansenee, 2017). Perinatal outcome rates worsen in mothers with a lupus flare, significant proteinuria, or renal impairment and in those with chronic hypertension, preeclampsia, or both (Lazzaroni, 2016). Adverse outcomes are also more common in women with neuropsychiatric lupus (de Jesus, 2017). Reasons at least partially responsible for adverse fetal consequences include decidual vasculopathy with placental infarction and decreased perfusion (Hanly, 1988).

Neonatal Lupus Syndrome

This is characterized by newborn skin lesions—lupus dermatitis; a variable number of hematological and systemic derangements; and occasionally congenital heart block (Hahn, 2015). Cutaneous manifestations can be present in 30 to 40 percent of infants and appears at 4 to 6 weeks of age (Silverman, 2010). These are usually associated with anti-SS-A and SS-B antibodies, and approximately 40 percent of women with SLE are positive for these (Buyon, 2015). Thrombocytopenia and hepatic involvement are seen in 5 to 10 percent of affected infants.

In a review of outcomes in 91 infants born to women with lupus, eight of these were possibly affected—four had definite neonatal lupus and four had possible disease (Lockshin, 1988). Cutaneous lupus, thrombocytopenia, and autoimmune hemolysis are transient and clear within a few months (Zuppa, 2017). This is not always so for congenital heart block, discussed next. In subsequent offspring, the recurrence risk for neonatal lupus may near 25 percent (Julkunen, 1993).

Congenital Heart Block

Fetal and neonatal heart block results from diffuse myocarditis and fibrosis in the region between the atrioventricular (AV) node and bundle of His. Congenital heart block develops almost exclusively in fetuses of women with antibodies to the SS-A or SS-B antigens (Buyon, 1993). Even in the presence of such antibodies, however, the incidence of fetal myocarditis is only 2 to 3 percent but rises to 20 percent with a prior affected child (Bramham, 2012; Lockshin, 1988). Fetal cardiac monitoring is performed between 18 and 26 weeks' gestation in pregnancies with either of these antibodies. The cardiac lesion is permanent, and a pacemaker is generally necessary. Long-term prognosis is poor. Of 325 infants with cardiac neonatal lupus, nearly 20 percent died, and of these, one third was stillborn (Izmirly, 2011).

Maternal administration of corticosteroids, plasma exchange, or intravenous immunoglobulin does not reduce the risk of congenital heart block. Maternal corticosteroid administration for treatment congenital

heart block is controversial, is currently not recommended, and is discussed further in Chapter 16 (Tachyarrhythmias). Although this therapy to treat fetal heart block has not been studied in randomized trials, some evidence suggests that early fetal exposure to the mother's corticosteroid treatment for SLE may mitigate fetal myocarditis. Namely, Shinohara and coworkers (1999) reported no heart block in 26 neonates whose mothers received corticosteroids before 16 weeks' gestation as part of SLE maintenance therapy. By contrast, 15 of 61 neonates with heart block were born to women in whom corticosteroid therapy was begun after 16 weeks for an SLE exacerbation.

There are reports that maternal treatment with hydroxychloroquine (Plaquenil) is associated with a lower incidence of fetal heart block (Izmirly, 2012). Research in this area is ongoing.

Long-Term Prognosis and Contraception

The survival rate for women with SLE is 95 percent at 5 years, 90 percent at 10 years, and 78 percent at 20 years (Hahn, 2015). In general, women with lupus and chronic vascular or renal disease may limit family size because of morbidity associated with the disease and greater risks for adverse perinatal outcomes. For contraception, combination oral contraceptives did not increase the incidence of lupus flares in two large multicenter trials (Petri, 2005; Sánchez-Guerrero, 2005). Progestin-only implants and injections provide effective contraception with no known effects on lupus flares (Sammaritano, 2014). Concerns that intrauterine device (IUD) use and immunosuppressive therapy lead to greater infection rates in these patients are not evidenced-based. Notably, comorbid antiphospholipid antibodies are a contraindication to hormonal methods. Tubal sterilization may be advantageous and is performed with greatest safety postpartum or whenever SLE is quiescent.

ANTIPHOSPHOLIPID SYNDROME

This syndrome is an autoantibody-mediated acquired thrombophilia with recurrent thrombosis or pregnancy morbidity as part of its clinical constellation (Moutsopoulos, 2015). Specifically, antiphospholipid syndrome (APS) is diagnosed in women with persistently positive serum tests for antiphospholipid antibodies *and* with arterial and/or venous thromboses or obstetrical morbidity. Antibodies include lupus anticoagulant, anticardiolipin antibody, and anti-β_2 glycoprotein-I antibody.

Phospholipids are the main lipid constituents of cell and organelle membranes. There are proteins in plasma that associate noncovalently with these phospholipids. Antiphospholipid antibodies are directed against these phospholipids or phospholipid-binding proteins (Giannakopoulos, 2013; Tsokos, 2011). This antibody group may be of IgG, IgM, and IgA classes, alone or in combination. Antiphospholipid antibodies are most common with SLE, other connective tissue disorders, and APS. However, a small proportion of otherwise normal women and men have low levels of these antibodies.

The stimulus for autoantibody production is unclear, but it possibly is due to a preceding infection. The pathophysiology encountered is mediated by one or more of the following: (1) activation of various procoagulants, (2) inactivation of natural anticoagulants, (3) complement activation, and (4) inhibition of

syncytiotrophoblast differentiation (Tsokos, 2011). Clinically, these actions lead to arterial or venous thromboses or to pregnancy morbidity. Virtually every organ system may be affected.

Central nervous system involvement is one of the most prominent clinical manifestations. In addition to cerebrovascular arterial and venous thrombotic events, there may be psychiatric features and even multiple sclerosis (Binder, 2010). Renovascular involvement may lead to renal failure that can be difficult to differentiate from lupus nephritis (D'Cruz, 2009). Peripheral and visceral thromboses are also a feature. For example, Ahmed and associates (2009) reported a postpartum woman who developed spontaneous cecal perforation following a mesenteric vessel infarction. Obstetrical complications encompass recurrent pregnancy loss and placental dysfunction reflected by fetal-growth restriction, stillbirth, preeclampsia, and preterm birth. Treatment using aspirin, anticoagulation, and close monitoring has increased live birth rates to more than 70 percent in these women (Schreiber, 2016).

A small proportion of these patients develop the *catastrophic antiphospholipid antibody syndrome (CAPS)* or *Asherson syndrome.* This is defined as a rapidly progressive thromboembolic disorder simultaneously affecting three or more organ systems or tissues (Schreiber, 2016). It has a high mortality rate from activation of a cytokine storm. In half of cases, a "triggering" event is identified.

Specific Antiphospholipid Antibodies

As mentioned, several antibodies in APS are directed against a specific phospholipid or phospholipid-binding protein:

1. β_2-*Glycoprotein I*—also known as apolipoprotein H—is a phospholipid-binding plasma protein that inhibits prothrombinase activity within platelets and inhibits platelet aggregation (Giannakopoulos, 2013). Thus, its normal action is to limit procoagulant binding and thereby prevent coagulation cascade activation. Logically, antibodies directed against this glycoprotein would reverse its anticoagulant activity and promote thrombosis. This is important from an obstetrical viewpoint because β_2-glycoprotein I is expressed in high concentrations on the syncytiotrophoblast surface. Complement activation may contribute to its pathogenesis (Avalos, 2009; Tsokos, 2011). Teleologically, this seems appropriate because the decidua intuitively should be a critical area to prevent coagulation that might lead to intervillous space thrombosis. Another possibility is that β_2-glycoprotein I may be involved in implantation, and this glycoprotein may result in pregnancy loss via an inflammatory mechanism (Iwasawa, 2012; Meroni, 2011).

2. *Lupus anticoagulant (LAC)* is a heterogeneous group of antibodies directed against phospholipid-binding proteins. This antibody group induces prolongation in vitro of the prothrombin, partial thromboplastin, and Russell viper venom times. Thus, paradoxically, this so-called anticoagulant is actually powerfully thrombotic in vivo.

3. *Anticardiolipin antibodies (ACAs)* are directed against one of the many phospholipid cardiolipins found in mitochondrial membranes and platelets.

Antibodies against Natural Anticoagulants

Some antiphospholipid antibodies are also directed against the natural anticoagulant proteins C and S (Robertson, 2006). Another is directed against the anticoagulant protein annexin V, which is expressed in high concentrations by syncytiotrophoblast (Giannakopoulos, 2013). Testing for these other antibodies is not recommended (American College of Obstetricians and Gynecologists, 2017). However, some studies have evaluated these nonconventional antiphospholipid antibodies in women who clinically meet APS criteria but do not have the classic antibody profile. In one study, treatment of women with these nonconventional antibodies offered some benefits, such as a lower pregnancy loss rate (Mekinian, 2016).

Clinical features shown in Table 59-5 provide indications for testing. By international consensus, APS is diagnosed based on laboratory and clinical criteria found in Table 18-5. First, one of two clinical criteria—which are vascular thrombosis or certain pregnancy morbidity—must be present. With laboratory criteria, elevated levels of LAC, ACA, and anti-β_2-glycoprotein I should be confirmed on two occasions 12 weeks apart. The diagnosis can be further stratified based on the number of these tests that are positive (Miyakis, 2006).

TABLE 59-5

Some Clinical Features of Antiphospholipid Syndrome

Venous thrombosis—thromboembolism, thrombophlebitis, livedo reticularis
Arterial thrombosis—stroke, transient ischemic attack, Libman-Sacks cardiac vegetations, myocardial ischemia, distal extremity and visceral thrombosis and gangrene
Hematological—thrombocytopenia, autoimmune hemolytic anemia
Other—neurological manifestations, migraine headaches, epilepsy; renal artery, vein, or glomerular thrombosis; arthritis and arthralgia
Pregnancy—preeclampsia syndrome, recurrent miscarriage, preterm delivery, fetal-growth restriction, fetal death

Data from Giannakopoulos, 2013; Moutsopoulos, 2015.

Tests for LAC are nonspecific coagulation tests. The *partial thromboplastin time* is generally prolonged because the anticoagulant interferes with conversion of prothrombin to thrombin in vitro. Tests considered more specific are the *dilute Russell viper venom test* and the *platelet neutralization procedure*. There is currently disagreement as to which of these two is best for screening. If either is positive, then identification of LAC is confirmed.

Branch and Khamashta (2003) recommend conservative interpretation of results based on repeated tests from a reliable laboratory that are consistent with each clinical case. Only approximately 20 percent of patients with APS have a positive LAC assay alone. Thus, ACA enzyme-linked immunosorbent assay (ELISA) testing should also be performed. Efforts have been made to standardize ACA assays, however, these remain without international standards (Adams, 2013). For each APS test, interlaboratory variation can be large, and agreement between commercial kits is poor.

Pregnancy and Antiphospholipid Antibodies

As noted, nonspecific low levels of antiphospholipid antibodies are identified in approximately 5 percent of normal adults (Branch, 2010). When Lockwood and coworkers (1989) first studied 737 normal pregnant women, they reported that 0.3 percent had LAC and 2.2 percent had elevated concentrations of either IgM or IgG ACAs. Subsequent investigations confirmed this, and taken together, they totaled almost 4000 normal pregnancies with an average prevalence for antiphospholipid antibodies of 4.7 percent. This is similar to that for normal nonpregnant individuals (Harris, 1991; Yasuda, 1995).

In women with high ACA levels, and especially when LAC is identified, risks for decidual vasculopathy, placental infarction, fetal-growth restriction, early-onset preeclampsia, and recurrent fetal death are increased (Saccone, 2017). Some of these women, like those with SLE, also have a high incidence of venous and arterial thromboses, cerebral thrombosis, hemolytic anemia, thrombocytopenia, and pulmonary hypertension (American College of Obstetricians and Gynecologists, 2017; Clowse, 2008). In 191 LAC-negative women with APS, women with antibodies to cardiolipin and β_2-glycoprotein I had significantly higher miscarriage rates than if either one alone was positive (Liu, 2013). Women with higher titers tend to have more adverse outcomes (Hadar, 2017).

Pregnancy Pathophysiology

It is not precisely known how antiphospholipid antibodies cause damage, but it is likely that their actions are multifactorial. Platelets may be damaged directly by antiphospholipid antibody or indirectly by binding β_2-glycoprotein I, which causes platelets to be susceptible to aggregation (Giannakopoulos, 2013). One theory proposes that phospholipid-containing endothelial cell or syncytiotrophoblast membranes may be damaged directly by the antiphospholipid antibody or indirectly by antibody binding to either β_2-glycoprotein I or annexin V (Rand, 1997, 1998). This prevents the cell membranes from protecting the syncytiotrophoblast and endothelium. This exposes the basement membrane, to which damaged platelets can adhere and form a thrombus.

Pierro and associates (1999) reported that antiphospholipid antibodies decreased decidual production of the vasodilating prostaglandin E_2. Diminished protein C or S activity and greater prothrombin activation may also be contributory (Zangari, 1997). Evidence also supports that thrombosis with APS stems from activation of the tissue factor pathway (Amengual, 2003). Finally, uncontrolled placental complement activation by antiphospholipid antibodies may play a role in fetal loss and growth restriction (Holers, 2002).

Complications from APS cannot be completely explained by thrombosis alone. Animal models suggest that effects are due to inflammation rather than thrombosis (Cohen, 2011). Some investigators hypothesize that APS-associated clotting is triggered as a "second hit" from innate inflammatory immune responses. These investigators recommend treatment with antiinflammatory agents (Meroni, 2011).

Adverse Pregnancy Outcomes

Overall, antiphospholipid antibodies are generally associated with higher rates of fetal wastage (Chap. 18, Midtrimester Abortion). In most early reports that describe these outcomes, however, women were included *because* they had had repeated adverse outcomes. Both antibody prevalence and miscarriage are common—recall that the incidence of antiphospholipid antibodies in the general obstetrical population is about 5 percent and early pregnancy loss approximates 20 percent. Accordingly, current data are too limited to conclude the exact risks for adverse effects of these antibodies on pregnancy outcomes. Fetal deaths, however, are more characteristic with APS than are first-trimester miscarriages (Oshiro, 1996; Roque, 2004). Moreover, women with higher titers have worse obstetrical outcomes compared with those with low titers (Hadar, 2017; Nodler, 2009).

When otherwise unexplained fetal deaths are examined, the data are mixed. One study measured ACA levels in 309 pregnancies with fetal death and found no differences in their frequency compared with levels in 618 normal pregnancies (Haddow, 1991). In another of women with recurrent pregnancy loss, those with antiphospholipid antibodies had a higher rate of preterm delivery (Clark, 2007). In a case-control study of 582 stillbirths and 1547 live births, a three- to fivefold higher risk for stillbirth was found in women with elevated ACA and anti-β_2-glycoprotein I levels (Silver, 2013). In women with antiphospholipid antibodies, adverse outcomes are more common in the presence of: (1) all three classic antiphospholipid antibody types, (2) comorbid SLE or systemic autoimmune diseases, and (3) prior thrombosis and pregnancy morbidity. Logistic regression found the probability of pregnancy failure was 93 percent with two or more antiphospholipid antibody types but was 63 percent for those with only one (Ruffatti, 2011).

Thrombosis Prevention in Pregnancy

Because of study heterogeneity, current treatment recommendations for women with antiphospholipid antibodies can be confusing. Therapy is directed at thrombosis prevention. As discussed, antiphospholipid antibodies are immunoglobulins that may be of G, M, or A classes. Those directed against the phospholipids (PL) are termed GPL, MPL, and APL, respectively. During testing, these are reported as semiquantified phospholipid binding-unit levels and expressed as negative, low-positive, medium-positive, or high-positive (American College of Obstetricians and Gynecologists, 2017). Of the three, higher titers for GPL and MPL anticardiolipin antibodies are clinically important, whereas low-positive titers are of questionable clinical significance.

As discussed in Chapter 52 (Acquired Thrombophilias), women with prior thromboembolic events who have antiphospholipid antibodies are at risk for recurrence in subsequent pregnancies. For these women, prophylactic anticoagulation with heparin throughout pregnancy and then for 6 weeks postpartum with

either heparin or warfarin is recommended (American College of Obstetricians and Gynecologists, 2017). For those without prior thromboembolic events, recommendations for management from the American College of Obstetricians and Gynecologists (2017) and the American College of Chest Physicians (Bates, 2012) vary and are listed in Table 52-6. Some acceptable schemes include close antepartum maternal observation with or without prophylactic or intermediate-dose heparin, and some form of postpartum anticoagulation for 4 to 6 weeks. Sciascia and coworkers (2016) have presented preliminary salutary results with treatment with hydroxychloroquine.

Several trials have questioned the need for heparin for women with antibodies but no history of thrombosis (Branch, 2010). Although this is less clear, some recommend that women be treated if they have medium- or high-positive ACA titers or LAC activity and a prior second- or third-trimester fetal death not attributable to other causes (Dizon-Townson, 1998; Lockshin, 1995). Some report that women with recurrent early pregnancy loss and medium- or high-positive titers of antibodies may benefit from therapy (Robertson, 2006).

Described earlier (Antiphospholipid Syndrome), catastrophic antiphospholipid syndrome is treated aggressively with full anticoagulation, high-dose corticosteroids, plasma exchange, and/or intravenous immunoglobulins (Cervera, 2010; Tenti, 2016). If needed, rituximab may be added (Sukara, 2015).

Due to the risk of fetal-growth abnormalities and stillbirth, serial sonographic assessment of fetal growth and antepartum testing in the third trimester is recommended by the American College of Obstetricians and Gynecologists (2016a, 2017).

Specific Therapy in Pregnancy

There are other agents used to treat pregnant women with APS, but with no prior thromboembolic event. *Aspirin,* in doses of 60 to 80 mg orally daily, blocks conversion of arachidonic acid to thromboxane A_2 while sparing prostacyclin production. This reduces synthesis of thromboxane A_2, which usually causes platelet aggregation and vasoconstriction, and simultaneously spares prostacyclin, which normally has the opposite effect. There appear to be no major side effects from low-dose aspirin other than a slight risk of small-vessel bleeding during surgical procedures. Low-dose aspirin does not reduce adverse pregnancy outcomes in antiphospholipid antibody-positive women without the complete APS syndrome (Amengual, 2015). Its use is recommended for women with SLE or APS (American College of Obstetricians and Gynecologists, 2016b).

Unfractionated heparin is given subcutaneously in dosages of 5000 to 10,000 units every 12 hours. Some prefer low-molecular-weight heparin, such as 40 mg enoxaparin (Lovenox) once daily (Kwak-Kim, 2013). With therapeutic dosing, measurement of heparin levels may be useful because clotting tests can be altered by LAC. The rationale for heparin therapy is to prevent venous and arterial thrombotic episodes. Heparin therapy also prevents thrombosis in the microcirculation, including the decidual-trophoblastic interface (Toglia, 1996). As discussed, heparin binds to β_2-glycoprotein I, which coats the syncytiotrophoblast. This prevents binding of ACAs and anti-β_2-glycoprotein I antibodies to their surfaces, which likely prevents

cellular damage (Tsokos, 2011). Heparin also binds to antiphospholipid antibodies in vitro and likely in vivo. Aspirin plus heparin therapy is the most efficacious regimen (de Jesus, 2014). However, heparin therapy is associated with several complications that include bleeding, thrombocytopenia, osteopenia, and osteoporosis. A description of various heparins and their adverse effects is found in Chapter 52 (Management).

Corticosteroids generally should not be used with *primary APS*—that is, without an associated connective tissue disorder. For women with SLE or those being treated for APS who develop SLE, corticosteroid therapy is indicated (Carbone, 1999). In such cases of *secondary APS* seen with SLE, the dose of prednisone should be maintained at the lowest effective level to prevent flares.

Intravenous immunoglobulin therapy (IVIG) is controversial and has usually been reserved for women with overt disease—including CAPS or heparin-induced thrombocytopenia or both (Alijotas-Reig, 2013). It is used when other first-line therapies have failed, especially in the setting of preeclampsia and fetal-growth restriction. IVIG is administered by some in doses of 0.4 g/kg/d for 5 days—total dose of 2 g/kg. This is repeated monthly, or it is given as a single dose of 1 g/kg each month. Treatment is expensive, as one course costs more than $10,000. A recent literature review found no benefits from adding IVIG to low-dose aspirin and low-molecular-weight heparin (Tenti, 2016). And, a Cochrane review found no improvement in the live birth rate for immunotherapy given to women with recurrent pregnancy loss (Wong, 2014). Trials are needed before application of this expensive and cumbersome therapy becomes widespread.

Immunosuppression with hydroxychloroquine may be beneficial with APS by reducing the risk of thrombosis and improving pregnancy outcomes in women with APS (Mekinian, 2015; Sciascia, 2016). Hydroxychloroquine is commonly used with low-dose aspirin in the treatment of women with antiphospholipid antibodies and SLE.

Statins have been examined due to their protective effects on endothelium. In a small trial in 21 women with APS who developed fetal-growth restriction or preeclampsia, the addition of pravastatin to low-dose aspirin and low-molecular-weight heparin improved placental blood flow, preeclampsia features, and pregnancy outcomes (Lefkou, 2016). Larger trials are needed.

Treatment Efficacy

Fetal loss is common in women with APS if untreated (Rai, 1995). Even with treatment, recurrent fetal loss rates remain at 20 to 30 percent (Branch, 2003; Empson, 2005; Ernest, 2011). Shown in Table 59-6 are pregnancy outcomes from 750 treated women with primary APS—the PREGNANTS study (Saccone, 2017). Participants were treated with low-dose aspirin and prophylactic low-molecular-weight heparin starting in the first trimester. Importantly, some women with SLE and antiphospholipid antibodies have normal pregnancy outcomes without treatment. Also, it is emphasized that women with LAC and prior bad pregnancy outcomes have had liveborn neonates without treatment.

TABLE 59-6

Pregnancy Outcomes (%) in 750 Women Treated for the Antiphospholipid Syndrome—the PREGNANTS Study

Outcome	Triple-Positive (n = 20)	Double-Positive LAC Negative (n = 90)	LAC Alone (n = 54)	ACA Alone (n = 458)	Anti-β_2 Glycoprotein (n = 128)
Livebirth	30	43	80	56	48
Stillbirth	45	34	7	21	30
Preeclampsia[a]	55	54	11	34	48

ACA = anticardiolipin antibodies; LAC = lupus anticoagulant.

[a]Nonsevere only.

Data from Saccone, 2017.

In a manner similar to neonatal lupus syndrome (Perinatal Mortality and Morbidity), up to 30 percent of newborns demonstrate passively acquired antiphospholipid antibodies, and thus there is concern for their adverse neonatal effects (Nalli, 2017). One group found higher rates of learning disabilities in these children (Tincani, 2009). Simchen and colleagues (2009) reported a fourfold greater risk for perinatal strokes. Of 141 newborns followed in a European registry, the rate of preterm birth was 16 percent; low birthweight, 17 percent; and later behavioral abnormalities in 4 percent of the children. There were no cases of neonatal thrombosis (Motta, 2012). A 7-year study of 26 women who had APS with 36 pregnancies reported three cases of autism spectrum disorder, all associated with persistent neonatal anti-β_2-glycoprotein-1 IgG antibodies (Abisror, 2013).

RHEUMATOID ARTHRITIS

This chronic inflammatory disease stems from immunological dysfunction, and infiltrating T cells secrete cytokines to cause inflammation, polyarthritis, and systemic symptoms. The cardinal feature is inflammatory synovitis that usually involves the peripheral joints. The disease has a propensity for cartilage destruction, bony erosions, and joint deformities. Pain, aggravated by movement, is accompanied by swelling and tenderness. Extraarticular manifestations include rheumatoid nodules, vasculitis, and pleuropulmonary symptoms. Other complaints are fatigue, anorexia, and depression. The American College of Rheumatology criteria for rheumatoid arthritis diagnosis are shown in Table 59-7. A score of 6 or greater fulfills the requirements for definitive diagnosis.

TABLE 59-7

Criteria for Classification of Rheumatoid Arthritis

Factor	Criteria	Score
Joint involvement	1 large—shoulder, elbow, hip, knee, ankle	0
	2–10 large	1
	1–3 small—MCP, PIP, thumb IP, MTP, wrists	2
	4–10 small	3
	>10—at least 1 small	5
Serological testing	Negative RF and negative ACPA	0
	Low-positive RF or anti-CCP	2
	High-positive RF or anti-CCP	3
Acute-phase reactants	Normal CRP and ESR	0
	Abnormal CRP or ESR	1
Duration of symptoms	Less than 6 weeks	0
	6 weeks or longer	1

ACPA = anti-citrullinated peptide antibody; CCP = cyclic citrullinated peptides; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IP = interphalangeal joint; MCP = metacarpophalangeal joint; MTP = metatarsophalangeal joint; PIP = proximal interphalangeal joint; RF = rheumatoid factor.

Criteria established in collaboration with the American College of Rheumatology and the European League Against Rheumatism. A score ≥ 6 fulfills criteria for diagnosis.

Data from Aletaha, 2010; Shah, 2015.

The worldwide prevalence of rheumatoid arthritis is 0.5 to 1 percent, women are affected three times more often than men, and peak onset is from 25 to 55 years (Shah, 2015). There is a genetic predisposition, and heritability is estimated at 15 to 30 percent (McInnes, 2011). Genome-wide associated studies have identified more than 30 loci involved in rheumatoid arthritis pathogenesis (Kurkó, 2013). There is an association with

the class II major histocompatibility complex molecule HLA-DR4 and HLA-DRB1 alleles (McInnes, 2011; Shah, 2015). Pregnancy provides a protection against rheumatoid arthritis development, and this may be related to HLA-disparate fetal microchimerism (Guthrie, 2010). Of other influences, cigarette smoking raises the risk of rheumatoid arthritis (Papadopoulos, 2005).

Management

Treatment is directed at pain relief, inflammation reduction, protection of articular structures, and preservation of function. Physical and occupational therapy and self-management instructions are essential. Until recently, aspirin and other NSAIDs were the cornerstone of therapy, but they do not retard disease progression. According to Shah and St. Clair (2015), methotrexate has become the preferred disease-modifying antirheumatic drug (DMARD). NSAIDs serve as adjunctive therapy but are important to pregnancy because methotrexate is contraindicated. Conventional NSAIDs nonspecifically inhibit both cyclooxygenase-1 (COX-1), which is an enzyme critical to normal platelet function, and COX-2, which mediates inflammatory response mechanisms. Because gastritis with acute bleeding is an unwanted side effect common to conventional NSAIDs, the more specific COX-2 inhibitors have been recommended. However, their long-term use is associated with higher risk for myocardial infarction and major vascular events (Patrono, 2016).

In one systematic review, a higher rate of cardiac malformations was found in newborns exposed to NSAIDs in the first trimester (Adams, 2012). In addition, NSAIDs are associated with early spontaneous abortions, ductus arteriosus constriction, and neonatal pulmonary hypertension. Thus, risks versus benefits of these medications must be considered.

Glucocorticoid therapy in low-to-moderate doses is given to achieve more rapid symptom control. Of these, prednisone, 7.5 mg orally daily for the first 2 years of active disease, substantively reduces progressive joint erosions (Kirwan, 1995; Shah, 2015).

The American College of Rheumatology recommends several DMARDs that may reduce or prevent joint damage (Singh, 2016). Leflunomide, like methotrexate, is teratogenic (Briggs, 2015) (Chap. 12, Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs). Sulfasalazine and hydroxychloroquine are safe for use in pregnancy (Partlett, 2011). These, combined with COX-2 inhibitors and with relatively low-dose prednisone—7.5 to 20 mg daily—usually successfully treat flares. In one review of drug exposure, a fourth of women with rheumatoid arthritis took a DMARD within 6 months of conception (Kuriya, 2011). During pregnancy, 4 percent of 393 pregnant women were given a category D or X medication. Methotrexate was the most common— 2.9 percent.

Biological DMARDs have revolutionized the treatment of rheumatoid arthritis. These include tumor necrosis factor alpha (TNF-α) inhibitors—infliximab, adalimumab, golimumab, certolizumab, and etanercept (Shah, 2015). Their use in pregnancy is limited, and fetal safety is a concern (Makol, 2011; Ojeda-Uribe, 2013). In one drug-exposure review, 13 percent of 393 women were given a biological cytokine-inhibiting DMARD—primarily etanercept (Kuriya, 2011). In another review of 300 exposures, no fetal effects were noted (Berthelot, 2009). A prospective study of 38 women found similar results (Hoxha, 2017). In 74 women exposed

to adalimumab during pregnancy, no risks were identified (Burmester, 2017). There is also little known regarding pregnancy effects of anakinra, an interleukin-1 receptor antagonist, or of rituximab, an antagonist to the B-cell CD20 antigen.

Pregnancy and Rheumatoid Arthritis

In up to 90 percent of women with rheumatoid arthritis, their disease will improve during pregnancy (de Man, 2008). Animal studies suggest this may be due to regulatory T-cell alterations (Munoz-Suano, 2012). Even so, some women develop disease during pregnancy, and others become worse (Nelson, 1997).

A downside to this respite during pregnancy is that postpartum exacerbation is common (Østensen, 2007). This may stem from postpartum alterations in innate immunity (Häupl, 2008b). In one review, a postpartum flare was more common if women were breastfeeding (Barrett, 2000a). These same investigators followed 140 women with rheumatoid arthritis during 1 to 6 months postpartum (Barrett, 2000b). There was only a modest fall in objective disease activity, and only 16 percent had complete remission. They observed that although overall disease actually did not exacerbate postpartum, the mean number of inflamed joints rose significantly.

Some studies report a protective effect of pregnancy against developing new-onset rheumatoid arthritis. In a case-control study of 88 affected women, there was a protective effect of pregnancy in the long term, but the likelihood of new-onset rheumatoid arthritis was increased sixfold during the first 3 postpartum months (Silman, 1992). Pikwer and colleagues (2009) reported a significant reduction in the risk of subsequent arthritis in women who breastfed longer than 12 months.

These findings may reflect the interference of sex hormones with several putative processes involved in arthritis pathogenesis, including immunoregulation (Häupl, 2008a,b). First, Unger and associates (1983) reported that amelioration of rheumatoid arthritis correlated with serum levels of *pregnancy-associated alpha$_2$-glycoprotein.* This compound has immunosuppressive properties. Second, Nelson and coworkers (1993) noted that amelioration of disease was associated with a disparity in HLA class II antigens between mother and fetus. They suggested that the maternal immune response to paternal HLA antigens may play a role in pregnancy-induced remission of arthritis. In addition to monocyte activations, there also may be T-lymphocyte activation (Förger, 2008).

Juvenile Rheumatoid Arthritis

This group of diseases is the most frequent cause of chronic arthritis in children and persists into adulthood. In 76 pregnancies of 51 affected Norwegian women, pregnancy had no effects on clinical presentation, but disease activity usually became quiescent or remained so during pregnancy (Østensen, 1991). Postpartum flares were common as was discussed for rheumatoid arthritis. Joint deformities often developed in these women, and 15 of 20 cesarean deliveries were done for contracted pelves or joint prostheses. Results from a summary of 39 Polish women with juvenile rheumatoid arthritis were similar (Musiej-Nowakowska, 1999).

This arthritis portends few adverse pregnancy outcomes. The risk for preterm birth is increased, but later fetal development is normal (Mohamed, 2016; Rom, 2014; Wallenius, 2014). Disease severity in early pregnancy was predictive of preterm delivery and fetal-growth restriction in a cohort study (Bharti, 2015). Another study of 190 pregnancies followed from first trimester to delivery found patients with low disease activity scores in the first trimester were likely to have low disease activity or remission in the third trimester (Ince-Askan, 2017). In a study of 1807 births, Remaeus and associates (2017) reported increased incidences of preterm birth, fetal-growth restriction, and preeclampsia.

Primary treatment of symptomatic women during pregnancy is with aspirin and NSAIDs. These are used with appropriate concerns for first-trimester effects, impaired hemostasis, prolonged gestation, premature ductus arteriosus closure, and persistent pulmonary circulation. Low-dose corticosteroids are also prescribed as indicated. Gold compounds have been administered in pregnancy (Almarzouqi, 2007).

Immunosuppressive therapy with azathioprine, cyclophosphamide, or methotrexate is not routinely used during pregnancy. Only azathioprine is considered during early pregnancy because the other agents are teratogens (Briggs, 2015). As discussed in Management, DMARDs including sulfasalazine and hydroxychloroquine are acceptable for use in pregnancy.

If the cervical spine is involved, particular attention is warranted during pregnancy. Subluxation is common, and pregnancy, at least theoretically, predisposes to this because of joint laxity. Importantly, there are anesthesia concerns during endotracheal intubation.

Following pregnancy in women with rheumatoid arthritis and its juvenile form, contraceptive counseling may include combination oral contraceptives. These are a logical choice because of their effectiveness and their potential to improve disease (Farr, 2010). That said, all methods of contraception are appropriate.

SYSTEMIC SCLEROSIS—SCLERODERMA

This is a chronic multisystem connective tissue disorder of unknown etiology. It is characterized by microvascular damage, immune system activation leading to inflammation, and excessive deposition of collagen in the skin and often in the lungs, heart, gastrointestinal tract, and kidneys. It is uncommon, displays a 5-to-1 female dominance, and typically affects those aged 30 to 50 years (Meier, 2012; Varga, 2015).

This strong prevalence of scleroderma in women and its greater incidence in the years following childbirth give credence to the hypothesis that *microchimerism* is involved as discussed earlier (Systemic Lupus Erythematosus) (Lambert, 2010). Artlett and coworkers (1998) demonstrated Y-chromosomal DNA in almost half of women with systemic sclerosis compared with only 4 percent of controls. Rak and colleagues (2009b) identified male microchimerism in peripheral blood mononuclear cells more frequently in women with limited versus diffuse scleroderma—20 versus 5 percent.

Clinical Course

The hallmark is overproduction of normal collagen. In the more benign form—*limited cutaneous systemic sclerosis*—progression is slow. With *diffuse cutaneous systemic sclerosis*, skin thickening progresses rapidly, and skin fibrosis is followed by gastrointestinal tract fibrosis, especially the distal esophagus (Varga, 2015). Pulmonary interstitial fibrosis along with vascular changes may cause pulmonary hypertension, which develops in 15 percent of patients. Antinuclear antibodies are found in 95 percent of patients, and immunoincompetence often develops.

Raynaud phenomenon, which includes cold-induced episodic digital ischemia, is seen in 95 percent of patients, and there may also be swelling of the distal extremities and face. Half of patients have symptoms from esophageal involvement, especially fullness and epigastric burning pain. Pulmonary involvement is frequent and causes dyspnea. The 10-year cumulative survival rate is 70 percent in those with pulmonary fibrosis, and pulmonary arterial hypertension is the main cause of death (Joven, 2010; Varga, 2015). Women with limited cutaneous disease such as the *CREST syndrome—calcinosis, Raynaud phenomenon, esophageal involvement, sclerodactyly, and telangiectasia*—have milder disease.

Overlap syndrome refers to systemic sclerosis with features of other connective tissue disorders. *Mixed connective tissue disease* is a term used for the syndrome involving features of SLE, systemic sclerosis, polymyositis, rheumatoid arthritis, and high titers of anti-ribonucleoprotein (RNP) antibodies (see Table 59-1). The disorder is also termed *undifferentiated connective tissue disease* (Spinillo, 2008).

Although systemic sclerosis is incurable, treatment directed at end-organ involvement can sometimes relieve symptoms and improve function. Renal involvement and hypertension are often comorbid. At times, ACE inhibitors may be required for blood pressure control despite their known teratogenicity. *Scleroderma renal crisis* develops in up to a fourth of these patients and is characterized by obliterative vasculopathy of the renal cortical arteries. This leads to renal failure and malignant hypertension. Interstitial restrictive lung disease is common and frequently becomes life threatening. Associated pulmonary hypertension is treated with bosentan or sildenafil (Chap. 49, Pulmonary Hypertension).

Pregnancy and Systemic Sclerosis

The prevalence of scleroderma in pregnancy approximates 1 in 22,000 pregnancies (Chakravarty, 2008). These women usually have stable disease during gestation if their baseline function is good. As perhaps expected, dysphagia and reflux esophagitis are aggravated by pregnancy (Steen, 1999). Dysphagia results from loss of esophageal motility due to neuromuscular dysfunction. A decrease in amplitude or disappearance of peristaltic waves in the lower two thirds of the esophagus is seen using manometry. Symptomatic treatment for reflux is described in Chapter 54 (Gastroesophageal Reflux Disease).

Women with renal insufficiency and malignant hypertension have a higher incidence of superimposed preeclampsia. With rapidly worsening renal or cardiac disease, pregnancy termination should be considered. As discussed, renal crisis is life threatening and is treated with ACE inhibitors, but it does not improve with delivery (Gayed, 2007). Pulmonary hypertension usually contraindicates pregnancy.

Vaginal delivery may be anticipated, unless the soft tissue thickening wrought by scleroderma produces dystocia requiring cesarean delivery. Tracheal intubation for general anesthesia has special concerns because of limited ability of these women to open their mouths widely (Sobanski, 2016). Because of esophageal dysfunction, aspiration is also more likely, and epidural analgesia is preferable. Warming the delivery room and intravenous fluids, extra blankets, and socks and gloves are recommended to improve impaired circulation from Raynaud phenomenon. If corticosteroids were used frequently, stress doses of hydrocortisone are recommended (Sobanski, 2016).

Maternal and fetal outcomes correlate with underlying disease severity. In a review of 214 gravidas with systemic sclerosis, 45 percent had diffuse disease. Major complications included renal crisis in three and greater rates of preterm birth (Steen, 1989, 1999). Chung and coworkers (2006) also reported elevated rates of preterm delivery, fetal-growth restriction, and perinatal mortality. A multicenter study of 109 pregnancies from 25 centers reported higher rates of preterm delivery, fetal-growth restriction, and very-low-birthweight newborns (Taraborelli, 2012). These are likely related to placental abnormalities that include decidual vasculopathy, acute atherosis, and infarcts (Sobanski, 2016).

Scleroderma may be associated with subfertility (Bernatsky, 2008; Lambe, 2004). For women who do not choose pregnancy, several reversible contraceptive methods are acceptable. However, hormonal agents, especially combination oral contraceptives, probably should not be used, especially in women with pulmonary, cardiac, or renal involvement. Due to the often unrelenting progression of systemic sclerosis, permanent sterilization is also considered.

VASCULITIS SYNDROMES

Inflammation and damage to blood vessels may be primary or caused by another disease. Immune-complex deposition is presumed to underlie most cases (Langford, 2015). Primary types include polyarteritis nodosa, temporal or giant-cell arteritis, Takayasu arteritis, Henoch-Schönlein purpura, Behçet syndrome, and cutaneous or hypersensitivity arteritis (Goodman, 2014). Small vessel vasculitides such as *granulomatosis with polyangiitis* and *eosinophilic granulomatosis with polyangiitis* have antibodies directed against proteins in the cytoplasmic granules of leukocytes—*antineutrophil cytoplasmic antibodies—ANCA (Pagnoux, 2016)*.

Polyarteritis Nodosa

This necrotizing vasculitis of small and medium-sized arteries is characterized clinically by myalgia, neuropathy, gastrointestinal disorders, hypertension, and renal disease (Goodman, 2014). Of cases, approximately a third is associated with hepatitis B antigenemia (Langford, 2015). Symptoms are nonspecific, and fever, weight loss, and malaise are present in more than half of cases. Diagnosis is made by biopsy, and treatment consists of high-dose prednisone plus cyclophosphamide. Vasculitis due to hepatitis B antigenemia responds to antivirals, glucocorticosteroids, and plasma exchange (Chap. 55, Chronic Viral Hepatitis).

Only a few reports describe polyarteritis nodosa associated with pregnancy. Of 12 affected gravidas, polyarteritis first manifested during pregnancy in seven, and it was rapidly fatal by 6 weeks postpartum (Owen, 1989). The diagnosis was not made until autopsy in six of the seven women. Four women continued pregnancy, which resulted in one stillborn and three successful outcomes.

Granulomatosis with Polyangiitis

Formerly Wegener granulomatosis, this is a small-vessel necrotizing granulomatous vasculitis affecting the upper and lower respiratory tract and kidney (Pagnoux, 2016). Disease frequently includes sinusitis and nasal disease—90 percent; pulmonary infiltrates, cavities, or nodules—85 percent; glomerulonephritis—75 percent; and musculoskeletal lesions—65 percent (Sneller, 1995). At least 90 percent have polyangiitis (Langford, 2015). It is uncommon and usually encountered after age 50. Koukoura and associates (2008) reviewed 36 cases in association with pregnancy and found a higher preterm birth rate. In another report, a second woman had disease-related pneumonitis, but pregnancy did not appear to affect disease activity (Pagnoux, 2011). Because subglottic stenosis is found in up to a fourth of patients, the anesthesia team is ideally consulted antepartum (Engel, 2011).

Corticosteroids are standard treatment, but azathioprine, cyclosporine, and IVIG therapy may also be used. For severe disease in the late second or third trimester, cyclophosphamide in combination with prednisolone seems acceptable.

Takayasu Arteritis

Also called *pulseless disease,* this is a chronic inflammatory arteritis affecting large vessels (Goodman, 2014). Unlike *temporal arteritis*, which develops almost exclusively after age 55, the onset of Takayasu arteritis is almost always before age 40. It is associated with abnormal angiography of the upper aorta and its main branches and with upper extremity vascular impairment. Death usually results from congestive heart failure or cerebrovascular events. Computed tomography or magnetic resonance angiography can detect this disorder before the development of severe vascular compromise. Takayasu arteritis may respond symptomatically to corticosteroid therapy, however, it is not curative. Surgical bypass or angioplasty improves survival rates.

Comorbid severe renovascular hypertension, cardiac involvement, or pulmonary hypertension worsen pregnancy prognosis (Singh, 2015). Hypertension is relatively common and should be carefully controlled. Blood pressure is most accurately measured in the lower extremity. Overall, the prognosis for pregnancy is good (Johnston, 2002). A study of 58 women with Takayasu arteritis found an elevated risk of pregnancy-related hypertension and preeclampsia but overall favorable maternal and fetal outcomes (Gudbrandsson, 2017). A study of 52 patients comparing obstetrical outcomes before and after diagnosis reported higher rates of obstetrical complications after diagnosis. These included preeclampsia, preterm birth, and fetal-growth restriction or death (Comarmond, 2015). Involvement of the abdominal aorta portends worse perinatal outcome (Sharma, 2000). Vaginal delivery is preferred, and epidural analgesia has been advocated for labor and delivery.

Other Vasculitides

Henoch-Schönlein purpura is uncommon after childhood. Tayabali and associates (2012) reviewed 20 pregnancies complicated by this vasculitis and described cutaneous lesions in three fourths. Approximately half had arthralgias. For *Behçet disease,* Gungor and colleagues (2014) described 298 pregnancies in 94 women and found higher miscarriage rates and smaller babies compared with healthy controls. Formerly *Churg-Strauss vasculitis,* eosinophilic granulomatosis with polyangiitis is rare in pregnancy (Jennette, 2013). Hot and associates (2007) described a pregnant woman who responded to IVIG therapy. Corradi and associates (2009) described an affected 35-year-old woman at term whose necrotizing vasculitis involved the heart, and she subsequently underwent cardiac transplantation. Edwards (2015) described one woman who developed postpartum relapses of this vasculitis in each of two pregnancies.

INFLAMMATORY MYOPATHIES

These are acquired and potentially treatable causes of skeletal muscle weakness with a prevalence of 1 in 100,000 persons (Dalakas, 2012). There are three major groups: polymyositis, dermatomyositis, and inclusion-body myositis, which all present with progressive asymmetrical muscle weakness. They have a variable association with connective tissue diseases, malignancy, drugs, systemic autoimmune disease such as Crohn disease, and viral, bacterial, and parasitic infections.

Polymyositis is a subacute inflammatory myopathy that is frequently associated with one of the autoimmune connective tissue disorders. *Dermatomyositis* manifests as a characteristic rash accompanying or preceding weakness. Laboratory findings include elevated muscle enzyme levels in serum and an abnormal electromyogram. Confirmation is by biopsy, which shows perivascular and perimysial inflammatory infiltrates, vasculitis, and muscle fiber degeneration. It usually develops alone but can overlap with systemic sclerosis or mixed connective tissue disease.

Prevailing theories suggest that the syndromes are caused by viral infections, autoimmune disorders, or both. *Importantly, approximately 15 percent of adults who develop dermatomyositis have an associated malignant tumor.* The timing of myositis and tumor appearance may be separated by several years. The most common sites of associated cancer are breast, lung, stomach, and ovary. The disease usually responds to high-dose corticosteroid therapy, immunosuppressive drugs such as azathioprine or methotrexate, or IVIG (Dalakas, 2012; Linardaki, 2011).

Experiences in pregnancy are garnered mostly from case series and reviews. Chen and colleagues (2015) found 17 women with polymyositis/dermatomyositis in an Australian population-based cohort of births. These women had higher rates of hypertension (23 percent), antepartum hemorrhage (11 percent), cesarean delivery (88 percent), and preterm birth (35 percent). Another series of 60 women with dermatomyositis and 38 with polymyositis found that in 80 percent, pregnancy had no adverse effect on their disease. Similar results have been reported by others (Missumi, 2015; Pinal-Fernandez, 2014). Rosenzweig and colleagues (1989) reviewed 24 pregnancy outcomes in 18 women with primary disease. Of these, a fourth had an exacerbation in the second or third trimester. In 12 in whom disease became manifest first during pregnancy,

half of the eight pregnancies resulted in perinatal death, and one woman died postpartum. From their review, Doria and associates (2004) concluded that pregnancy outcome was related to dermatomyositis activity and that new-onset disease was particularly aggressive.

HEREDITARY CONNECTIVE TISSUE DISORDERS

Numerous inherited mutations involve genes that encode for structural proteins of bone, skin, cartilage, blood vessels, and basement membranes. Although connective tissues contain many complex macromolecules such as elastin and more than 30 proteoglycans, the most common constituents are fibrillar collagen types I, II, and III. Various mutations, some recessively and some dominantly inherited, result in clinical syndromes that include Marfan and Ehlers-Danlos syndromes, osteogenesis imperfecta, chondrodysplasias, and epidermolysis bulla. Of concern during pregnancy is the predilection for these disorders to result in aortic aneurysms (Schoenhoff, 2013).

Marfan Syndrome

This is an autosomal dominant connective tissue disorder that has a population prevalence of 1 in 3000 to 5000 (Prockop, 2015). Marfan syndrome affects both sexes equally. The syndrome is due to abnormal fibrillin—a constituent of elastin—caused by any of several different mutations in the *FBN1* gene (Biggin, 2004). Located on chromosome 15q21, the *FBN1* gene has a high mutation rate, and there are many mild, subclinical cases. A 50-percent risk of disease transmission to the offspring exists, however, the ability to predict disease severity in progeny is limited by the lack of distinct genotype-phenotype correlation and large clinical variability. Currently, preimplantation and prenatal diagnoses are limited to the 80 percent of cases in which the mutation in the *FBN1* gene is known (Smok, 2014).

In severe disease, there is degeneration of the elastic lamina in the media of the aorta. This weakness predisposes to aortic dilation or dissecting aneurysm, which appears more commonly during pregnancy (Curry, 2014; Roman, 2016). Marfan syndrome complicating pregnancy is discussed in more detail in Chapter 49, Diseases of the Aorta.

Ehlers-Danlos Syndrome

This disease is characterized by various connective tissue changes, including skin hyperelasticity. In the more severe types, rupture of any of several arteries can cause either stroke or bleeding. There are several disease types based on skin, joint, or other tissue involvement. Some are autosomal dominant, some recessive, and some X-linked (Solomons, 2013). Their aggregate prevalence approximates 1 in 5000 births (Prockop, 2015). Types I, II, and III are autosomally dominant, and each accounts for approximately 30 percent of cases. Type IV is uncommon but is known to predispose to preterm delivery, maternal great-vessel rupture, postpartum bleeding, and uterine rupture (Pepin, 2000). In most, the underlying molecular defect affects collagen or procollagen.

In general, women with Ehlers-Danlos syndrome reportedly have a higher frequency of preterm rupture of membranes, preterm delivery, and antepartum and postpartum hemorrhage (Volkov, 2006). That said, a recent cohort study of 314 women reported no greater risk of adverse pregnancy outcome, including preterm birth (Sundelin, 2017). Several cases of spontaneous uterine rupture have been described (Rudd, 1983). Tissue fragility makes episiotomy repair and cesarean delivery difficult. Hurst and colleagues (2014) surveyed 1769 respondents of the Ehlers-Danlos National Foundation and found a preterm birth rate of 25 percent and infertility rate of 44 percent. A maternal and fetal death from spontaneous rupture of the right iliac artery has been reported (Esaka, 2009). Bar-Yosef and associates (2008) described a newborn with multiple congenital skull fractures and intracranial hemorrhage caused by Ehlers-Danlos type VIIC.

Osteogenesis Imperfecta

This disorder has a prevalence of 1 in 20,000 births for type I and 1 in 60,000 for type II. It is characterized by brittle bones and affected patients often have blue sclerae, hearing loss, multiple prior bone fractures, and dental abnormalities. There are up to 15 subtypes based on the causative gene and clinical picture, which ranges from mild to severe (Van Dijk, 2010). Genetic inheritance includes autosomal dominant, autosomal recessive, and sporadic patterns. Type I is the mildest form, and the typical mutation affects the *COL1A1* gene (Sykes, 1990). Type II is typically lethal in utero (Prockop, 2015).

Women with osteogenesis imperfecta, most commonly type I, may have successful pregnancies. That said, several risks in pregnancy include fractures, complications related to scoliosis with restrictive lung disease, micrognathia, brittle teeth, an unstable cervical spine, uterine rupture, and cephalopelvic disproportion. A retrospective cohort of 295 women with osteogenesis imperfecta found greater risks of antepartum hemorrhage, abruption, fetal-growth restriction, congenital malformations, and preterm birth (Ruiter-Ligeti, 2016). It is not unusual for affected women to enter pregnancy having had 20 to 30 prior fractures. Most require minimal treatment other than management of the fractures and consideration of bisphosphonates to decrease bone loss.

Depending on the type of osteogenesis imperfecta, the fetus may be affected and may also suffer fractures in utero or during delivery (Chap. 10, Skeletal Abnormalities). Prenatal diagnosis is available in many situations, if desired, and in utero stem cell therapy is being evaluated (Couzin-Frankel, 2016).

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CHAPTER 60: Neurological Disorders

Epilepsy appears to have no effect on pregnancy, though at the time of labour it may be mistaken for eclampsia by inexperienced observers. If the attacks are frequent the patient should be put upon large doses of potassium bromide and treated just as at other times.

—J. Whitridge Williams (1903)

INTRODUCTION

Although several neurological diseases are relatively common in women of childbearing age, less than two pages were devoted to Diseases of the Nervous System in this textbook's first edition. In the past, some may have precluded pregnancy, however, few do so now. Most encountered during pregnancy are the same as for nonpregnant women, however a few neurological disorders may be seen more frequently in pregnant women. Examples are Bell palsy, specific types of strokes, and benign intracranial hypertension or pseudotumor cerebri. Neurovascular disorders are an important cause of maternal mortality and accounted for nearly 7 percent of maternal deaths in the United States from 2011 through 2013 (Creanga, 2017).

Many neurological disorders frequently precede pregnancy. Most women with chronic neurological disease who become pregnant will have successful outcomes, but some disorders have specific risks. Conversely, other women will have new-onset neurological symptoms during pregnancy, and these often must be distinguished from pregnancy complications. Psychiatric disorders can also manifest with cognitive and neuromuscular abnormalities and should be considered in the evaluation.

CENTRAL NERVOUS SYSTEM IMAGING

Computed tomography (CT) and magnetic resonance (MR) imaging assist in the diagnosis, classification, and management of many neurological and psychiatric disorders. As discussed in Chapter 46 (Computed Tomography), these imaging methods can be used safely during pregnancy. CT scanning is often used when rapid diagnosis is necessary and is excellent for detecting recent hemorrhage. Because it does not use radiation, MR imaging is often preferred and is particularly helpful to diagnose demyelinating diseases, arteriovenous malformations, congenital and developmental nervous system abnormalities, posterior fossa lesions, and spinal cord diseases. Whenever either test is done, the woman with advanced pregnancy should be positioned in a left lateral tilt with a wedge under one hip to prevent hypotension and to diminish aortic pulsations, which may degrade the image.

Cerebral angiography with contrast injection, usually via the femoral artery, is a valuable adjunct to the diagnosis and treatment of some cerebrovascular diseases. Fluoroscopy delivers more radiation but can be performed with abdominal shielding. Positron emission tomography (PET) and functional MR imaging (fMRI) have not been evaluated for use in pregnant patients (Chiapparini, 2010).

HEADACHE

In one national survey in the United States in 2012, 17 percent of those aged 18 to 44 years reported a severe headache or migraine within the past 3 months (Blackwell, 2014). Burch and coworkers (2015) reported that 24 percent of nonpregnant women in this age group were similarly affected. Of pregnant women presenting with headache who received a neurological consultation, two thirds were due to primary disorders, with over 90 percent due to migraine. Of the other third due to secondary conditions, over half were due to hypertensive disorders (Robbins, 2015). Interestingly, Aegidius and associates (2009) reported a decline in the rate of all headache types during pregnancy in nulliparas, especially during the third trimester.

The classification by the International Headache Society (2013) is shown in Table 60-1. In pregnant women, primary headaches are more common than those stemming from secondary causes (Digre, 2013; Sperling, 2015). Migraine headaches are those most likely to be affected by the hormonal changes of pregnancy (Pavlovic, 2017). The incidences of severe headache causes in pregnancy are shown in Figure 60-1.

TABLE 60-1

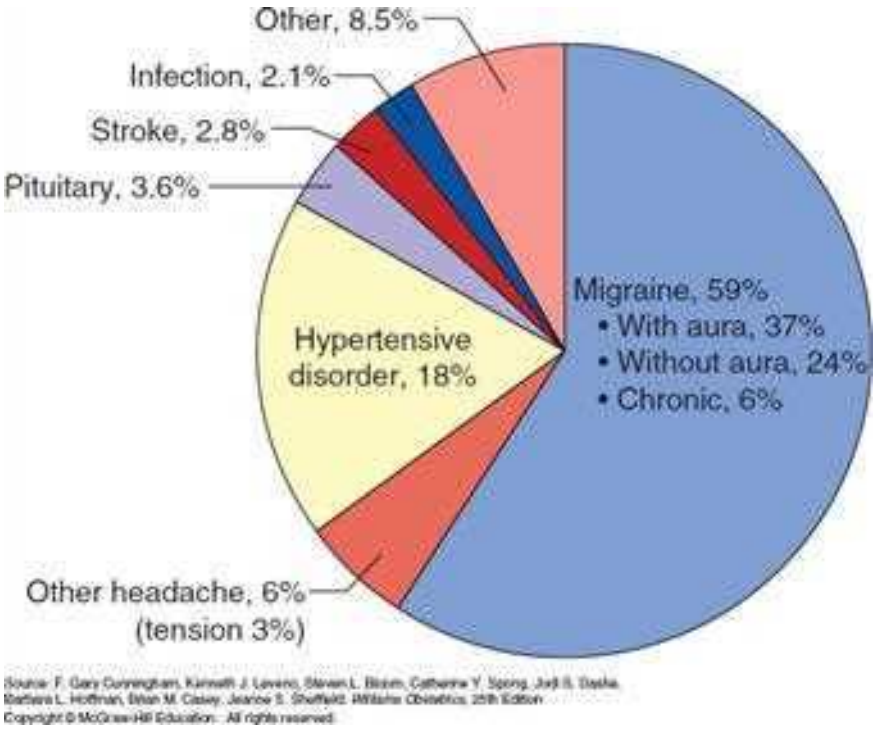
Headache Classification

Primary
Migraine
Tension-type
Trigeminal cephalalgia
Other
Secondary
Trauma
Vascular disorders
Substance abuse
Infection
Disorders of homeostasis
Craniofacial disorders
Psychiatric disorders

Data from International Headache Society, 2013.

FIGURE 60-1

Incidences of headache causes in 140 consecutive pregnant women for whom in-hospital neurology consultation was requested. (Data from Robbins, 2015.)



Tension-Type Headache

These are the most frequent cause of all headaches. Characteristic features include muscle tightness and mild-to-moderate pain in the back of the neck and head that can persist for hours. Neurological disturbances or nausea are typically absent. The pain usually responds to rest, massage, application of heat or ice, antiinflammatory medications, or mild tranquilizers. Hospital admission is seldom necessary.

Migraine Headache

The term *migraine* describes a periodic, sometimes incapacitating neurological disorder with episodic attacks of severe headache and autonomic nervous system dysfunction (Goadsby, 2015). The International Headache Society (2013) classifies three migraine types based on chronicity and on the presence or absence of an aura.

1. *Migraine without aura*—formerly termed common migraine—is characterized by a unilateral throbbing headache, nausea and vomiting, or photophobia.
2. *Migraine with aura*—formerly termed classic migraine—has similar symptoms preceded by premonitory neurological phenomena such as visual scotoma or hallucinations. A third of patients have this type of migraine, which sometimes can be averted if medication is taken at the first premonitory sign.

3. *Chronic migraine* is defined by a migraine headache occurring at least 15 days each month for more than 3 months.

These are the most common reason for admission for headache evaluation and management. Migraines may begin in childhood, peak in adolescence, and tend to diminish in both frequency and severity with advancing years. According to Lipton and associates (2007), their annual prevalence is 17 percent in women and 6 percent in men. Another 5 percent of women have *probable migraine,* that is, they have all criteria but one (Silberstein, 2007). Specific polymorphisms have been identified that modulate the risk of migraines (Chen, 2015; Schürks, 2010). These headaches are especially common in young women and have been linked to hormone levels (Charles, 2017; Pavlovic, 2017). They are frequently encountered during pregnancy.

Sensory sensitivity with migraines is likely caused by monoaminergic sensory control systems in the brainstem and hypothalamus (Goadsby, 2015). This exact pathophysiology is uncertain, but they occur when neuronal dysfunction leads to decreased cortical blood flow, activation of vascular and meningeal nociceptors, and stimulation of trigeminal sensory neurons (Brandes, 2007; D'Andrea, 2010). A predilection for the posterior circulation has been described (Kruit, 2004). Migraines—especially those with aura in young women—are associated with increased risk for ischemic strokes. The risk is greater in those who smoke or use combination oral contraceptives.

Migraine in Pregnancy

The prevalence of migraine headaches in the first trimester is 2 percent (Chen, 1994). Most migraineurs have improvement during pregnancy (Kvisvik, 2011). Still, migraines—usually those with an aura—occasionally appear for the first time during pregnancy. Pregnant women with preexisting migraine symptoms may have other symptoms suggestive of a more serious disorder, and new neurological symptoms should prompt a complete evaluation (Detsky, 2006; Heaney, 2010).

Although conventional thinking has been that migraine headaches do not pose increased maternal or fetal risks, several recent studies have refuted this (Allais, 2010). In these, rates of preeclampsia, gestational hypertension, preterm birth, and other cardiovascular morbidities, including ischemic stroke, were increased (Grossman, 2017; Wabnitz, 2015). Bushnell and coworkers (2009) identified an incidence of migraines during pregnancy of 185 per 100,000 deliveries. Of diagnoses associated in these gravid migraineurs, risks were significantly higher for stroke, 16-fold; myocardial infarction, fivefold; heart disease, twofold; venous thromboembolism, twofold; and preeclampsia/gestational hypertension, twofold.

Management

Data are limited regarding nonpharmacological management in pregnancy such as biofeedback techniques, acupuncture, and transcranial magnetic stimulation (Airola, 2010; Dodick, 2010). Effective medications include nonsteroidal antiinflammatory drugs (NSAIDs), and most migraine headaches respond to simple analgesics such as ibuprofen, acetaminophen, or Midrin, especially if given early.

Severe migraines are vexing for the patient and her caregivers. Multitargeted drug therapy is necessary in most cases for migraine relief (Gonzalez-Hernandez, 2014). Headaches are treated aggressively with intravenous hydration and parenteral antiemetics and opioids for immediate pain relief. Although a 2-g infusion of magnesium sulfate has gained favor in the past few years, a metaanalysis reported no benefits (Choi, 2014). Ergotamine derivatives are potent vasoconstrictors and are avoided in pregnancy because of their uterotonic effects (Briggs, 2015).

Triptans are serotonin 5-$HT_{1B/2D}$-receptor agonists that effectively relieve headaches by causing intracranial vasoconstriction (Contag, 2010). They also relieve nausea and vomiting and greatly reduce the need for analgesics. Triptans can be given as an oral tablet, injection, rectal suppository, or intranasal spray. They are best used in combination with NSAIDs (Goadsby, 2015). The greatest experience is with sumatriptan (Imitrex), and although not studied extensively in pregnancy, it appears to be safe (Briggs, 2015; Nezvalová-Henriksen, 2010). However, in one follow-up study at 36 months of children exposed to triptans in pregnancy, Wood and colleagues (2016) found neurodevelopment differences, including emotionality and activity problems.

Some women will benefit from peripheral nerve blocks, and Govindappagari and coworkers (2014) described their experiences with 13 pregnant women. For women with frequent migraine headaches, oral prophylactic therapy is warranted. Amitriptyline (Elavil), 10 to 175 mg daily; propranolol (Inderal), 40 to 120 mg daily; or metoprolol (Lopressor, Toprol), 25 to 100 mg daily, have been used with success (Contag, 2010; Goadsby, 2015; Lucas, 2009).

Cluster Headache

This rare primary headache disorder is characterized by severe unilateral lancinating pain radiating to the face and orbit, lasting 15 to 180 minutes, and occurring with autonomic symptoms and agitation. Pregnancy does not affect symptom severity. Affected women should avoid tobacco and alcohol. Acute management includes 100-percent oxygen therapy and sumatriptan given as a 6-mg dose subcutaneously (VanderPluym, 2016). If recurrent, prophylaxis is administered using a calcium-channel blocking agent.

SEIZURE DISORDERS

The Centers for Disease Control and Prevention reported that the prevalence of epilepsy in adults in 2005 was 1.65 percent—thus over 1 million American women of childbearing age are affected (Kobau, 2008). After headaches, seizures are the next most prevalent neurological condition encountered in pregnancy, and they complicate 1 in 200 births (Brodie, 1996; Yerby, 1994). Importantly, epilepsy accounted for 5 percent of maternal deaths in the United Kingdom for the 2011 to 2013 triennium (Knight, 2015).

Pathophysiology

A seizure is defined as a paroxysmal disorder of the central nervous system characterized by an abnormal neuronal discharge with or without loss of consciousness. Some identifiable causes of convulsive disorders in young adults include head trauma, alcohol- and other drug-induced withdrawals, cerebral infections, brain tumors, biochemical abnormalities, and arteriovenous malformations. A search for these is prudent with a new-onset seizure disorder in a pregnant woman. The diagnosis of idiopathic epilepsy is one of exclusion.

Epilepsy encompasses different syndromes whose cardinal feature is a predisposition to recurrent unprovoked seizures. The International League Against Epilepsy Commission on Classification and Terminology recently updated the following definitions (Fisher, 2014).

Focal Seizures

These originate in one localized brain area and affect a correspondingly localized area of neurological function. They are believed to result from trauma, abscess, tumor, or perinatal factors, although a specific lesion is rarely demonstrated. *Focal seizures without dyscognitive features* start in one region of the body and progress toward other ipsilateral areas of the body, producing tonic and then clonic movements. Simple seizures can affect sensory function or produce autonomic dysfunction or psychological changes. Cognitive function is not impaired, and recovery is rapid. *Focal seizures with dyscognitive features* are often preceded by an aura and followed by impaired awareness manifested by sudden behavioral arrest or motionless stare. Involuntary movements such as picking motions or lip smacking are common.

Generalized Seizures

These involve both brain hemispheres and may be preceded by an aura before an abrupt loss of consciousness. There is a strong hereditary component. In *generalized tonic-clonic seizures*, loss of consciousness is followed by tonic contraction of the muscles and rigid posturing, and then by clonic contractions of all extremities while the muscles gradually relax. Return to consciousness is gradual, and the patient may remain confused and disoriented for several hours. *Absence* seizures—also called *petit mal seizures*—are a form of generalized epilepsy that involve a brief loss of consciousness without muscle activity and are characterized by immediate recovery of consciousness and orientation.

Preconceptional Counseling

Women with epilepsy ideally are counseled before pregnancy and relevant points are presented also in Chapter 8 (Epilepsy). Folic acid supplementation with 0.4 mg per day is begun at least 1 month before conception. The dose is increased to 4 mg when the woman taking antiepileptic medication becomes pregnant. These medications are assessed and adjusted with a goal of monotherapy using the least teratogenic medication. If this is not feasible, then attempts are made to reduce the number of medications used and to use them at the lowest effective dose (Patel, 2016). Medication withdrawal should be considered if a woman is seizure free for 2 years or more.

Epilepsy During Pregnancy

The major pregnancy-related risks to women with epilepsy are fetal malformations and increased seizure rates. Seizure control is the main priority to avoid its attendant morbidity and mortality risks. Early studies described worsening seizure activity during pregnancy, however, this is less so now because of more effective drugs. Contemporary studies cite higher rates of seizure activity in only 20 to 30 percent of pregnant women (Mawer, 2010; Vajda, 2008). Women who are seizure free for at least 9 months before conception will likely remain so during pregnancy (Harden, 2009b).

Greater seizure frequency is often associated with decreased and thus subtherapeutic anticonvulsant serum levels, a lower seizure threshold, or both. An impressive number of pregnancy- associated alterations can result in subtherapeutic serum levels. These include nausea and vomiting, slower gastrointestinal motility, antacid use that diminishes drug absorption, pregnancy hypervolemia offset by protein binding, induction of hepatic enzymes such as cytochrome oxidases, placental enzymes that metabolize drugs, and increased glomerular filtration that hastens drug clearance. Importantly, some women discontinue medication because of teratogenicity concerns. Finally, the seizure threshold can be affected by pregnancy-related sleep deprivation and by hyperventilation and pain during labor.

Pregnancy Complications

Women with epilepsy have a small increased risk of pregnancy complications that include spontaneous abortion, hemorrhage, hypertensive disorders, preterm birth, fetal-growth restriction, and cesarean delivery (Harden, 2009b; Viale, 2015). Importantly, MacDonald (2015) also reports a tenfold higher maternal death rate, and, as mentioned earlier, epilepsy accounted for 5 percent of maternal deaths in the United Kingdom. Postpartum depression rates are also reportedly higher in epileptic women (Turner, 2009). Finally, children of epileptic mothers have a 10-percent risk of developing a seizure disorder.

Embryofetal Malformations

For years, it was difficult to separate effects of epilepsy from those of its therapy as the primary cause of fetal malformations. As discussed in Chapter 8 (Epilepsy), it is now believed that untreated epilepsy is not associated with an elevated fetal malformation rate (Thomas, 2008). That said, the fetus of an epileptic mother who takes certain anticonvulsant medications has an indisputably greater risk for congenital malformations. Moreover, monotherapy is associated with a lower birth defect rate compared with multiagent therapy. Thus, if necessary, increasing monotherapy dosage is at least initially preferable to adding another agent (Buhimschi, 2009).

Specific drugs, when given alone, increase the malformation rate (Chap. 12, Antiepileptic Medications). Some of these are listed in Table 60-2. Phenytoin and phenobarbital increase the major malformation rate two- to threefold above baseline (Perucca, 2005; Thomas, 2008). Valproate is a particularly potent teratogen, which has a dose-dependent effect and raises the malformation risk four- to eightfold (Eadie, 2008; Klein, 2014; Wyszynski, 2005). Valproate is also associated with

lower cognitive performance (Kasradze, 2017). In general, with polytherapy, the risk rises with each drug added. A metaanalysis of 31 studies found lamotrigine and levetiracetam to carry the lowest risk of malformations (Weston, 2016).

TABLE 60-2

Teratogenic Effects of Common Anticonvulsant Medications

Drug (Brand Name)	Abnormalities Described	Affected	Embryofetal Risks[a]
Valproate (Depakote)	Neural-tube defects, clefts, cardiac anomalies; associated developmental delay	10% with monotherapy; higher with polytherapy	Yes
Phenytoin (Dilantin)	Fetal hydantoin syndrome—craniofacial anomalies, fingernail hypoplasia, growth deficiency, developmental delay, cardiac anomalies, clefts	5–11%	Yes
Carbamazepine; oxcarbazepine (Tegretol; Trileptal)	Fetal hydantoin syndrome, as above; spina bifida	1–2%	Yes
Phenobarbital	Clefts, cardiac anomalies, urinary tract malformations	10–20%	Suggested
Lamotrigine (Lamictal)	Increased risk for clefts (Registry data)	Up to 1% (4- to 10-fold higher than expected)	Suggested
Topiramate (Topamax)	Clefts	2–3% (15- to 20-fold higher than expected)	Suggested
Levetiracetam (Keppra)	Theoretical—skeletal abnormalities; impaired growth in animals	Preliminary observations	Suggested

[a]Risk categories from Briggs, 2015; Food and Drug Administration, 2011; Harden, 2009b; Holmes, 2008; Hunt, 2008.

Management in Pregnancy

The American Academy of Neurology and the American Epilepsy Society have guidelines regarding treatment in pregnant women (Harden, 2009a–c). The major goal is seizure prevention. To accomplish this, treatment for nausea and vomiting is provided, seizure-provoking stimuli are avoided, and medication compliance is emphasized. The fewest necessary anticonvulsants are given at the lowest dosage effective for seizure control. Although some providers routinely monitor serum drug levels, these concentrations may be unreliable because of altered protein binding. Free or unbound drug levels, although perhaps more accurate, are not widely available. Importantly, there is no evidence that such monitoring improves seizure control (Adab, 2006). For these reasons, drug levels may be most informative if measured following seizures or if noncompliance is suspected.

For women taking anticonvulsant drugs, a targeted sonographic examination at midpregnancy is recommended by some to search for anomalies. Testing to assess fetal well-being is generally not indicated for women with uncomplicated epilepsy.

For women desiring to breastfeed, data regarding the safety of the various anticonvulsant medications are limited. That said, no obvious deleterious effects, such as long-term cognitive issues, have been reported (Briggs, 2015; Harden, 2009c). Of birth control methods, oral contraceptive pill failure rates are higher with some of the anticonvulsant agents, especially lamotrigine. Thus, other more reliable methods should be considered (Chap. 38, Introduction).

CEREBROVASCULAR DISEASES

Abnormalities of the cerebrovascular circulation include strokes—both ischemic and hemorrhagic, as well as anatomical anomalies, such as arteriovenous malformations and aneurysms. Cerebral ischemia is caused by reduction in blood flow that lasts longer than several seconds. Early, neurological symptoms may manifest. After a few minutes, however, infarction often follows. Hemorrhagic stroke is caused by bleeding directly into or around the brain. It produces symptoms by its mass effect, by toxic effects of blood, or by increasing intracranial pressure. Of strokes in pregnant women, roughly half are ischemic and the other half hemorrhagic (Zofkie, 2018).

The current obesity endemic in this country, along with concomitant increases in rates of heart disease, hypertension, and diabetes, has increased the prevalence of strokes (Centers for Disease Control and Prevention, 2012). Women have higher lifetime risk of stroke than men and greater associated mortality rates (Martínez-Sánchez, 2011; Roger, 2012). Moreover, pregnancy increases the immediate and lifetime risk of both ischemic and hemorrhagic stroke (Jamieson, 2010; Jung, 2010).

Stroke is relatively uncommon in pregnant women, occurring in 10 to 40 per 100,000 births, but it contributes disparately to maternal mortality rates (Leffert, 2016; Miller, 2016; Yoshida, 2017). The incidence is rising as measured by pregnancy-related hospitalizations for stroke (Callaghan, 2008; Kuklina, 2011). Importantly, most

are associated with hypertensive disorders or heart disease. Of the pregnancy-related mortality rate in the United States, 6.6 percent is due to cerebrovascular accidents, and 7.4 percent is associated with preeclampsia (Creanga, 2017). Of maternal deaths after 42 days postpartum, 9.8 percent were attributable to cerebrovascular accidents.

Risk Factors

Most strokes in pregnancy manifest either during labor and delivery or in the puerperium. In a study of 2850 pregnancy-related strokes, approximately 10 percent developed antepartum, 40 percent intrapartum, and almost 50 percent postpartum (James, 2005). In contrast, Leffert (2016) reports a timing of 45 percent antepartum, 3 percent intrapartum, and 53 percent postpartum in 145 women. Several risk factors—unrelated and related to pregnancy—have been reported from studies that included more than 10 million pregnancies. These include age; migraines, hypertension, obesity, and diabetes; cardiac disorders such as endocarditis, valvular prostheses, and patent foramen ovale; and smoking. Those related to pregnancy include hypertensive disorders, gestational diabetes, obstetrical hemorrhage, and cesarean delivery. *By far, the most common risk factors are pregnancy-associated hypertensive disorders.* A third of strokes are associated with gestational hypertension, and hypertensive women compared with normotensive counterparts have a three- to eightfold greater risk of stroke (Scott, 2012; Wang, 2011). Women with preeclampsia undergoing general anesthesia may be at higher risk of stroke compared with those given neuraxial anesthesia (Huang, 2010). Another risk factor for peripartum stroke is cesarean delivery, which raises the risk 1.5-fold compared with vaginal delivery (Lin, 2008).

Pregnancy-induced effects on cerebrovascular hemodynamics include enhanced autoregulation that maintains blood flow despite changes in systemic blood pressure (van Teen, 2016). Although cerebral blood flow *decreases* by 20 percent from midpregnancy until term, it *increases* significantly with gestational hypertension (Zeeman, 2003, 2004b). Such hyperperfusion at least intuitively would be dangerous for women with certain vascular anomalies.

Ischemic Stroke

Acute occlusion or embolization of an intracranial blood vessel causes cerebral ischemia, which may result in death of brain tissue (Fig. 60-2). The more common associated conditions and etiologies of ischemic stroke are shown in Table 60-3. A *transient ischemic attack (TIA)* is caused by reversible ischemia, and symptoms usually last less than 24 hours. Approximately 10 percent of these patients have a stroke by 1 year (Amarenco, 2016). Patients with a stroke usually have a sudden onset of severe headache, hemiplegia or other neurological deficits, or occasionally seizures. In contrast, focal neurological symptoms accompanied by an aura usually signify a first-episode migraine (Liberman, 2008).

TABLE 60-3

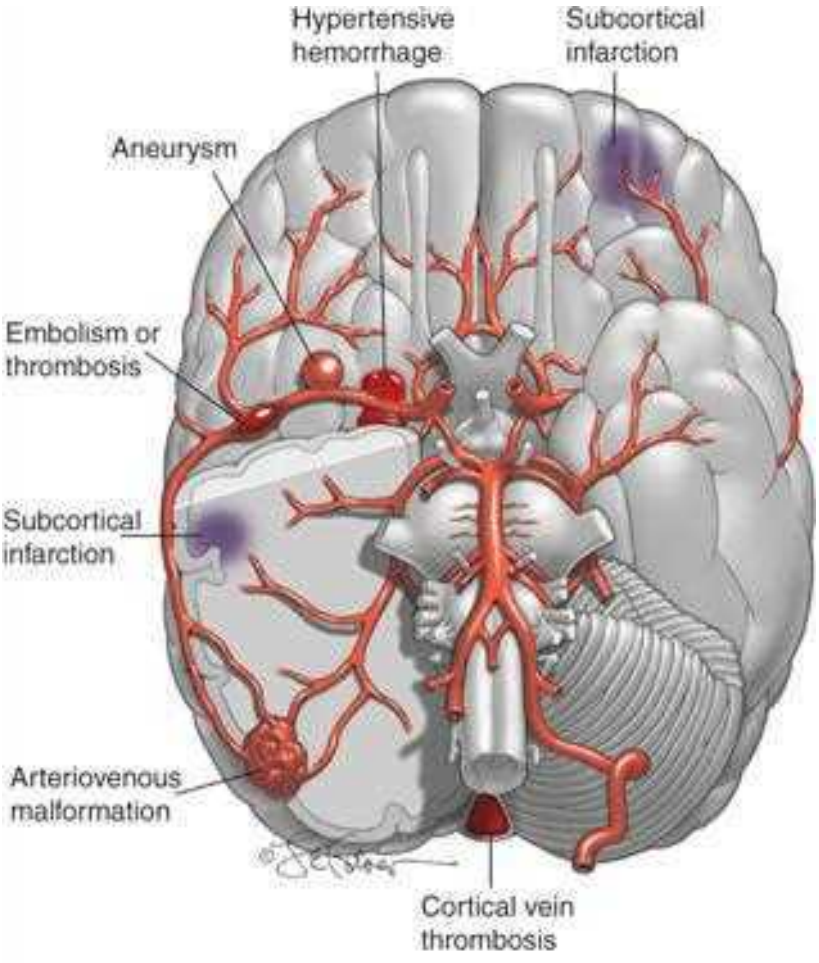
Some Associated Disorders or Causes of Ischemic and Hemorrhagic Strokes During Pregnancy or the Puerperium

Ischemic Stroke	Hemorrhagic Stroke
Preeclampsia syndrome	Chronic hypertension
Arterial thrombosis	Preeclampsia syndrome
Venous thrombosis	Arteriovenous malformation
Lupus anticoagulant	Saccular aneurysm
Antiphospholipid antibodies	Angioma
Thrombophilias	Cocaine, methamphetamines
Migraine induced	Vasculopathy
Paradoxical embolus	
Cardioembolic	
Sickle hemoglobinopathy	
Arterial dissection	
Vasculitis	
Moyamoya disease	
Cocaine, amphetamines	

From Smith, 2015; Yager, 2012.

FIGURE 60-2

Illustrations of a brain showing various types of strokes seen in pregnancy: (1) subcortical infarction (preeclampsia), (2) hypertensive hemorrhage, (3) aneurysm, (4) embolism or thrombosis in middle cerebral artery, (5) arteriovenous malformation, and (6) cortical vein thrombosis.



Evaluation of an ischemic stroke includes echocardiography and cranial imaging with CT, MR, or angiography. Serum lipids are measured with the caveat that their values are distorted by normal pregnancy (Appendix, Serum and Blood Constituents). Tests to detect antiphospholipid antibodies and lupus anticoagulant are performed. These underlie up to a third of ischemic strokes in otherwise healthy young women (Chap. 59, Antiphospholipid Syndrome). Also, sickle-cell syndromes are evaluated when indicated (Buonanno, 2016).

With a thorough evaluation, most causes of embolism can be identified, although treatment is not always available. Some of these include cardiac- associated embolism, vasculitis, or vasculopathy such as Moyamoya disease (Ishimori, 2006; Miyakoshi, 2009; Simolke, 1991). Outcomes of embolic strokes were reported to be favorable and similar to those of nonpregnant women (Leffert, 2016). Thrombolysis for ischemic stroke during pregnancy has been reported (Tversky, 2016).

Preeclampsia Syndrome

In reproductive-age women, a significant proportion of pregnancy-related ischemic strokes are caused by gestational hypertension and preeclampsia (Jeng, 2004; Miller, 2016). As shown in Figure 60-2, areas of subcortical perivascular edema and petechial hemorrhage may progress to cerebral infarction (Aukes, 2007, 2009; Zeeman, 2004a). Although these are usually clinically manifest by an eclamptic convulsion, a few women will suffer a symptomatic stroke from a larger cortical infarction (Chap. 40, Eclampsia).

Other conditions with findings similar to preeclampsia include *thrombotic microangiopathies* (Chap. 56, Thrombotic Microangiopathies) and the *reversible cerebral vasoconstriction syndrome* (Chap. 40, Long-Term Consequences). The latter, also termed *postpartum angiopathy,* can cause extensive cerebral edema with necrosis and widespread infarction with areas of hemorrhage (Edlow, 2013; Katz, 2014; Miller, 2016).

Cerebral Embolism

These strokes usually involve the middle cerebral artery (see Fig. 60-2). The diagnosis can be made with confidence only after thrombosis and hemorrhage have been excluded and is more certain if an embolic source is identified. Hemorrhage may be more difficult to exclude because embolization and thrombosis are both followed by hemorrhagic infarction. Paradoxical embolism is an uncommon cause, even considering that more than a fourth of adults have a patent foramen ovale through which right-sided venous thromboemboli are deported (Scott, 2012). Foraminal closure may not improve outcomes in these patients, however, this

procedure has been performed during pregnancy (Dark, 2011). Assorted cardioembolic causes of stroke include arrhythmias—especially atrial fibrillation, valvular lesions, mitral valve prolapse, mural thrombus, infective endocarditis, and peripartum cardiomyopathy.

Management of embolic stroke in pregnancy consists of supportive measures and antiplatelet therapy. Thrombolytic therapy and anticoagulation in pregnancy are controversial issues (Li, 2012).

Cerebral Artery Thrombosis

Most thrombotic strokes affect older individuals and are caused by atherosclerosis, especially of the internal carotid artery. Many are preceded by one or more TIAs. Thrombolytic therapy with a *recombinant tissue plasminogen activator (rt-PA)* is recommended. *Alteplase* is one of these and given within the first 3-hour window if there is measurable neurological deficit and if neuroimaging has excluded hemorrhage. This recombinant enzyme can be used in pregnancy. A principal risk is hemorrhagic transformation of an ischemic stroke in 3 to 5 percent of treated patients (Smith, 2015; van der Worp, 2007).

Cerebral Venous Thrombosis

In one study in the United States, 7 percent of cerebral venous thromboses were associated with pregnancy (Wasay, 2008). But, in the Nationwide Inpatient Sample of more than 8 million deliveries, James and associates (2005) reported that venous thrombosis caused only 2 percent of pregnancy-related strokes (Saposnik, 2011). There are numerous predisposing causes, and for gravidas, late pregnancy and the puerperium are times of greatest risk.

Thrombosis of the lateral or superior sagittal venous sinus usually occurs in the puerperium and often in association with preeclampsia, sepsis, or thrombophilia (see Fig. 60-2). It is more common in patients with inherited thrombophilias or antiphospholipid antibodies (Chaps. 52, Inherited Thrombophilias and 59, Antiphospholipid Syndrome). Headache is the most frequent presenting symptom, neurological deficits are common, and up to a third of patients have convulsions (Wasay, 2008). The diagnosis is made using MR venography (Saposnik, 2011).

Management includes anticonvulsants for seizures, and although heparinization is recommended by most, its efficacy is controversial (Saposnik, 2011; Smith, 2015). Antimicrobials are given if there is septic thrombophlebitis, and fibrinolytic therapy is reserved for those women failing systemic anticoagulation. The acute prognosis for venous thrombosis in pregnant women is better than in nonpregnant subjects, and mortality rates are less than 10 percent (McCaulley, 2011).

In women with a prior cerebral venous thrombosis, one systematic review found only one recurrence in 217 pregnancies and five noncerebral venous thrombotic events in 186 pregnancies (Aguiar de Sousa, 2016). In a study of 52 women on prophylactic anticoagulation with prior cerebral venous thrombosis, there were no cases of recurrent thrombosis or bleeding, however 24 percent had late obstetrical complications (Martinelli, 2016).

Recurrence Risk of Ischemic Stroke

Women with prior ischemic stroke have a low risk for recurrence during a subsequent pregnancy unless a specific, persistent cause is identified. During a 5-year follow-up of 373 women with arterial ischemic strokes, there were 187 pregnancies in 125 women. Thirteen women had a recurrent ischemic stroke, and of these, only two were associated with pregnancy. The authors concluded that the risk of stroke recurrence is low and a previous ischemic stroke is not a contraindication to pregnancy (Lamy, 2000). In one study of 1770 nonpregnant women with antiphospholipid-related ischemic stroke, investigators reported no difference in the recurrence risk as long as preventative treatment was given with warfarin or aspirin (Levine, 2004).

Currently, no firm guidelines define prophylaxis in pregnant women with a stroke history (Helms, 2009). The American Heart Association stresses the importance of controlling risk factors such as hypertension and diabetes (Furie, 2011). Women with antiphospholipid syndrome or certain cardiac conditions should be considered for prophylactic anticoagulation as discussed in Chapter 49 (Surgically Corrected Heart Disease) and 52 (Acquired Thrombophilias).

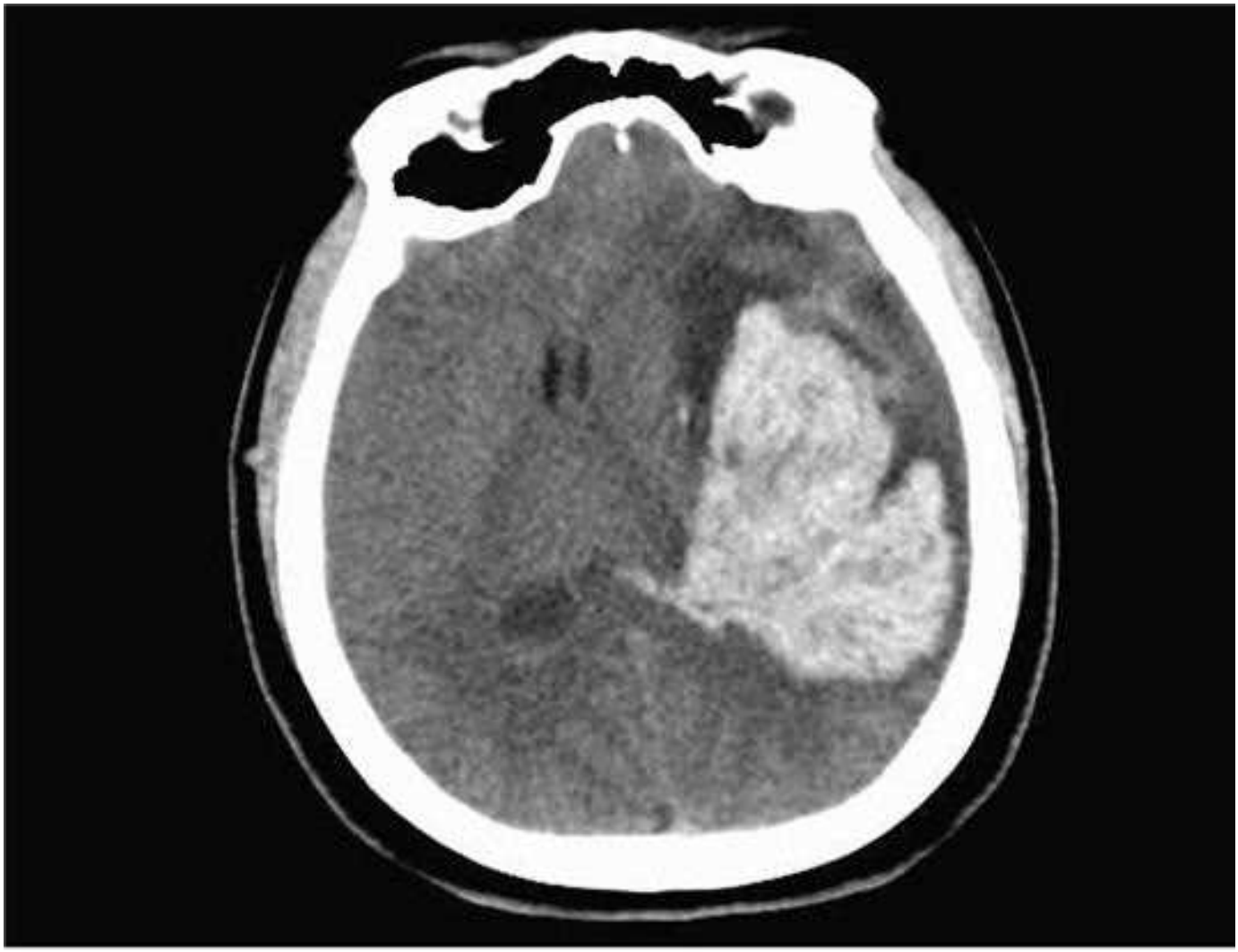
Hemorrhagic Stroke

The two distinct categories of spontaneous intracranial bleeding are intracerebral and subarachnoid hemorrhage. The symptoms of a hemorrhagic stroke are similar to those of an ischemic stroke, and their differentiation is only possible with CT or MR imaging (Morgenstern, 2010; Smith, 2015).

Intracerebral Hemorrhage

Bleeding into the brain parenchyma most often is caused by spontaneous rupture of small vessels previously damaged by chronic hypertension (see Fig. 60-2). Thus, pregnancy-associated hemorrhagic strokes such as the one shown in Figure 60-3 are often associated with chronic hypertension and superimposed preeclampsia (Cunningham, 2005; Martin, 2005). Because of its location, this type of hemorrhage has much higher morbidity and mortality rates than does subarachnoid hemorrhage (Smith, 2015). Pressure-induced rupture causes bleeding into the putamen, thalamus, adjacent white matter, pons, and cerebellum. In the 28 women described by Martin and associates (2005), half died and most survivors had permanent disabilities. This cautions for the importance of proper management for gestational hypertension—especially systolic hypertension—to prevent cerebrovascular pathology (Chap. 40, Management Considerations).

FIGURE 60-3
A 37-year-old gravida with intrapartum eclampsia at term. A noncontrast computed tomography axial head image demonstrates a large intraparenchymal hemorrhage.



Subarachnoid Hemorrhage

In a study of 639 cases of pregnancy-related subarachnoid hemorrhage from the Nationwide Inpatient Sample, the incidence was 5.8 per 100,000 pregnancies, with half occurring postpartum (Bateman, 2012). A remarkably similar incidence was reported in Japanese women (Yoshida, 2017). These bleeds are more likely caused by an underlying cerebrovascular malformation in an otherwise normal patient (see Fig. 60-2). Ruptured saccular or "berry" aneurysms cause 80 percent of all subarachnoid hemorrhages. The remaining cases are caused by a ruptured arteriovenous malformation, coagulopathy, angiopathy, venous thrombosis, infection, drug abuse, tumors, or trauma. Such cases are uncommon, and a ruptured aneurysm or angioma or bleeding from a vascular malformation has an incidence of 1 in 75,000 pregnancies. Although this frequency is not different from that in the general population, the mortality rate during pregnancy is reported to be as high as 35 percent (Yoshida, 2017).

Intracranial Aneurysm.

Approximately 1 to 2 percent of adults have this lesion (Lawton, 2017). Fortunately, only a small percentage rupture. The rate approximates 0.1 percent for aneurysms <10 mm and 1 percent for those >10 mm (Smith, 2015). Most aneurysms identified during pregnancy arise from the circle of Willis, and in 20 percent of case, there are multiple lesions. Pregnancy does not raise the risk for aneurysmal rupture. However, because of their high prevalence, they are more likely to cause subarachnoid bleeding than other etiologies (Hirsch, 2009; Tiel Groenestege, 2009). A systematic review of 44 women with 50 aneurysms in pregnancy reported that 72 percent ruptured during pregnancy, and 78 percent of these did so during the third trimester (Barbarite, 2016). This proclivity for rupture late in pregnancy was also reported by Yoshida and colleagues (2017).

The cardinal symptom of a subarachnoid hemorrhage from an aneurysm rupture is sudden severe headache that is accompanied by visual changes, cranial nerve abnormalities, focal neurological deficits, and altered consciousness. Patients typically have signs of meningeal irritation, nausea and vomiting, tachycardia, transient hypertension, low-grade fever, leukocytosis, and proteinuria. Prompt diagnosis and treatment may prevent potentially lethal complications. The American Heart Association recommends noncontrast cranial CT imaging as the first diagnostic test, although MR imaging may be superior (Connolly, 2012; Smith, 2015).

Treatment of subarachnoid hemorrhage includes bed rest, analgesia, and sedation, with neurological monitoring and strict blood pressure control. Repair of a potentially accessible aneurysm during pregnancy depends in part on the risk of recurrent hemorrhage versus the surgical risks. At least in nonpregnant patients, the risk of subsequent bleeding with conservative treatment is 20 to 30 percent for the first month and then 3 percent per year. The risk of rebleeding is highest within the first 24 hours, and recurrent hemorrhage leads to death in 70 percent.

Early repair after the sentinel hemorrhage is done by surgical clipping of the aneurysm. Also, an endovascular coil can be placed using fluoroscopic angiography, while attempting to limit fetal radiation exposure. Barbarite and colleagues (2016) report lower complication rates with coil embolization than clipping. For unruptured aneurysms, surgical management resulted in a third fewer complications than no treatment. For gravidas remote from term, repair without hypotensive anesthesia seems optimal. For women near term, cesarean delivery followed by aneurysm repair is a consideration, and we have successfully done this in several cases.

For aneurysms repaired either before or during pregnancy, most allow vaginal delivery if labor ensues remote from aneurysmal repair. Problems arise in defining "remote," and although some recommend 2 months, the time for complete healing is unknown. For women who survive subarachnoid hemorrhage, but in whom surgical repair is not done, we agree with Cartlidge (2000) and recommend against bearing down—put another way, we favor cesarean delivery.

Arteriovenous Malformations.

These are congenital focal abnormal conglomerations of dilated arteries and veins with subarteriolar disorganization (see Fig. 60-2). They lack capillaries and have resultant arteriovenous shunting. Although unclear, the risk of bleeding may rise with gestational age. When arteriovenous malformations (AVMs) bleed, half do so into the subarachnoid space, whereas half are intraparenchymal with subarachnoid extension (Smith, 2015). They are uncommon and are estimated to occur in 0.01 percent of the general population. Of 65 identified cases of AVM in pregnancy, 83 percent ruptured during pregnancy or postpartum, and more than 80 percent of these ruptured in the second or third trimester. Hemorrhage upon presentation is associated with poor maternal outcome (Lu, 2016).

Bleeding does not appear to be more likely during pregnancy. Although these malformations are correspondingly rare during pregnancy, AVM bleeding accounted for 17 percent of hemorrhagic strokes in one study (Yoshida, 2017). At Parkland Hospital in a 33-year period during which there were about 466,000 births, 57 women had a CVA, and five of these strokes were due to a bleeding AVM (Simolkie, 1991; Zofkie, 2018).

Treatment of AVMs in nonpregnant patients is largely individualized. No consensus guides whether all accessible lesions should be resected. Factors include AVM symptoms; its anatomy and size; presence of an associated aneurysm, which is found in up to 60 percent of cases; and especially, prior AVM bleeding. After hemorrhage, the risk of recurrent bleeding in unrepaired lesions is 6 to 20 percent within the first year, and 2 to 4 percent per year thereafter (Friedlander, 2007; Smith, 2015). The mortality rate with a bleeding AVM is 10 to 20 percent. In pregnancy, the decision to operate is usually based on neurosurgical considerations, and Friedlander (2007) recommends strong consideration for treatment if bleeding occurs. Because of the high risk of recurrent hemorrhage from an unresected or inoperable lesion, we favor cesarean delivery.

DEMYELINATING OR DEGENERATIVE DISEASES

The *demyelinating diseases* are neurological disorders characterized by immune-mediated focal or patchy destruction of myelin sheaths accompanied by an inflammatory response. The *degenerative diseases* are multifactorial and are characterized by progressive neuronal death.

Multiple Sclerosis

In the United States, multiple sclerosis (MS) is second only to trauma as a cause of neurological disability in middle adulthood (Hauser, 2015b). The disease affects women twice as often as men, and it usually begins in the 20s and 30s. The familial recurrence rate of MS is 15 percent, and the incidence in offspring is increased 15-fold. Studying California deliveries, Fong and colleagues (2018) reported that 0.03 percent of deliveries were complicated by MS between 2001 and 2009.

The demyelinating characteristic of this disorder results predominately from T cell-mediated autoimmune destruction of oligodendrocytes that synthesize myelin. There is a genetic susceptibility and likely an environmental trigger such as exposure to certain bacteria and viruses. Of these, *Chlamydophila pneumoniae,* human herpesvirus 6, or Epstein-Barr virus are implicated (Frohman, 2006; Goodin, 2009).

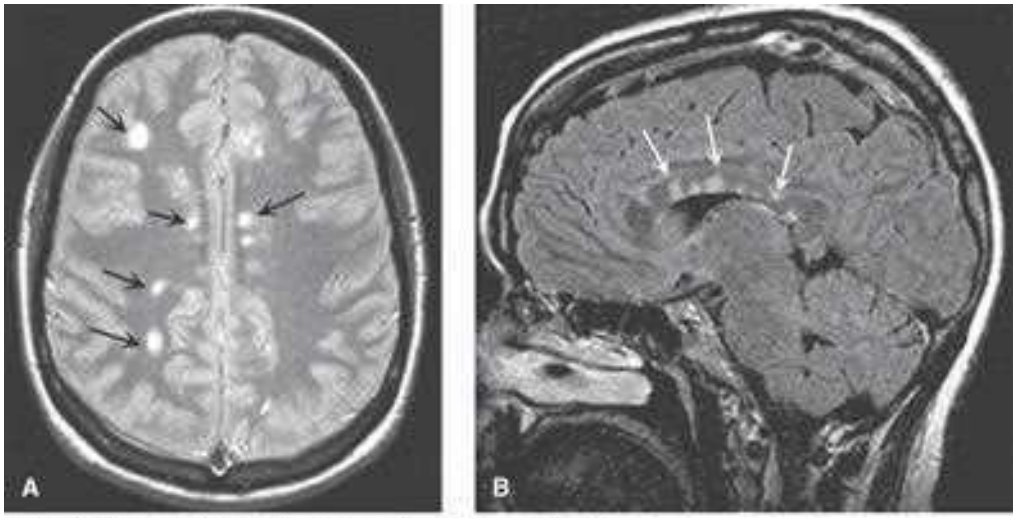
There are four clinical types of MS:

1. *Relapsing-remitting MS* accounts for initial presentation in 85 percent of affected individuals. With it, unpredictable recurrent episodes of focal or multifocal neurological dysfunction usually are followed by full recovery. Over time, however, relapses lead to persistent deficits.
2. *Secondary progressive MS* disease is relapsing-remitting disease that begins to pursue a progressive downhill course after each relapse. All patients likely develop this type eventually.
3. *Primary progressive MS* accounts for 15 percent of cases. With it, disability gradually progresses from the time of initial diagnosis.
4. *Progressive-relapsing MS* refers to primary progressive MS with apparent relapses.

Classic findings of MS include sensory loss, visual symptoms from optic neuritis, weakness, paresthesias, and a host of other neurological symptoms. Almost 75 percent of women with isolated optic neuritis develop MS within 15 years. Clinical diagnosis is confirmed by MR imaging and cerebrospinal fluid analysis. In greater than 95 percent of cases, MR imaging shows characteristic multifocal white matter plaques that represent discrete areas of demyelination (Fig. 60-4). Their appearance and extent are less helpful for predicting treatment response. Similarly, identification of serum antibodies against myelin oligodendrocyte glycoprotein and myelin basic protein is not predictive of recurrent disease activity (Kuhle, 2007).

FIGURE 60-4

Magnetic resonance cranial images from a woman with multiple sclerosis. **A.** T2-weighted axial image shows bright signal abnormalities in white matter, typical for multiple sclerosis. **B.** Sagittal T2-FLAIR image shows hyperintense areas within the corpus callosum that are representative of demyelination in multiple sclerosis. (Reproduced with permission from Hauser SL, Goodin DS: Multiple Sclerosis and other demyelinating diseases. In Kasper DL, Fauci AS, Hauser SL, et al (eds): Harrison's Principles of Internal Medicine, 19th ed. McGraw-Hill, New York, 2015b.)



Effects of Pregnancy

The *PR*egnancy *I*n *M*ultiple *S*clerosis—*PRIMS*—study was a European prospective multicenter study in which 254 pregnancies were described (Vukusic, 2006). Relapse risk was reduced 70 percent during pregnancy, but with a significantly greater relapse rate postpartum. This may be related to higher pregnancy-induced numbers of T-helper lymphocytes and an increased T2/T1 ratio (Airas, 2008). In a metaanalysis of women with more than 1200 pregnancies complicated by MS, their relapse rate was 0.4 per year before pregnancy; 0.26 per year during pregnancy; and this increased to 0.7 per year after delivery (Finkelsztejn, 2011). Bove and associates (2014) reached similar conclusions after a systematic review. Factors associated with postpartum relapse include a high relapse rate before pregnancy, relapses during pregnancy, and a high MS disability score (Portaccio, 2014; Vukusic, 2006). Breastfeeding has no apparent effect on postpartum relapses (Hellwig, 2015; Portaccio, 2011).

Effects of Multiple Sclerosis on Pregnancy

With uncomplicated disease, there are usually no adverse effects on pregnancy outcome (Bove, 2014). Some women may become fatigued more easily, those with bladder dysfunction are predisposed to urinary infection, and women with spinal lesions at or above T_6 are at risk for autonomic dysreflexia. In one study of 449 pregnancies in affected women, the labor induction rate was higher, and second-stage labor was longer (Dahl, 2006). The greater induction rate and elective operations contributed to the overall higher cesarean delivery rate. In an analysis of 649 affected women, the mean birthweight was lower but the perinatal mortality rate was similar compared with that of controls (Dahl, 2005). Other studies have corroborated that MS does not significantly affect obstetrical and neonatal outcomes (Finkelsztejn, 2011; Fong, 2018).

Management in Pregnancy

Goals are to arrest acute or initial attacks, employ disease-modifying agents, and provide symptomatic relief. Some treatments may need to be modified during pregnancy. Acute or initial attacks are treated with high-dose intravenous methylprednisolone—500 to 1000 mg daily for 3 to 5 days, followed by oral prednisone for 2 weeks. Plasma exchange may be considered. Symptomatic relief can be provided by analgesics; carbamazepine, phenytoin, or amitriptyline for neurogenic pain; baclofen for spasticity; α_2-adrenergic blockade for bladder neck relaxation; and cholinergic and anticholinergic drugs to stimulate or inhibit bladder contractions.

Several disease-modifying therapies can be used for relapsing MS or for exacerbations. Examples include interferons β1a (Rebif), β1b (Betaseron), and glatiramer acetate (Copaxone), which lower relapse rates by a third (Rudick, 2011). Data concerning safety in pregnancy are limited but overall reassuring (Amato, 2010; Salminen, 2010). In clinical trials, natalizumab (Tysabri), an α_4-integrin antagonist, especially when combined with interferon β1a, significantly reduced MS clinical relapse rates (Polman, 2006; Rudick, 2006). In a review of 35 pregnancies, first-trimester drug exposure did not worsen outcomes (Hellwig, 2011). If these drugs are used in pregnancy, the neonate should be monitored for thrombocytopenia and anemia (Alroughani, 2016).

Fetal exposure in 89 pregnancies to fingolimod (Gilenya), another immune-modulating drug, was associated with six fetal malformations and nine spontaneous losses. Because of this and associated animal teratogenicity, its use in pregnancy is not recommended. Due to its prolonged persistence, contraception is recommended for 2 months after drug cessation (Alroughani, 2016; Karlsson, 2014).

Prevention of relapses postpartum is afforded by treatment with intravenous immunoglobulin (IVIG), given in a dose of 0.4 g/kg daily for 5 days during weeks 1, 6, and 12 (Argyriou, 2008).

Huntington Disease

This adult-onset neurodegenerative disease stems from an autosomal dominant expanded CAG trinucleotide repeat within the Huntington gene on chromosome 4. It is characterized by choreoathetotic movements, progressive dementia, and psychiatric manifestations. Because the mean age of onset is 40 years, Huntington

disease rarely complicates pregnancy. Prenatal diagnosis is discussed in Chapter 14 (Carrier Screening for Genetic Disorders). Prenatal screening is controversial, and because this usually is a late-onset adult disease, extensive counseling is important (Schulman, 2015).

Myasthenia Gravis

This autoimmune-mediated neuromuscular disorder affects approximately 1 in 7500 persons. It is more common in women, and its incidence peaks in their 20s and 30s. The etiology is unknown, but genetic factors likely play a role. Most patients demonstrate antibodies to the acetylcholine receptor, although 10 to 20 percent are seronegative (Drachman, 2015). The latter often have antibodies to muscle-specific tyrosine kinase (MuSK), which regulates assembly of the acetylcholine receptor subunits at the neuromuscular junction (Pal, 2011).

Cardinal features of myasthenia are weakness and easy fatigability of facial, oropharyngeal, extraocular, and limb muscles. Deep tendon reflexes are preserved. Cranial muscles are involved early and disparately, and diplopia and ptosis are common. Facial muscle weakness causes difficulty in smiling, chewing, and speaking. In 85 percent of patients, the weakness becomes generalized. Other autoimmune diseases may coexist, and hypothyroidism should be excluded. The clinical course is marked by exacerbations and remissions, especially when it first becomes clinically apparent. Remissions are not always complete and are seldom permanent. Systemic diseases, concurrent infections, and even emotional upset may precipitate exacerbations, of which there are three types:

1. *Myasthenic crises*—characterized by severe muscle weakness, inability to swallow, and respiratory muscle paralysis.
2. *Refractory crises*—characterized by the same symptoms but unresponsive to the usual therapy.
3. *Cholinergic crises*—excessive cholinergic medication leads to nausea, vomiting, muscle weakness, abdominal pain, and diarrhea.

All three of these can be life threatening, but a refractory crisis is a medical emergency. Those with bulbar myasthenia are at particular risk because they may be unable to swallow or even ask for help.

Management

Myasthenia is manageable but not curable. Oral pyridostigmine is the first-line treatment. Thymectomy is recommended but postponed until after pregnancy (Sanders, 2016). Anticholinesterase medications improve symptoms by impeding acetylcholine degradation but seldom produce normal muscle function. Ironically, overdose is manifest by increased weakness—*cholinergic crisis*—that may be difficult to differentiate from myasthenic symptoms. Most of those refractory to anticholinesterase therapy respond to immunosuppressive therapy with glucocorticoids, azathioprine, or cyclosporine in pregnancy. When short-term, rapid clinical improvement is needed—such as for a surgical procedure or a myasthenic crisis—high-dose IVIG or plasma exchange is usually effective (Barth, 2011; Cortese, 2011; Sanders, 2016).

Myasthenia and Pregnancy

Because the greatest period of risk is within the first year following diagnosis, postponing pregnancy until there is sustained improvement is reasonable. Antepartum management of myasthenia includes close observation with liberal rest and prompt treatment of infections (Heaney, 2010; Kalidindi, 2007). Women in remission who become pregnant while taking corticosteroids or azathioprine should continue these. Thymectomy has been successfully performed during pregnancy in refractory cases (Ip, 1986). Acute onset of myasthenia or its exacerbation demands prompt hospitalization and supportive care. Plasmapheresis and high-dose IVIG are options for emergency situations (Drachman, 2015).

Although pregnancy does not appear to affect the overall course of myasthenia, fatigue common to most pregnancies may be exacerbated, and the expanding uterus may compromise respiration. Maternal hypotension or hypovolemia are ideally avoided as they can trigger crises. The clinical course of myasthenia during pregnancy is unpredictable, and frequent hospitalizations are the norm. Up to a third of women have worsening myasthenia during pregnancy, and exacerbations occur equally in all three trimesters (Djelmis, 2002; Podciechowski, 2005). In women with stable disease, most will remain stable throughout pregnancy but likely worsen in the first few months postpartum (Sanders, 2016).

Myasthenia gravis has no significant adverse effects on pregnancy outcomes (Wen, 2009). Preeclampsia is a concern because magnesium sulfate may precipitate a severe myasthenic crisis (Hamaoui, 2009; Heaney, 2010). Although phenytoin use is also problematic in this regard, its adverse effects are less troublesome. Thus, many choose it for neuroprophylaxis in women with severe preeclampsia.

Because smooth muscle is unaffected, most women have normal labor. Oxytocin is given for the usual indications, and cesarean delivery is reserved for obstetrical indications. Narcotics may cause respiratory depression, and close observation and respiratory support are essential during labor and delivery. Curariform drugs are avoided—examples include magnesium sulfate discussed above, muscle relaxants used with general anesthesia, and aminoglycosides. Neuraxial analgesia is accomplished with amide-type local agents. Regional analgesia is preferred unless there is significant bulbar involvement or respiratory compromise (Almeida, 2010; Blichfeldt-Lauridsen, 2012). During second-stage labor, some women may have impaired voluntary expulsive efforts that may warrant operative vaginal delivery.

Neonatal Effects

As discussed above, 80 percent of mothers with myasthenia gravis have anti-acetylcholine-receptor immunoglobulin G (IgG) antibodies. These and anti-MuSK antibodies cross transplacentally, and the fetus can be affected. Poor fetal swallowing may yield hydramnios (Heaney, 2010). Similarly, 10 to 20 percent of neonates manifest myasthenia symptoms (Jovandaric, 2016). Transient symptoms usually include a feeble cry, poor suckling, and respiratory distress. Symptoms usually respond to cholinesterase inhibitors and resolve within a few weeks as maternal IgG antibodies clear.

NEUROPATHIES

Peripheral neuropathy is a general term used to describe disorders of peripheral nerve(s) from various sources. *Polyneuropathies* can be axonal or demyelinating as well as acute, subacute, or chronic (Amato, 2015). These are often associated with systemic diseases such as diabetes, with drug or environmental toxin exposure, or with genetic disease.

Mononeuropathies are relatively common in pregnancy and signify focal involvement of a single nerve trunk. These imply local causation such as trauma, compression, or entrapment. Traumatic pudendal, obturator, femoral, and common fibular mononeuropathies are usually caused by childbirth and are discussed in Chapter 36 (Pain, Mood, and Cognition).

Guillain-Barré Syndrome

In 75 percent of cases, this acute demyelinating polyradiculoneuropathy has clinical or serological evidence for an acute infection. Commonly associated are infections with *Campylobacter jejuni*, cytomegalovirus, Zika virus, and Epstein-Barr virus; surgical procedures; and immunizations (Haber, 2009; Hauser, 2015a; Pacheco, 2016). Guillain-Barré syndrome is thought to be immune-mediated from antibodies formed against nonself antigens. Demyelination causes sensory and motor conduction blockade, and remyelination yields recovery in most cases.

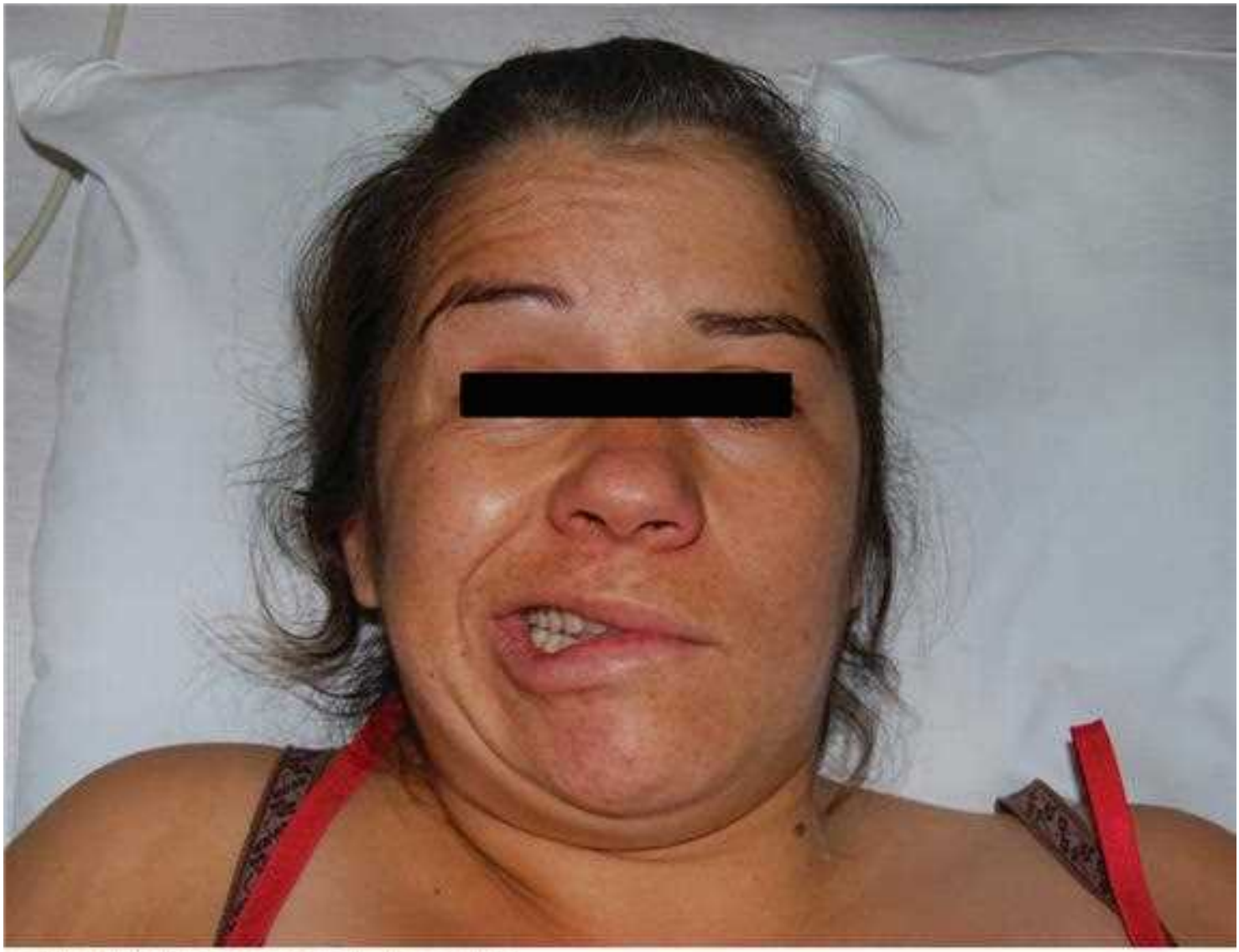
Clinical features include areflexic paralysis—usually ascending—with or without sensory disturbances. Autonomic dysfunction is common. The full syndrome develops over 1 to 3 weeks. Some manifest as *chronic inflammatory demyelinating polyneuropathy,* and our experiences indicate that this may be relatively common in these young women.

Guillain-Barré syndrome is not more common in pregnancy, and its clinical course mirrors that for nonpregnant individuals. After an insidious onset, paresis and paralysis most often continue to ascend to cause ventilatory weakness. Management is supportive and incorporates venous thromboembolism prophylaxis, pressure ulcer prevention, and enteral nutrition. In the worsening phase, patients are hospitalized, and a fourth requires ventilatory assistance. IVIG or plasmapheresis is beneficial if begun within 1 to 2 weeks of motor symptoms, however, neither decreases mortality rates (Cortese, 2011; Gwathmey, 2011; Pritchard, 2016). Up to 10 percent of patients deteriorate after initial improvement on therapy, and retreatment with 2 g/kg IVIG over 5 days is recommended. Although most patients recover fully within several months to a year, the mortality rate is 5 percent, mainly due to pulmonary complications and arrhythmias (Hauser, 2015a; Pacheco, 2016).

Bell Palsy

This disfiguring palsy is usually a mononeuropathic acute facial paralysis that is relatively common in reproductive-aged women (Fig. 60-5). It has a female predominance, and pregnant women carry a fourfold risk compared with nonpregnant women (Cohen, 2000; Heaney, 2010). The disease is characterized by facial nerve inflammation and often is associated with reactivation of herpes simplex virus or herpes zoster virus.

FIGURE 60-5
Bell facial nerve palsy developing on the day of cesarean delivery for dichorionic twins. This woman was treated with prednisone and antiviral medication, and the palsy had almost resolved 3 weeks postpartum.



Bell palsy usually has an abrupt and painful onset with maximum weakness by 48 hours. In some cases, hyperacusis and loss of taste accompany paralysis (Beal, 2015). Management includes supportive care with facial muscle massage and eye protection against corneal lacerations from drying. There is general consensus that prednisone, 1 mg/kg given orally daily for 5 days, will improve outcomes and shorten the recovery period (Salinas, 2016; Sullivan, 2007). It is controversial whether addition of an antiviral medication will add benefits (de Almeida, 2009; Gagyor, 2015; Quant, 2009).

It is unclear if pregnancy alters the prognosis for spontaneous facial palsy recovery. Gillman and associates (2002) found that only half of pregnant women recovered to a satisfactory level after 1 year, compared with approximately 80 percent of nonpregnant women and men. Some prognostic markers for incomplete recovery are bilateral palsy, recurrence in a subsequent pregnancy, greater percentage of nerve function loss, and a faster rate of loss (Cohen, 2000; Gilden, 2004). Other than a fivefold greater rate for gestational hypertension or preeclampsia, women with Bell palsy do not have increased adverse pregnancy outcomes rates (Katz, 2011; Shmorgun, 2002).

Carpal Tunnel Syndrome

This syndrome results from compression of the median nerve and is the most frequent mononeuropathy in pregnancy (Padua, 2010). Symptoms include burning, numbness, or tingling along the inner half of one or both hands. Others are wrist pain and numbness extending into the forearm and sometimes into the shoulder (Katz, 2002). Symptoms are bilateral in 80 percent of gravidas, and 10 percent have evidence for severe denervation (Seror, 1998). Differential diagnosis includes cervical radiculopathy of C_6–C_7 and de Quervain tendonitis. The latter is caused by swelling of the conjoined tendons and their sheaths near the distal radius. Nerve conduction studies may be helpful for clarification (Alfonso, 2010).

In pregnancy, the reported incidence of carpal tunnel syndrome is 7 to 43 percent and varies greatly because the range of symptoms is marked (Meems, 2015; Padua, 2010). Symptomatic treatment with a splint applied to a slightly flexed wrist during sleep lightens pressure and usually provides relief. Although symptoms typically are self-limited, occasionally surgical decompression and corticosteroid injections are necessary (Keith, 2009; Shi, 2011). Symptoms may persist in more than half of patients at 1 year and in a third at 3 years (Padua, 2010).

SPINAL CORD INJURY

According to the National Spinal Cord Injury Statistical Center (2017), there are approximately 17,000 new spinal cord injuries each year. The average age is 42 years, and males account for 80 percent of new cases. Cord injury severity determines the short- and long-term prognosis as well as that for pregnancy. For women, many have altered sexual function and transient hypothalamic pituitary hypogonadism. That said, pregnancy is not uncommon if menstruation resumes (Bughi, 2008). In a review of nearly 2000 women in the National Spinal Cord Injury Database, 2 percent reported pregnancy in the prior 12 months (Iezzoni, 2015).

Gravidas with spinal cord injury have an increased frequency of pregnancy complications that include preterm and low-birthweight neonates. Recent observations in nonpregnant women note that the vaginal microbiota is altered in these women (Pires, 2016). Perhaps related, most have asymptomatic bacteriuria with sporadic symptomatic urinary infections. Bowel dysfunction causes constipation in more than half, and anemia and pressure-necrosis skin lesions are also common.

Two serious and life-threatening events can complicate spinal cord injuries. First, if the cord is transected above T_{10}, the cough reflex is impaired, respiratory function may be compromised, and pneumonitis from covert aspiration can be serious. Pulmonary function tests are considered to assess this risk, and some women may need ventilatory support in late pregnancy or in labor.

Second, women with lesions above T_5–T_6 are at risk for *autonomic dysreflexia*. With this, stimuli from structures innervated below the level of the spinal lesion lead to massive, disordered sympathetic stimulation. Abrupt catecholamine release can cause vasoconstriction with severe hypertension and symptoms that include throbbing headaches, facial flushing, sweating, bradycardia, tachycardia, arrhythmias, and respiratory distress. Dysreflexia can be precipitated by various stimuli. These include urethral catheterization, bladder distention from urinary retention, rectal or cervical stretch during digital examinations, uterine contractions and cervical dilation, or any manipulation of other pelvic structures (American College of Obstetricians and Gynecologists, 2016; Krassioukov, 2009). In one report, 12 of 15 women at risk for autonomic dysreflexia suffered at least one episode during pregnancy (Westgren, 1993).

Because uterine contractions are not affected by spinal cord lesions, labor is usually easy—even precipitous, and comparatively painless. If the lesion is below T_{12}, uterine contractions are felt normally. For lesions above T_{12}, the risk of out-of-hospital delivery is substantial and can be minimized by teaching women to palpate for uterine contractions. This is especially important because up to 20 percent of women deliver preterm (Westgren, 1993). Some recommend tocodynamometry and weekly cervical examinations beginning at 28 to 30 weeks. Another reasonable option that we frequently employ at Parkland Hospital is elective hospitalization after 36 to 37 weeks' gestation (Hughes, 1991).

Spinal or epidural analgesia extending to T_{10} prevents autonomic dysreflexia and should be instituted at the start of labor. If there are severe symptoms before epidural placement, steps are taken to abolish the provoking stimulus. A parenteral antihypertensive agent such as hydralazine or labetalol is given. Labor and vaginal delivery with epidural or spinal analgesia is preferable and will minimize autonomic dysreflexia (Kuczkowski, 2006). Operative vaginal delivery is frequently necessary.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Also known as *pseudotumor cerebri*, this disorder is typified by increased intracranial pressure without hydrocephalus. The cause is unknown, but it may result from overproduction or under absorption of cerebrospinal fluid (CSF). Symptoms include headache in at least 90 percent of cases, visual disturbances such as loss of a visual field or central visual acuity in 70 percent, and commonly occurring papilledema that may be sight-threatening (Evans, 2000; Heaney, 2010). Other complaints are stiff neck, back pain, pulsatile tinnitus, and cranial nerve palsies.

The syndrome is often found in young women and is prevalent in those who are obese, who recently gained weight, or both (Fraser, 2011). Along with symptoms, other criteria for diagnosis include elevated intracranial pressure >25 cm H_2O, normal CSF composition, normal cranial CT or MR imaging findings, papilledema, and no evidence for systemic disease. If papilledema is not present, other criteria are required (Friedman, 2013).

Idiopathic intracranial hypertension is usually self-limited. Visual defects can be prevented by lowering the CSF pressure, and agents include acetazolamide to reduce fluid production, furosemide, or topiramate. Corticosteroids are now rarely used. Surgical intervention is occasionally necessary and is accomplished by either lumboperitoneal shunting of spinal fluid or optic nerve sheath fenestration.

It is controversial if pregnancy is a risk factor for idiopathic intracranial hypertension. Certainly, symptoms may first appear in pregnancy, and women previously diagnosed may become symptomatic. Symptoms usually develop by midpregnancy, tend to be self-limited, and usually resolve postpartum.

Pregnancy does not alter management. Some recommend serial visual field testing to forestall permanent vision loss. In a report of 16 pregnant women, visual field loss developed in four, and it became permanent in one (Huna-Baron, 2002). Visual field loss is often coincident with the development of papilledema, for which acetazolamide is given. Lee and associates (2005) reported successful treatment of 12 pregnant women. Although outmoded for treatment of nonpregnant individuals, repeated lumbar punctures are generally successful in providing temporary relief throughout pregnancy. In some pregnant women, surgical therapy becomes necessary, and we and others have had promising results with optic nerve sheath fenestration (Thambisetty, 2007).

Pregnancy complications are likely due to associated obesity and not to intracranial hypertension. In a review of 54 pregnancies, rates of adverse perinatal outcomes were not elevated (Katz, 1989). The route of delivery depends on obstetrical indications, and conduction analgesia is safe (Aly, 2007; Karmaniolou, 2011).

MATERNAL VENTRICULAR SHUNTS

Pregnancies in women with previously placed ventricular shunts for obstructive hydrocephalus usually have satisfactory outcomes (Landwehr, 1994). Shunts may be ventriculoperitoneal, ventriculoatrial, or ventriculopleural. Partial obstruction of a shunt is common, especially late in pregnancy (Schiza, 2012). In one report of 17 such pregnancies, neurological complications were reported in 13 (Wisoff, 1991). Findings included headaches in 60 percent, nausea and vomiting in 35 percent, lethargy in 30 percent, and ataxia or gaze paresis, each in 20 percent. Most symptoms respond to conservative management. However, if CT scanning during symptom evaluation discloses acute hydrocephaly, then the shunt is tapped or pumped several times daily. In some cases, surgical revision is necessary and may be emergently indicated (Murakami, 2010).

Another shunting procedure is placement of an endoscopic third ventriculostomy for hydrocephalus (de Ribaupierre, 2007). With this, a small hole is created in the floor of the third ventricle to allow CSF to flow directly into lower cisterns. One report described successful results in five pregnant women who underwent endoscopic ventriculostomy (Riffaud, 2006). In a review, however, reproductive function and miscarriage rates were found to significantly worsen in these women (Bedaiwy, 2008).

Vaginal delivery is preferred in women with shunts, and unless there is a meningomyelocele, conduction analgesia is permitted. Antimicrobial prophylaxis is indicated if the peritoneal cavity is entered for cesarean delivery or tubal sterilization.

MATERNAL BRAIN DEATH

Brain death is rare in obstetrics. Life-support systems and parenteral alimentation for up to 15 weeks while awaiting delivery have been described (Hussein, 2006; Powner, 2003; Souza, 2006). Some women were treated with aggressive tocolysis and antimicrobial therapy. In one review of 17 women with persistent vegetative state who were given various levels of support, five women died after delivery, and most of the others remained in their vegetative state (Chiossi, 2006).

With a diagnosis of *brain death* using the uniform Determination of Death Act definition, there are no published reports of neurological recovery (Wijdicks, 2010). Few institutional brain-death policies address pregnancy (Lewis, 2016). The ethical, financial, and legal implications, both civil and criminal, that arise from attempting or not attempting such care are profound (Farragher, 2005; Feldman, 2000). In some women, perimortem cesarean delivery is performed as discussed in Chapter 47 (Cardiopulmonary Resuscitation).

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CHAPTER 61: Psychiatric Disorders

FIGURE 61-1

The insanity of pregnancy is usually a manifestation of autointoxication, and may be accompanied by melancholic or maniacal symptoms. It usually persists throughout gestation, but disappears shortly after labour, unless the patient has an hereditary tendency to mental derangement.

—J. Whitridge Williams (1903)

INTRODUCTION

The subject of mental illness was only briefly addressed by Williams in 1903, when it appears that acute puerperal psychoses were manifestations of eclampsia or sepsis. More than 100 years later, we have learned that pregnancy and the puerperium are at times sufficiently stressful to provoke mental illness. Such illness may represent recurrence or exacerbation of a preexisting psychiatric disorder, or it may signal the onset of a new condition. This 25th edition of *Williams Obstetrics* marks only the second edition with a focused chapter dedicated to psychiatric illnesses. To emphasize the rising national interest, American College of Obstetricians and Gynecologists President Dr. Gerald F. Joseph Jr. declared postpartum depression as an initiative in 2009.

Psychiatric disorders during pregnancy are associated with less prenatal care, substance use, poor obstetrical and neonatal outcomes, and higher rates of postpartum psychiatric illness (Frieder, 2008). Despite these known risks, obstetrical providers often are reluctant to confront or fail to identify some of these mental health issues during pregnancy. For example, Lyell and colleagues (2012) found that the diagnosis of depression was not documented in nearly half of the records of depressed women. Yet, perinatal mood disorders can have far-reaching consequences beyond the immediate effect on maternal mental health and social function by adversely affecting the mother-child relationship (Weinberg, 1998).

Also, suicide is a primary cause of death among women during the perinatal period in the United States, and major depression is among the strongest predictors of suicidal ideation (Melville, 2010). Between 2004 and 2012, self-harm, suicide, or drug overdose was the leading cause of maternal death in Colorado (Metz, 2016). In a 10-year analysis of Washington state hospitalizations, Comtois and associates (2008) studied 355 women with a postpartum suicide attempt. Substance abuse was linked with a sixfold higher and prior psychiatric hospitalization with a 27-fold greater risk for suicide. These rates rose further if there were multiple hospitalizations. Also of note, 54 percent of pregnancy-associated suicides involve intimate-partner conflict (Palladino, 2011).

PSYCHOLOGICAL ADJUSTMENTS TO PREGNANCY

Biochemical factors and life stressors can markedly influence mental health and mental illness during the perinatal period. Intuitively, pregnancy exacerbates some coexisting psychological disorders. Namely, an increased risk for mood disorders is linked with pregnancy-related shifts in sex steroid and monoamine neurotransmitter levels, dysfunction of the hypothalamic-pituitary-adrenal axis, thyroid dysfunction, and alterations in immune response (Yonkers, 2011). These changes, coupled with familial clustering of depression cases, suggest that there may be a subgroup of women at risk for developing a unipolar major depressive disorder during pregnancy.

Women respond in various ways to stressors of pregnancy, and some express persistent concerns regarding fetal health, child care, lifestyle changes, or fear of childbirth pain. Anxiety, sleep disorders, and functional impairment are common (Romero, 2014; Vythilingum, 2008). However, according to Littleton and coworkers (2007), anxiety symptoms in pregnancy are associated with psychosocial variables similar to those for nonpregnant women. The level of perceived stress is significantly higher for women whose fetus is at high risk for a malformation, for those with preterm labor or delivery, and for those with other medical complications (Alder, 2007; Ross, 2006). Hippman and colleagues (2009) screened for depression in 81 women who had an increased risk for a fetus with aneuploidy. Half of these women had a positive depression screening score, whereas only 2.4 percent of those with a normal pregnancy did so.

Several steps can be taken to diminish psychological stress in the event of a poor obstetrical outcome. For example, following a stillbirth, Gold (2007) encouraged parental contact with the newborn and provision of photographs and other infant memorabilia. Addressing associated sleep disorders also seems reasonable (Juulia Paavonen, 2017; Romero, 2014).

The Puerperium

This is a particularly stressful time for women, and risks for mental illness are increased. Up to 15 percent of women develop a nonpsychotic postpartum depressive disorder within 6 months of delivery (Tam, 2007; Yonkers, 2011). A few have a psychotic illness following delivery, and half of these manifest a bipolar disorder. Depressive disorders are more likely in women with obstetrical complications such as severe preeclampsia or fetal-growth restriction, especially if associated with early delivery. Houston and coworkers (2015) found that expectations at delivery also increased the risk for postpartum depression.

Importantly, stressors beyond those directly related to the pregnancy can raise perinatal depression rates. Tarney and colleagues (2015) identified spouse deployment as a factor for postpartum depression in a study at Womack Army Medical Center. But, among women with a history of bipolar disorder, these elements play a lesser role in the development of mania or depression (Yonkers, 2011).

Maternity Blues

Also called *postpartum blues*, this is a time-limited period of heightened emotional reactivity experienced by half of women within the first week after parturition. Prevalence estimates for the blues range from 26 to 84 percent depending on diagnostic criteria (O'Hara, 2014). This emotional state generally peaks on the fourth or fifth postpartum day and normalizes by day 10 (O'Keane, 2011).

The predominant mood is happiness, but affected mothers are more emotionally labile. They also may have insomnia, weepiness, depression, anxiety, poor concentration, and irritability. Mothers may be transiently tearful for several hours and then recover completely, only to be tearful again the next day. Supportive treatment is indicated, and affected women are reassured that the dysphoria is transient and most likely due to biochemical changes. They should be monitored for development of depression and other severe psychiatric disturbances.

Perinatal Evaluation and Screening

Both the American College of Obstetricians and Gynecologists (2016a) and the United States Preventative Services Task Force now recommend screening at least once during the perinatal period for depression and anxiety (Siu, 2016). Identification of psychiatric disorders in pregnancy can be challenging because changes in behavior and mood are often attributed to pregnancy. To differentiate these, Yonkers (2011) recommends assessment of cognitive symptoms—for example, loss of concentration. Excessive symptoms of anxiety and insomnia—even during periods of infant sleep—can also suggest postpartum depression. Specific factors for depression are reviewed and include a prior personal or family history of depression.

Universal-screening programs for depression continue to evolve (Venkatesh, 2016). At Parkland Hospital, mental illness screening is generally done at the first prenatal visit using a brief risk-based query and again postpartum using a universal-applied screening tool for postpartum depression. Questions search for psychiatric disorders, related therapy, prior or current use of psychoactive medications, and current symptoms. Women with a history of sexual, physical, or verbal abuse; substance abuse; and personality disorders are also at greater risk for depression (Akman, 2007; Janssen, 2012). History of neglect and abuse are especially powerful antecedents of depression in adolescent pregnancy (Meltzer-Brody, 2014). Smoking and nicotine dependence and obesity also raise rates of ***all*** mental disorders in pregnancy (Goodwin, 2007; Molyneaux, 2014). Finally, because eating disorders may be exacerbated by pregnancy, affected women are followed closely (Schizophrenia Spectrum Disorders).

Several screening instruments shown in Table 61-1 are available and have been validated for use during pregnancy and the puerperium. Use of one of these screening tools is encouraged because symptom- or risk-based screening alone may be insufficient (American College of Obstetricians and Gynecologists, 2016a). Cerimele and colleagues (2013) found that obstetricians and gynecologists failed to identify 60 percent of depressed women in clinical practice. As mentioned earlier, at Parkland Hospital, all women are screened during their first postpartum visit using the Edinburgh Postnatal Depression Scale (EPDS). In an analysis of more than 17,000 women, 6 percent had scores that indicated either minor or major depressive symptoms, and 12 women had thoughts of self-harm (Nelson, 2013). Similarly, Kim and coworkers (2015) assessed suicidal ideation in more than 22,000 women screened using the EPDS both during pregnancy and postpartum. They found rates of depression as high as 3.4 percent during the puerperium. A small fraction of those with thoughts of self-harm had a

credible plan, intent, and means for attempted suicide. Obviously, suicidal ideation warrants prompt psychiatric consultation for evaluation and management.

TABLE 61-1

Depression Screening Tools[a]

Screening Tool	Items	Time to Complete (min)	Available Resources Online[b]
Edinburgh Postnatal Depression Scale	10	<5	http://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf
Patient Health Questionnaire 9	9	<5	http://www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf
Center for Epidemiologic Studies Depression Scale	20	5–10	http://www.perinatalweb.org/assets/cms/uploads/files/CES-D.pdf

[a]All depression screening tools are also available in Spanish.

[b]Available free online.

Screening for perinatal depression without appropriate subsequent treatment is insufficient (American College of Obstetricians and Gynecologists, 2016a). That said, mechanisms to ensure adequate ensuing care can be problematic. In the study by Nelson and associates (2013) more than three fourths of the 1106 women with abnormally elevated EPDS scores did not keep their later appointment, which offered more formal psychiatric evaluation. Barriers include difficulties with access to care, personal perception of depression, and societal stigmata (Flynn, 2010; Smith, 2008). Women referred to a behavioral health provider located at the same site as their obstetrical care are four times more likely to access treatment than those referred elsewhere (Smith, 2009). To take advantage of this, at Parkland Hospital, mental health counselors also practice at postpartum clinic sites. Other promising interventions for puerperal depression include home visits, telephone-based peer support, and interpersonal psychotherapy (Dennis, 2013; Lavender, 2013; Yonemoto, 2017). A report from Kaiser Permanente, which describes the benefits and hurdles to system-based perinatal mental health care, provides a glimpse into the possible future of universal perinatal screening and treatment (Avalos, 2016; Flanagan, 2016).

Treatment Considerations

Many psychiatric disorders can be improved with counseling and psychotherapies. In some instances, psychotropic medications are needed. Treatment decisions are ideally shared between patients and their health-care providers. In particular, women taking psychotropic medication are informed of likely side effects. Many of these drugs are discussed in Chapter 12 and by the American College of Obstetricians and Gynecologists (2016b) in their Practice Bulletin No. 92. Some of these drugs are discussed subsequently.

Pregnancy Outcomes

Emerging information on psychiatric disorders and pregnancy outcomes suggest a link between maternal psychiatric illness and untoward outcomes such as preterm birth, low birthweight, and perinatal mortality (Grigoriadis, 2013; Steinberg, 2014; Straub, 2012; Yonkers, 2009). In a study of 16,334 deliveries, Shaw and coworkers (2014) identified a significant association between posttraumatic stress disorder and spontaneous preterm delivery. Domestic abuse—another aforementioned risk factor for perinatal mood disorder—is also linked with adverse perinatal outcomes (Yost, 2005). Finally, Littleton and associates (2007) reviewed 50 studies and concluded that anxiety symptoms, which are commonly comorbid with depression, had no adverse effect on perinatal outcomes.

MOOD DISORDERS

The *Diagnostic and Statistical Manual, Fifth Edition (DSM-5)* is the most recent version by the American Psychiatric Association (2013). It assists in classifying mental disorders and specifies criteria for each diagnosis.

Of categories, depressive disorders are common. According to the National Institute of Mental Health (2010), the lifetime prevalence of depressive disorders in the United States is 21 percent. Historically, depressive disorders include major depression—a unipolar disorder—and manic-depression—a bipolar disorder with both manic and depressive episodes. It also includes dysthymia, which is chronic, mild depression.

Major Depression

This is the most common depressive disorder, and the 12-month prevalence of major depressive episodes among U.S. women is 8.2 percent (Center for Behavioral Health Statistics and Quality, 2015). In 2011 to 2014, 16 percent of U.S. women had used an antidepressant in the prior month (Pratt, 2017). The diagnosis is made by identifying symptoms listed in Table 61-2, but very few patients manifest all of these.

TABLE 61-2

Symptoms of Depressive Illness[a]

Hopelessness and/or pessimism Persistent sad, anxious, or “empty” feelings
Guilt, worthlessness, and/or helplessness
Irritability, restlessness
Loss of interest in activities once pleasurable, including sex
Fatigue and decreased energy
Difficulty concentrating, remembering details, and making decisions
Insomnia, early-morning wakefulness, or excessive sleeping
Overeating or appetite loss
Thoughts of suicide, suicide attempts
Persistent aches or pains, headaches, cramps or digestive problems that do not ease with treatment

[a]Not all patients experience the same symptoms.

Modified with permission from National Institute of Mental Health, 2010.

Major depression is multifactorial and prompted by genetic and environmental factors. Families of affected individuals often also have members suffering with alcohol abuse and anxiety disorders. Provocative conditions leading to depression include life events that prompt grief reactions, substance abuse, use of certain medications, and other medical disorders. Although life events can trigger depression, genes influence the response to these events and render the distinction between genetic and environmental factors difficult. One genome-wide linkage analysis of more than 1200 mothers suggests that variation in chromosomes 1 and 9 raises susceptibility to postpartum mood symptoms (Mahon, 2009).

Pregnancy and Depression

It is unquestionable that pregnancy is a major life stressor that can precipitate or exacerbate depressive tendencies. In addition, various pregnancy-induced effects are implicated. Hormones certainly affect mood, as evidenced by premenstrual syndrome and menopausal depression. Estrogen has been linked to increased serotonin synthesis, decreased serotonin breakdown, and serotonin-receptor modulation (Deecher, 2008). Concordantly, women who experience postpartum depression often have higher predelivery serum estrogen and progesterone levels and experience a greater decline postpartum (Ahokas, 1999).

Dennis and associates (2007) queried the Cochrane Database and reported that the prevalence of antenatal depression averaged 11 percent. Melville and coworkers (2010) found it in nearly 10 percent of more than 1800 women enrolled for prenatal care at a single university clinic. Others have reported the incidence to be much higher depending on the population studied (Gavin, 2005; Hayes, 2012; Lee, 2007).

Postpartum Depression

Major or minor depression develops postpartum in 10 to 20 percent of women (Mental Health America, 2016). Available data indicate that unipolar major depression may be slightly more prevalent during the puerperium than among women in the general population (Yonkers, 2011). Postpartum depressive symptoms are associated with young maternal age, antenatal depression, unmarried status, smoking, newborns requiring intensive care, and those with a history of stressors during pregnancy (Ko, 2017; Silverman, 2017). Specifically, physical or verbal abuse during pregnancy is a potent risk for postpartum depression (McFarlane, 2014). Finally, serious adverse obstetrical events, especially those involving the neonate, are strongly linked to postpartum depression (Nelson, 2013, 2015).

Depression is frequently recurrent. Up to 70 percent of women with previous postpartum depression have a subsequent episode. Women with both prior puerperal depression and a current episode of "maternity blues" carry an inordinately high risk for major depression. Indeed, 2 to 9 months postpartum, assistance with postpartum depression was the fourth most common challenge identified in women in the Pregnancy Risk Assessment Monitoring System—PRAMS (Kanotra, 2007).

Postpartum depression is generally underrecognized and undertreated. Major depression during pregnancy or after delivery can have devastating consequences for affected women, their children, and families. One of the most significant contributions to the mortality rate among new mothers is suicide, which is most frequent among women with mental illness (Koren, 2012; Palladino, 2011). If left untreated, up to 25 percent of women with postpartum depression will be depressed 1 year later. As the duration of depression increases, so too does the number of sequelae and their severity. Maternal depression during the first weeks and months after delivery can lead to insecure attachment and later behavioral problems in the child.

Depression Treatment

Therapy for mood disorders during pregnancy and postpartum has undergone a significant evolution during the past decade. Babbitt (2014) and Pozzi (2014) and their associates have reviewed principles of antenatal and intrapartum care of women with major mental disorders. In general, for mild and mild-moderate depression, psychological treatment options, such as cognitive behavioral therapy, are considered first (Yonkers, 2011). Antidepressant medications together with some form of psychotherapy are indicated for moderate to severe depression during pregnancy or the puerperium (American College of Obstetricians and Gynecologists, 2016b).

Shown in Figure 61-1 is one algorithm regarding treatment of mood disorders. Some of these medications are listed in Table 61-3. For women with severe depression, a selective serotonin-reuptake inhibitor (SSRI) is selected initially. In contrast, tricyclic antidepressants and monoamine oxidase inhibitors are infrequently selected in contemporary practice. If depressive symptoms improve during a 6-week trial, the medication is continued for a minimum of 6 months to prevent relapse (Wisner, 2002). At least 60 percent of women taking antidepressant medication before pregnancy have symptoms during pregnancy. According to Hayes and colleagues (2012), approximately three fourths of women taking antidepressants before pregnancy stopped taking them before or during early pregnancy. For those who discontinue treatment, almost 70 percent have a relapse compared with approximately 25 percent who continue therapy. If the response is suboptimal or a relapse occurs, another SSRI is substituted, or psychiatric referral is considered.

TABLE 61-3

Drugs Used for Treatment of Major Mood Disorders in Pregnant Women

Indication	Examples	Comments
Antidepressants		
SSRIs[a]	Citalopram, sertraline, fluoxetine	Some have possible neonatal link with heart defects, withdrawal syndrome, and pulmonary hypertension
Others	Bupropion, duloxetine, nefazodone, venlafaxine	
Tricyclics	Amitriptyline, desipramine, doxepin, imipramine, nortriptyline	No evidence of teratogenicity, not commonly used
Antipsychotics		
Typical	Chlorpromazine, fluphenazine, haloperidol, thiothixene	
Atypical	Aripiprazole, clozapine, olanzapine, risperidone, ziprasidone	
Bipolar Disorders		
Lithium[a]	Lithium carbonate	Manic episodes; teratogenic for cardiac defects (Ebstein anomaly)
Valproic acid[b]		Teratogenic—neural-tube defects
Carbamazepine[b]		Antiepileptic—hydantoin syndrome

[a]Chapter 12 (Retinoids).

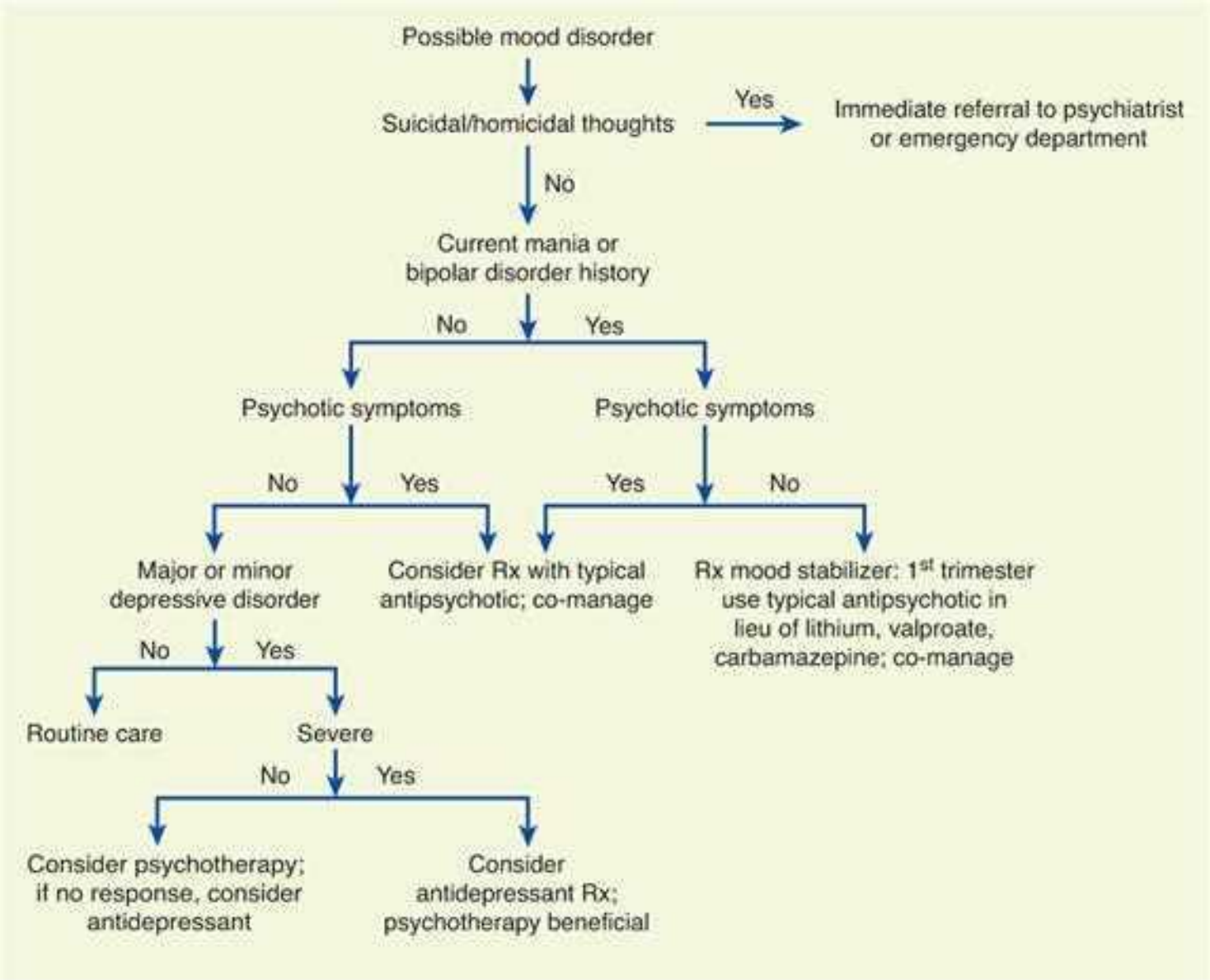
[b]Chapter 60 (Cerebrovascular Diseases).

SSRI = Selective serotonin-reuptake inhibitor.

Data from Briggs, 2015; Huybrechts, 2015; Koren, 2012.

FIGURE 61-1

Treatment algorithm for pregnant women with mood disorders.



Various dietary deficiencies have suggested links to perinatal depression (Yonkers, 2011). Supplements that include omega-3 fatty acids, iron, folate, riboflavin, vitamin D, calcium, and docosahexaenoic acid (DHA) have been studied (Keenan, 2014; Miller, 2013). However, evidence currently is insufficient to support use of these dietary supplements for this purpose.

Importantly, in a metaanalysis by Huang and coworkers (2014), women using antidepressants during pregnancy have higher rates of preterm birth and low-birthweight neonates. Nevertheless, in their review, Ray and Stowe (2014) concluded that the relative reproductive safety data are reassuring and that antidepressants remain a viable treatment option. Furthermore, recurrence sometime after medication is discontinued develops in 50 to 85 percent of women with an initial postpartum depressive episode. Women with a history of more than one depressive episode carry greater risk (American Psychiatric Association, 2000). Surveillance includes monitoring for thoughts of suicide or infanticide, emergence of psychosis, and response to therapy. For some women, the course of illness is severe enough to warrant hospitalization.

Fetal and Neonatal Effects of Therapy

Some known and possible fetal and neonatal effects of treatment are listed in Table 61-3. Some studies suggest that SSRIs pose an elevated teratogenic risk for fetal cardiac defects, and these have mainly focused on paroxetine (Paxil). Associations were most consistent for ventricular septal defects. The estimated risk is no greater than 1 in 200 exposed newborns (Koren, 2012). Nevertheless, the American College of Obstetricians and Gynecologists (2016b) recommends that paroxetine be avoided in women who are either pregnant or planning pregnancy. In women exposed to paroxetine in the first trimester, fetal echocardiography is considered. Jimenez-Solem and coworkers (2013) in their analysis of SSRIs found no association between exposure to SSRIs during pregnancy and perinatal mortality. Andersen and

associates (2014) found that women discontinuing SSRI treatment in early pregnancy had a small increased risk of miscarriage, but that this was similar to the risk in women discontinuing SSRI treatment months before pregnancy. Taken together, these investigators concluded that treatment with SSRIs during pregnancy should not be discontinued for fear of miscarriage.

Of other potential effects, the risk of persistent pulmonary hypertension of the newborn rose sixfold in neonates exposed to SSRIs after 20 weeks' gestation (Chambers, 2006). This translates to an overall risk of pulmonary hypertension that would be less than 1 in 100 exposed newborns (Koren, 2012). In contrast, a population-based cohort study of 1.6 million pregnancies identified a twofold greater rate in exposed neonates. This yields an estimated attributable risk of 2 cases per 1000 births (Kieler, 2012). In a study of more than 120,000 gravidas prescribed antidepressants, Huybrechts and coworkers (2015) found an attributed risk of 1 case per 1000 births.

In sum, the maternal risk associated with discontinuing or tapering SSRI use during pregnancy must be weighed against marginally increased neonatal risks (Ornoy, 2017). Women who abruptly discontinue either serotonin- or norepinephrine-reuptake inhibitor therapy typically experience some form of withdrawal.

Not surprisingly, up to 30 percent of exposed neonates may also exhibit withdrawal symptoms. Symptoms are similar to opioid withdrawal, but typically are less severe. Neonatal SSRI withdrawal is usually self-limited, and the newborn rarely remains in the nursery more than 5 days (Koren, 2009). Currently, convincing evidence of long-term neurobehavioral effects of fetal exposure to these medications is lacking (Koren, 2012). Grzeskowiak and coworkers (2016) found no increased risk of behavioral problems in 7-year-old children exposed to antidepressants prior to their birth.

Some psychotropic medications pass into breast milk. In most cases, however, levels are very low or undetectable. Effects may be transient irritability, sleep disturbances, and colic.

Electroconvulsive Therapy

This form of depression treatment is occasionally necessary during pregnancy for women with major mood disorders unresponsive to pharmacotherapy. Women undergoing electroconvulsive therapy (ECT) should be fasting for at least 6 hours. They are given a rapid-acting antacid before the procedure, and their airway is protected to decrease the likelihood of aspiration. After midpregnancy, a wedge is placed under the right hip to prevent sudden maternal hypotension from aortocaval compression. Other important preparatory steps include assessment of the cervix, discontinuation of nonessential anticholinergic medication, uterine and fetal heart rate monitoring, and intravenous hydration. During the procedure, excessive hyperventilation is avoided. In most cases, maternal and fetal heart rate and maternal blood pressure and oxygen saturation remain normal throughout the procedure.

With proper preparation, the risks to both mother and fetus appear to be reasonable (Pinette, 2007). That said, adverse maternal and perinatal outcomes have followed ECT. Balki and associates (2006) reported a pregnancy in which fetal brain damage likely was caused by sustained maternal hypotension associated with treatment of status epilepticus stimulated by ECT.

At least two extensive reviews have evaluated ECT outcomes in pregnancy. In the earlier one, Miller (1994) found 300 cases and reported complications in 10 percent. These included fetal arrhythmias, vaginal bleeding, abdominal pain, and self-limited contractions. Women not adequately prepared had increased risks for aspiration, aortocaval compression, and respiratory alkalosis. In the more recent review, Andersen and Ryan (2009) described 339 cases, undoubtedly with some homology with the earlier study. In most cases, ECT therapy was done to treat depression, and it was 78-percent effective. They reported a 5-percent maternal ECT-related complication rate. There was a 3-percent associated perinatal complication rate, which included two fetal deaths. For all of these reasons, we agree with Richards (2007) that ECT in pregnancy is not "low risk" and that it should be reserved for women whose severe depression is resistant to intensive pharmacotherapy.

Bipolar and Related Disorders

According to the National Institute of Mental Health (2010), the lifetime prevalence for manic-depression illness is 3.9 percent. The prevalence of bipolar disorder does not vary between gravidas and nonpregnant reproductive-aged women (Yonkers, 2011). It has a strong genetic component and has been linked to possible mutations on chromosomes 16 and 8 (Jones, 2007). The risk that monozygotic twins are both affected is 40 to 70 percent, and the risk for first-degree relatives is 5 to 10 percent (Muller-Oerlinghausen, 2002).

Periods of depression last at least 2 weeks. At other times, patients are manic, in which mood is abnormally raised, expansive, or irritable. Potential organic causes of mania include substance abuse, hyperthyroidism, and central nervous system (CNS) tumors. These are all excluded during an acute event. Importantly, pregnancy frequently prompts medication discontinuation, which poses a twofold increased

risk for relapse (Viguera, 2007). Affected women are considered high risk, and as many as 20 percent of patients with manic-depression illness commit suicide.

Bipolar Disorder in Pregnancy

This has also been associated with adverse perinatal outcomes, for example, preterm birth (Mei-Dan, 2015). Di Florio and associates (2013) found that those women who experience pregnancy complications are more likely to exhibit periods of mania or depression. Women who tend to be manic present with exacerbations earlier in the postpartum period.

Typical therapy for bipolar disorder includes mood stabilizers such as lithium, valproic acid, and carbamazepine, as well as antipsychotic medications (see Table 61-3). Treatment of bipolar disorder in pregnancy is complex and is ideally managed concurrently with a psychiatrist. Decisions include risks versus benefits of using mood stabilizers, some of which are teratogenic. For example, lithium has been linked to Ebstein anomaly in exposed fetuses. More recent data, however, suggest a lower risk of cardiac malformations than previously indicated (Micromedex, 2016; Patorno, 2017). Nevertheless, many recommend fetal echocardiography for lithium-exposed fetuses. Some limited evidence suggests that lithium in breast milk, when its elimination is impaired as in dehydration or immaturity, can adversely affect the infant (Davanzo, 2011). However, lithium use in mothers with a healthy, term fetus is considered moderately safe. A more detailed discussion of other mood stabilizers and antipsychotic medications side effects can be found in Chapter 12 (Immunosuppressant Medications).

Postpartum Psychosis

This severe mental disorder is usually a bipolar disorder, but it may be due to major depression (American Psychiatric Association, 2013). Its incidence is estimated to be 1 in every 1000 deliveries, and it is more common in nulliparas, especially those with obstetrical complications (Bergink, 2011; Blackmore, 2006). In most cases, illness manifests within 2 weeks of delivery. In one study of postpartum women with their first lifetime episode of psychosis, the median onset of psychiatric symptoms was 8 days after delivery, and the median duration of the episode was 40 days (Bergink, 2011). Because those with underlying psychiatric disease have a 10- to 15-fold risk for recurrence postpartum, close monitoring is imperative.

The most important risk for postpartum psychosis is a history of bipolar disease. These women typically exhibit symptoms within 1 to 2 days after delivery (Heron, 2007, 2008). Manic symptoms include feeling excited or elated, being active or energetic, feeling “chatty,” and suffering insomnia. Affected women have signs of confusion and disorientation but may also have lucid episodes.

Postpartum psychosis has a 50-percent recurrence risk in the next pregnancy. As a result, Bergink and associates (2012) recommend initiating lithium therapy immediately after delivery in women with a history of postpartum psychosis.

The clinical course of bipolar illness with postpartum psychosis is comparable with that for nonpregnant women. Patients usually require hospitalization, pharmacological treatment, and long-term psychiatric care. Psychotic women may have delusions leading to thoughts of self-harm or harm to their infants. Unlike women with nonpsychotic depression, these women commit infanticide, albeit uncommonly (Kim, 2008). In most instances, women with postpartum psychosis ultimately develop relapsing, chronic psychotic manic-depression.

Anxiety Disorders

These relatively common disorders—18 percent prevalence overall—include panic attack, panic disorder, social anxiety disorder, specific phobia, separation anxiety disorder, and generalized anxiety disorder. All are characterized by irrational fear, tension, and worry, which are accompanied by physiological changes such as trembling, nausea, hot or cold flashes, dizziness, dyspnea, insomnia, and frequent urination (Schneier, 2006). They are treated with psychotherapy and medication, including SSRIs, tricyclic antidepressants, monoamine oxide inhibitors, or others.

Anxiety Disorders in Pregnancy

Despite the relative high prevalence in childbearing-aged women, little specific attention has been directed to anxiety disorders in pregnancy. Most reports conclude that rates between pregnant and nonpregnant women do not differ. One recent analysis of 268 gravidas with generalized anxiety disorder demonstrated that both symptoms and severity of anxiety decline across pregnancy (Buist, 2011).

From their review, Ross and McLean (2006) concluded that some of the anxiety disorders may have important maternal-fetal implications. Some have been linked to preterm birth, fetal-growth restriction, and poor neurobehavioral development (Van den Bergh, 2005). Children

with a history of in utero exposure to maternal anxiety are felt to be at increased risk for various neuropsychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD). Hunter and coworkers (2012) analyzed infants of 60 mothers with an anxiety disorder and found that auditory sensory gating—a reflection of inhibitory neurotransmission—was impaired, particularly in offspring of untreated women. Conversely, Littleton and associates (2007) found no excessive adverse pregnancy outcomes with "anxiety symptoms." One important exception is their link with postpartum depression (Vythilingum, 2008).

Anxiety Disorder Treatment

Anxiety disorders can be effectively treated during pregnancy with psychotherapy, cognitive-behavioral therapy, or medications. Mood and anxiety disorders coexist in more than half of women identified with either diagnosis (Frieder, 2008). Thus, antidepressants listed in Table 61-3 are often the first line of pharmacotherapy.

Benzodiazepines are also commonly used to treat anxiety or panic disorders before and during pregnancy. Earlier case-control studies linked use of these CNS depressants to a possible increased risk for cleft lip and palate. A metaanalysis of more than 1 million exposed pregnancies, however, did not identify a teratogenic risk (Enato, 2011). Benzodiazepines, especially when taken during the third trimester, can cause neonatal withdrawal syndrome, which persists for days to weeks after delivery.

SCHIZOPHRENIA SPECTRUM DISORDERS

This major form of mental illness affects 1.1 percent of adults (National Institute of Mental Health, 2016). Schizophrenia spectrum disorders are defined by abnormalities in one or more of the following domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms. Brain-scanning techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) show that schizophrenia is a degenerative brain disorder. Subtle anatomical abnormalities are present early in life and worsen with time.

Schizophrenia has a major genetic component, and there is a 50-percent concordance in monozygotic twins. If one parent has schizophrenia, the risk to offspring is 5 to 10 percent. Some data, including a strong association between schizophrenia and the velocardiofacial syndrome, suggest that associated genes are located on chromosome 22q11 (Murphy, 2002). But sophisticated gene mapping studies clearly show that schizophrenia is not related to a single gene or mutation. Instead, multiple DNA variants likely interact to lead to schizophrenia (Kukshal, 2012). Other putative risks for subsequent schizophrenia in an exposed fetus include maternal iron-deficiency anemia, diabetes, and acute maternal stress (Insel, 2008; Malaspina, 2008; Van Lieshout, 2008). These remain unproven, as does the association with maternal influenza A infection.

Signs of illness begin approximately at age 20 years, and commonly, work and psychosocial functioning deteriorate over time. Women have a slightly later onset than men and are less susceptible to autism and other neurodevelopmental abnormalities. Thus, many investigators theorize that estrogen is protective. Affected women may become pregnant before symptoms manifest. With appropriate treatment, patients can experience a decrease or cessation of symptoms. Within 5 years from the first signs of illness, 60 percent have social recovery, 50 percent are employed, 30 percent are mentally handicapped, and 10 percent require continued hospitalization (American Psychiatric Association, 2013).

Schizophrenia in Pregnancy

Most studies have not found adverse maternal outcomes, although researchers in a Swedish study noted increased rates of low birthweight, fetal-growth restriction, and preterm delivery (Bennedsen, 1999). In a study of more than 3000 pregnancies in schizophrenic women, Jablensky and coworkers (2005) reported that placental abruption was increased threefold and "fetal distress"—vaguely defined—was increased 1.4-fold.

Because schizophrenia has a high recurrence if medications are discontinued, continued therapy during pregnancy is advised. After 40 years of use, no evidence links the conventional or "typical" antipsychotic drugs listed in Table 61-3 and adverse fetal or maternal sequelae (McKenna, 2005; Robinson, 2012; Yaeger, 2006). Because less is known about "atypical" antipsychotics, the American College of Obstetricians and Gynecologists (2016b) recommends against their routine use in pregnant and breastfeeding women. In response to adverse event reports, the Food and Drug Administration (2011) issued a safety communication alerting health-care providers concerning some antipsychotic medications. These have been associated with neonatal extrapyramidal and withdrawal symptoms similar to the neonatal behavioral syndrome seen in those exposed to SSRIs.

EATING DISORDERS

These include *anorexia nervosa*, in which the patient refuses to maintain minimally normal body weight, and *bulimia nervosa*, in which binge eating is usually followed by purging or excessive fasting to maintain normal body weight (Zerbe, 2008). Eating behavior disturbances largely affect adolescent females and young adults. With anorexia and bulimia, the lifetime prevalence for each is 2 to 3 percent (National Institute of Mental Health, 2016).

Bulik and coworkers (2009) studied pregnancy outcomes in almost 36,000 Norwegian women screened for eating disorders. Approximately 0.1 percent had anorexia nervosa, 0.85 percent had bulimia nervosa, and 5.1 percent reported a binge-eating disorder. This 6-percent pregnancy prevalence is similar to the 6-month prevalence for nonpregnant individuals (National Institute of Mental Health, 2016). The last subtype had a higher risk for large-for-gestational age neonates with a concomitantly increased cesarean delivery rate. All eating disorders begin with the desire to be slim, and women with chronic eating disorders may migrate between subtypes (Andersen, 2009).

Eating Disorders in Pregnancy

Early pregnancy complication rates are increased with both eating disorders, but especially in women with bulimia nervosa (Andersen, 2009; Hoffman, 2011). Generally, eating disorder symptoms improve during pregnancy, and remission rates may reach 75 percent. In contrast, typical cases of hyperemesis gravidarum may actually be a new or relapsing case of bulimia nervosa or of binge-purge type anorexia nervosa (Torgerson, 2008). As perhaps expected, anorexia is associated with low-birthweight neonates (Micali, 2007). Additional risks associated with eating disorders include poor wound healing and difficulties with breastfeeding (Andersen, 2009). At a minimum, closely monitoring gestational weight gain in women with a suspected history of an eating disorder seems prudent.

Care for these women involves a multidisciplinary team that includes an obstetrician, mental health provider, and either dietician or nutritionist (American Dietetic Association, 2006). Psychological treatment is the cornerstone for treatment in women with eating disorders and frequently includes cognitive-behavioral therapy. Anorexia nervosa often responds to motivational interactions with meal planning (Cardwell, 2013). After delivery, women with eating disorders are more prone to postpartum depression. Women with bulimia are at particular risk for disease rebound after delivery because of body image concerns.

PERSONALITY DISORDERS

These disorders are characterized by the chronic use of certain coping mechanisms in an inappropriate, stereotyped, and maladaptive manner. They are rigid and unyielding personality traits. The American Psychiatric Association (2013) recognizes three clusters of personality disorders:

1. Paranoid, schizoid, and schizotypal personality disorders, which are characterized by oddness or eccentricity.
2. Histrionic, narcissistic, antisocial, and borderline disorders, which are all characterized by dramatic presentations along with self-centeredness and erratic behavior.
3. Avoidant, dependent, compulsive, and passive-aggressive personalities, which are characterized by underlying fear and anxiety.

Genetic and environmental factors are important in the genesis of these disorders, whose prevalence may be as high as 20 percent. Although management is through psychotherapy, most affected individuals do not recognize their problem, and thus only 20 percent seek help. In an observational study of 202 women with borderline personality disorder, De Genna and associates (2012) noted that such women become pregnant during the most severe trajectory of their illness. They are at increased risk for teen and unintended pregnancies.

Personality disorders during pregnancy are probably no different than in nonpregnant women. Akman and colleagues (2007) reported that avoidant, dependent, and obsessive-compulsive disorders are associated with an excessive prevalence of postpartum major depression. Magnusson and associates (2007) found a link between some *personality traits*—not disorders—and excessive alcohol consumption, but not necessarily addiction or dependence. Conroy and coworkers (2010) found that a mother's ability to care for her newborn was impaired only when a personality disorder was coupled with depression.

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CHAPTER 62: Dermatological Disorders

Herpes Gestationis—This disease, more frequently known as dermatitis herpetiformis is an inflammatory superficially seated multiform herpetiform eruption, which is characterized by erythematous, vesicular, pustular, and bullous lesions.

—J. Whitridge Williams (1903)

PREGNANCY-SPECIFIC DERMATOSES

Four dermatoses considered unique to pregnancy include intrahepatic cholestasis of pregnancy, pruritic urticarial papules and plaques of pregnancy (PUPPP), atopic eruption of pregnancy (AEP), and pemphigoid gestationis (PG). Descriptions of these are given in Table 62-1. As a group, these are diagnosed in up to 5 percent of pregnancies (Chander, 2011). Their gross appearance may be similar to each other or to other skin disorders, and pruritus is a common feature of all four. Only intrahepatic cholestasis and pemphigoid gestationis have been linked with adverse fetal outcomes.

TABLE 62-1

Pregnancy-specific Dermatoses

Disorder	Frequency	Characteristic Lesion	Adverse Pregnancy Effects	Treatment
Cholestasis of pregnancy	Common	No primary lesions, secondary excoriations from scratching	Increased perinatal morbidity	Antipruritics, cholestyramine, ursodeoxycholic acid
Pruritic urticarial papules and plaques of pregnancy (PUPPP)	Common	Erythematous pruritic papules or plaques; patchy or generalized on abdomen, thighs, buttocks, especially within striae, but with umbilical sparing	None	
Atopic eruptions of pregnancy (AEP)			None	Antipruritics, emollients, topical corticosteroids, oral steroids if severe
Eczema of pregnancy	Common	Dry, red scaly patches on extremity flexures, neck, face		
Prurigo of pregnancy	Common	1–5 mm pruritic red papules on extensor surfaces, trunk		
Pruritic folliculitis of pregnancy	Rare	Small red papules, sterile pustules on trunk		
Pemphigoid gestationis	Rare	Erythematous pruritic papules, plaques, vesicles, and bullae; abdomen often with umbilical involvement, extremities	Preterm birth, fetal-growth restriction, transient neonatal lesions	

Intrahepatic Cholestasis of Pregnancy

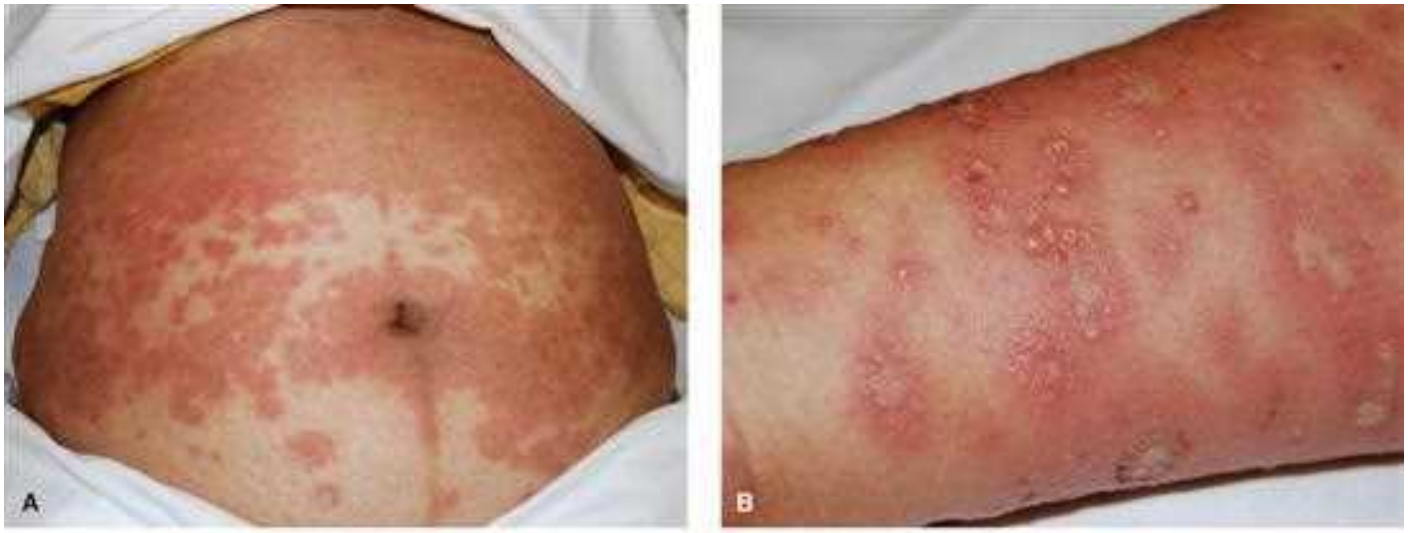
Previously termed pruritus gravidarum, this condition is found in 0.5 percent of pregnancies (Wikström Shemer, 2013). In contrast to the other pregnancy-specific dermatoses, intrahepatic cholestasis of pregnancy generally has no primary skin lesions. Rarely, a rash precedes pruritus, which is usually associated with abnormally elevated serum bile acid levels and mildly increased hepatic aminotransferase levels (Chao, 2011). Adverse fetal effects have been linked to this condition, and it is discussed in detail in Chapter 55 (Intrahepatic Cholestasis of Pregnancy).

Pemphigoid Gestationis

This rare autoimmune bullous disease is notable for its maternal and fetal effects. Initially, pruritic papules and urticarial plaques form and are then followed in most cases after 1 to 2 weeks by vesicles or bullae. Lesions are frequently distributed periumbilically, often develop on other skin surfaces, but spare mucous membranes, scalp, and face (Fig. 62-1).

FIGURE 62-1

Pemphigoid gestationis. **A.** Abdominal plaques classically involve the umbilicus. **B.** Blistered lesions on the wrist and forearm. (Used with permission from Dr. Kara Ehlers.)



Previously termed *herpes gestationis*, pemphigoid gestationis is not related to the herpesvirus. Instead, maternal immunoglobulin G (IgG) antibodies target collagen XVII found in the basement membrane of skin and amnionic epithelium (Kelly, 1988; Shimanovich, 2002). Collagen XVII is also termed bullous pemphigoid 180 (BP 180). Autoantibody binding to collagen XVII activates complement to promote eosinophil chemotaxis to the antigen-antibody complexes. Eosinophilic degranulation damages the dermal-epidermal junction and leads to blistering (Engineer, 2000).

Pregnancy

In most cases, PG develops during a first pregnancy. It may rarely be associated with gestational trophoblastic disease (Matsumoto, 2013; Takatsuka, 2012). Most subsequent pregnancies are also affected, usually earlier and more severely (Tani, 2015). Whites have a higher incidence, and other autoimmune diseases are frequent in affected women (Shornick, 1984, 1992).

PG usually begins during the second or third trimester, but postpartum onset or exacerbation is common (Lawley, 1978). The disease course is often marked by antepartum flares and remissions. And, especially in cases with early-onset and blistering, PG has an association with preterm birth and fetal-growth restriction (Al-Saif, 2016; Chi, 2009). One theory for this is mild placental insufficiency that stems from IgG and complement deposition along the amnionic basement membrane (Huilaja, 2013). Accordingly, antepartum surveillance of affected pregnancies is reasonable.

In 5 to 10 percent of cases, IgG antibodies passively transfer from the mother to cause similar skin lesions in the newborn (Erickson, 2002). These eruptions in the neonate require only wound care and clear spontaneously within a few weeks as the passively acquired IgG levels decline. Slowly following delivery, maternal lesions resolve without scarring, and most women are disease-free after 6 months (Jenkins, 1999). In some, however, resolution is protracted, and disease may be exacerbated during menses or by oral contraceptives (Semkova, 2009).

Diagnosis and Treatment

Before bullae form, these lesions may resemble pruritic urticarial papules and plaques of pregnancy. Other diagnoses include pustular psoriasis, dermatitis herpetiformis, erythema multiforme, linear IgA bullous dermatosis, urticaria, allergic contact dermatitis, bullous pemphigoid, and atopic eruption of pregnancy (Lipozenčić, 2012). Drug-induced blistering syndromes must also be excluded as some are life-threatening, for example, Stevens-Johnson syndrome and toxic epidermal necrolysis (Stern, 2012).

Skin biopsy and serum antibody assays are informative. Immunofluorescent staining of a skin punch biopsy sample is the gold standard, and C3 complement and sometimes IgG are seen deposited along the basement membrane between the epidermis and the dermis (Katz, 1976). Also, in many cases, circulating IgG antibodies against collagen XVII can be detected in maternal serum (Powell, 2005; Sitaru, 2004).

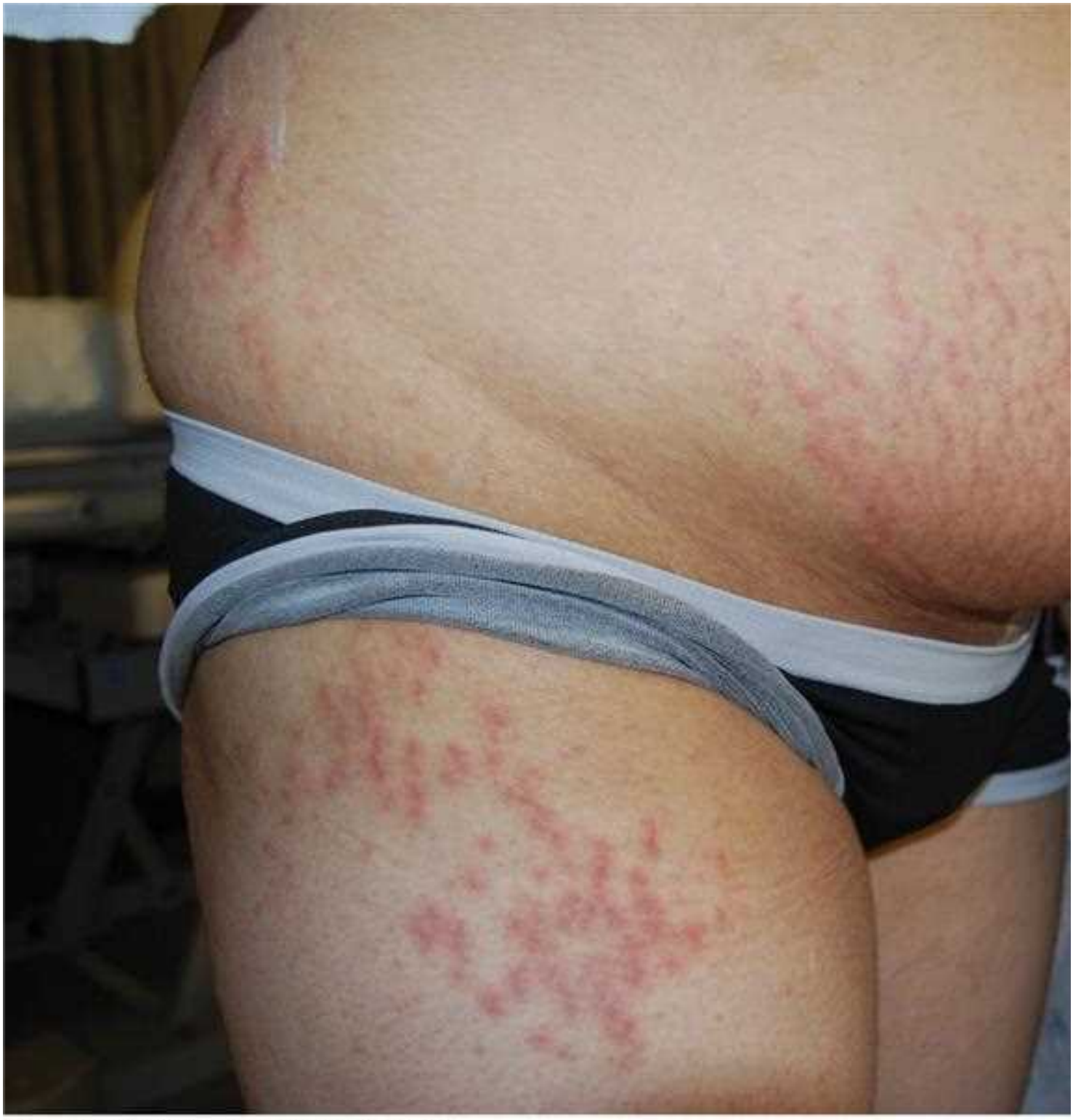
Pruritus can be severe. Early in its course, topical high-potency corticosteroids and oral antihistamines may be effective. Oral prednisone, 0.5 to 1 mg/kg daily gradually tapered to a maintenance dose, may be needed for relief and also for inhibition of new lesions. Plasmapheresis, high-dose intravenous immunoglobulin (IVIG) therapy, or cyclosporine has been used in intractable cases (Huilaja, 2015; Ko, 2014; Van de Wiel, 1980).

Pruritic Urticarial Papules and Plaques of Pregnancy

This relatively common pregnancy-specific dermatosis is characterized by its benign effects on pregnancy and by intensely pruritic 1- to 2-mm erythematous papules that coalesce to form urticarial plaques. Also known as *polymorphic eruption of pregnancy*, PUPPP usually appears late in pregnancy (Rudolph, 2005). Rarely, postpartum onset has been described (Park, 2013). The rash affects the abdomen and proximal thighs in 97 percent of women (Fig. 62-2). Lesions often initially form within striae but show periumbilical sparing. The face, palms, and soles also are rarely involved (High, 2005). It is more frequent in white and nulliparous women, those with multifetal gestation, and those carrying a male fetus (Regnier, 2008). PUPPP seldom recurs in subsequent pregnancies (Ahmadi, 2005). Its cause is unknown, but an autoimmune basis is not implicated (Lawley, 1979).

FIGURE 62-2

Pruritic urticarial papules and plaques of pregnancy (PUPPP) shows small papules on the buttock and proximal thigh and within abdominal striae.



PUPPP may be compared with several skin eruptions. Some include contact dermatitis, drug eruption, viral exanthem, insect bites, scabies infestation, pityriasis rosea, and the other pregnancy-specific dermatoses. It also may appear similar to early PG that has not yet blistered. In unclear cases, skin biopsy and negative serum collagen XVII antibody levels help to differentiate the two. Pruritus will usually respond to treatment with oral antihistamines, skin emollients, and topical corticosteroids. A few women will need systemic corticosteroids to relieve severe itching (Scheinfeld, 2008).

PUPPP usually resolves within several days following delivery and leaves no scarring. In 15 to 20 percent of women, however, symptoms persist for 2 to 4 weeks postpartum (Vaughan Jones, 1999).

Atopic Eruption of Pregnancy

This umbrella term encompasses three conditions previously considered separate: eczema in pregnancy, prurigo of pregnancy, and pruritic folliculitis of pregnancy (Ambros-Rudolph, 2006). Two thirds of women with atopic eruption have widespread eczematous changes, whereas the other third have papular lesions (American Academy of Dermatology, 2011). As a group, these pose no risk to the fetus. Diagnosis is greatly aided by a history of atopy and by rash characteristics.

Eczema in pregnancy has the appearance of traditional eczema but with a pregnancy onset. It is the most common pregnancy-specific dermatosis, and affected skin shows dry, thickened, scaly, red patches involving extremity flexures, nipples, neck, and face. In contrast, *prurigo of pregnancy*, also known as prurigo gestationis, is characterized by 5- to 10-mm, itchy, erythematous papules or nodules commonly found on the extensor surfaces and trunk. Last, *pruritic folliculitis of pregnancy* is rare and notable for small, erythematous follicular papules and sterile pustules predominantly on the trunk. Onset for all is during the second or third trimester, although eczema in pregnancy may develop earlier than the other two. All lesions commonly resolve with delivery, but may persist for up to 3 months postpartum. Recurrence with subsequent pregnancies is variable but common.

Diagnosis is one of exclusion. Serum bile acid levels are elevated but not greater than concentrations expected for normal pregnancy, and aminotransferase levels are normal. Serology specific for PG is negative. Many women with eczema of pregnancy have elevated serum IgE levels, which are not seen with the two other AEP dermatoses (Ambros-Rudolph, 2011).

For all three manifestations, skin lesions and pruritus are usually controlled with low- or moderate-potency topical corticosteroids and oral antihistamines. For severe eczema, second-line agents include short-course ultrapotent topical corticosteroids. In some cases, however, an oral corticosteroid, narrow-band ultraviolet B, or cyclosporine is required (Lehrhoff, 2013).

DERMATOLOGICAL CONDITIONS NOT SPECIFIC TO PREGNANCY

Any acute or chronic dermatological disorders can complicate pregnancy. Some of those chronic conditions are considered here.

Acne Vulgaris

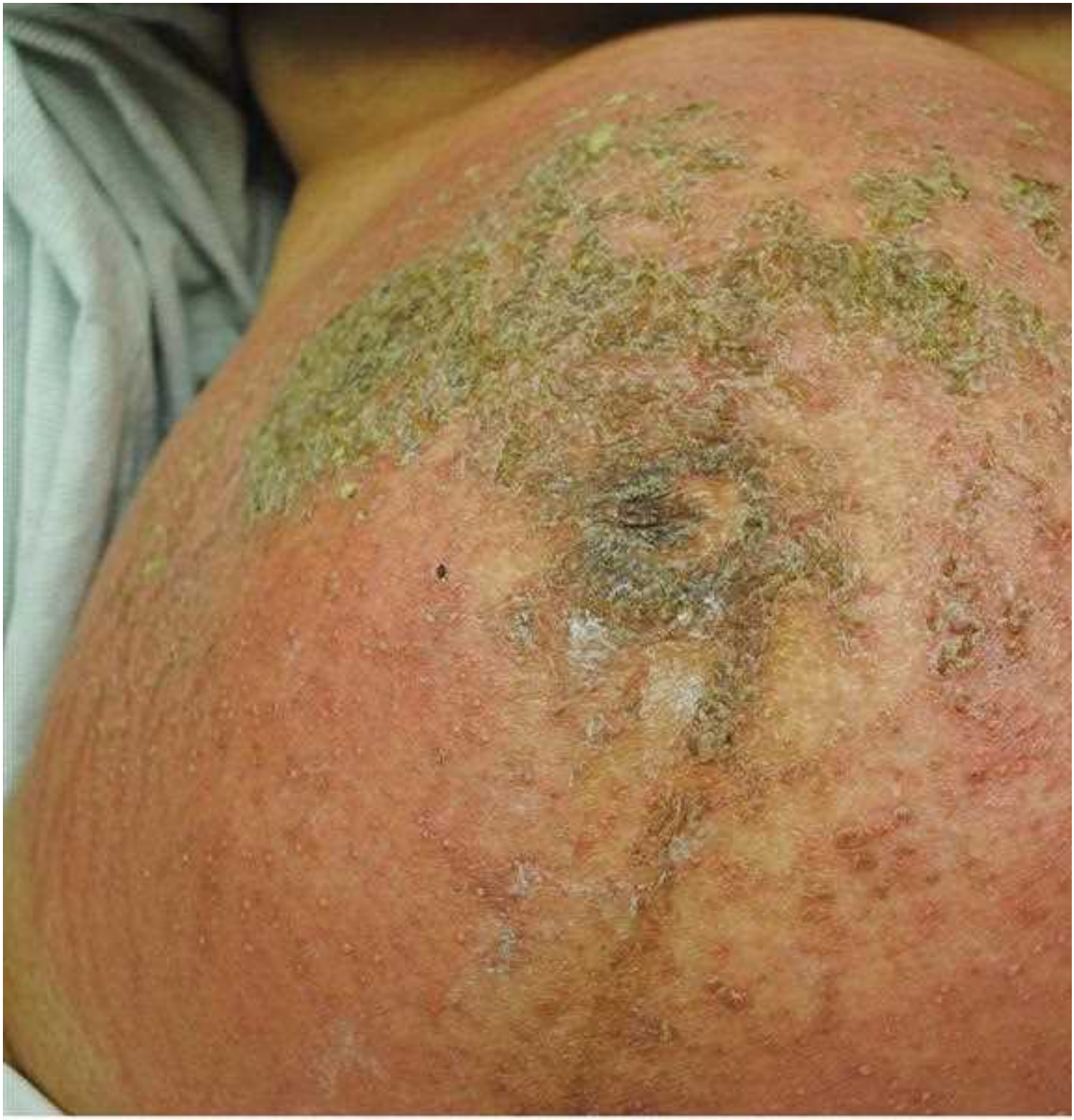
This common chronic dermatosis is unpredictably affected by pregnancy and, if necessary, is treated with benzoyl peroxide alone or coupled with either topical erythromycin or topical clindamycin (Zaenglein, 2016). In these combinations, benzoyl peroxide minimizes *Propionibacterium acnes* drug resistance. Azelaic acid is another comedolytic agent, which is category B. Topical salicylic acid is category C, but amounts in over-the-counter products are considered safe (Murase, 2014). Topical retinoids, which include tretinoin and adapalene, also appear safe, are category C drugs, but are probably best avoided during pregnancy, especially during the first trimester (Kaplan, 2015; Panchaud, 2012). Topical tazarotene is contraindicated. For more severe cases, oral antibiotics that include erythromycin, azithromycin, cephalexin, or amoxicillin may be coupled with benzoyl peroxide. Systemic antibiotics are ideally delayed until the second trimester, and therapy duration limited to 4 to 6 weeks (Chien, 2016).

Psoriasis and Pustular Psoriasis

This chronic dermatosis also has a variable course during pregnancy, however, postpartum flares are common (Oumeish, 2006). Emollients alone are given initially, and low- or moderate-potency topical corticosteroids can be added. In resistant cases, restrained use of high-potency or ultrapotent corticosteroids appears safe in the second and third trimesters. Ultraviolet B phototherapy can be used as a second-line option. Last, cyclosporine, systemic corticosteroids, or tumor necrosis factor (TNF)-α antagonists that include adalimumab, etanercept, and infliximab are third-tier agents for pregnancy (Bae, 2012). Overall, data do not support an increased risk of adverse pregnancy outcomes with psoriasis (Bobotsis, 2016). With severe disease, a small increased risk for low-birthweight neonates was found by some (Lima, 2012; Yang, 2011). Also, in general, psoriatic patients have higher associated rates of depression (Bandoli, 2017; Cohen, 2016).

Psoriasis is most commonly of the chronic plaque variety. In contrast, with *generalized pustular psoriasis of pregnancy,* severe systemic symptoms may develop. Formerly called impetigo herpetiformis, this rare pustular form has erythematous, sometimes pruritic plaques ringed by sterile pustules that enlarge and then crust (Fig. 62-3). Lesions initially involve intertriginous areas but may spread to the torso, extremities, and oral mucosa. Comorbid constitutional symptoms are common. Laboratory testing may reveal hypocalcemia, elevated erythrocyte sedimentation rate, leukocytosis, and hypoalbuminemia (Lehrhoff, 2013). Extensive lesions can lead to sepsis from secondary infection and to massive fluid loss with hypovolemia and placental insufficiency. First-line treatment is with oral prednisone, cyclosporine, infliximab, topical corticosteroids, or topical calcipotriene (Robinson, 2012). Phototherapy is a second-line option. For secondary infections, intravenous antibiotics are added (Huang, 2011). Pustular psoriasis typically resolves quickly in the puerperium, but recurrences have been reported in subsequent pregnancies and with menstruation or oral contraceptive use (Roth, 2011).

FIGURE 62-3
Generalized pustular psoriasis of pregnancy displays erythematous, sometimes pruritic plaques ringed by sterile pustules that enlarge and then form a scaling crust. (Used with permission from Dr. Paul Slocum.)



Erythema Nodosum

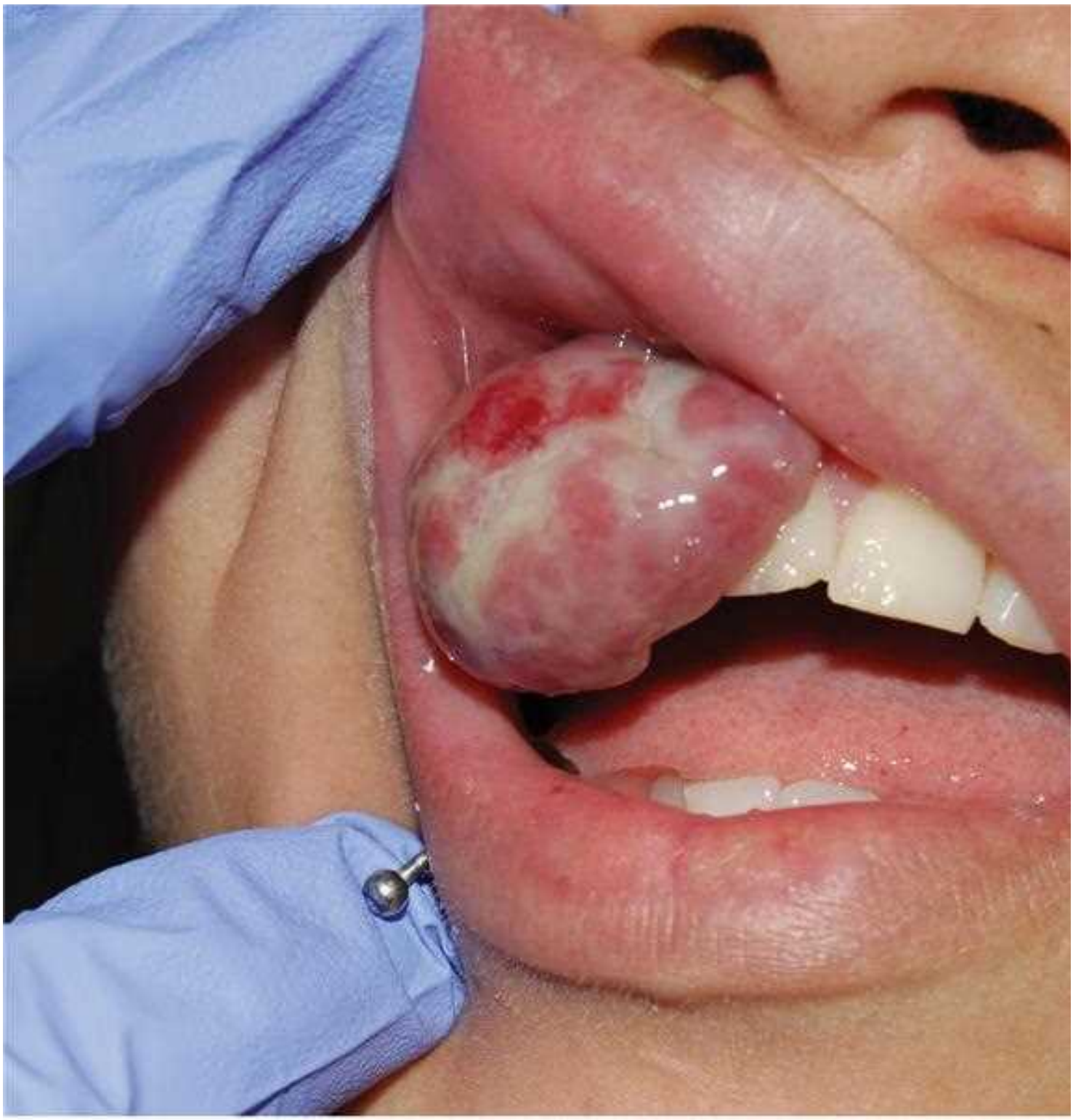
This skin condition represents inflammation of subcutaneous fat associated with numerous disorders, including pregnancy. Other triggers are infections, sarcoidosis, drugs, Behçet syndrome, inflammatory bowel disease, or a malignancy (Mert, 2007; Papagrigoraki, 2010). Characteristically, 1- to 6-cm tender, red, warm nodules and plaques develop rapidly on the extensor surface of the legs and arms. Within a few days, lesions flatten and undergo the color evolution of a bruise—from dark red and purple to yellow green. Constitutional symptoms may also be present. Initial evaluation and treatment focuses on the underlying etiology. Symptoms spontaneously resolve in 1 to 6 weeks without scarring but may leave residual hyperpigmentation (Acosta, 2013).

Pyogenic Granuloma

This lesion is frequently seen in pregnancy (Fig. 62-4). Poorly named, pyogenic granuloma is actually a lobular capillary hemangioma commonly forming on the mouth or hand in response to low-grade local irritation or traumatic injury. They grow quickly and bleed with minimal provocation. Active bleeding can be controlled with pressure and application of a silver nitrate stick or Monsel paste (ferric subsulfate). These growths often resolve within months postpartum. But with a symptomatic antepartum growth, a persistent postpartum lesion, or with an unclear diagnosis, excision can be done using suture and scalpel, electrosurgical curettage, laser photocoagulation, or cryotherapy. Oral lesions are best referred to oral health-care specialists.

FIGURE 62-4

Pyogenic granuloma is characterized grossly by a lobulated red growth on a pedunculated or sessile base. With minimal trauma, these vascular lesions bleed easily. (Used with permission from Dr. Abel Moron.)



Neurofibromatosis

These lesions are typified by benign cutaneous neurofibromas, café-au-lait spots, axillary and inguinal freckling, benign nodules of the iris (Lisch nodules), and optic nerve gliomas. Neurofibromas may increase in size and number during pregnancy (Cesaretti, 2013; Dugoff, 1996). With the more common neurofibromatosis type 1, higher rates of preclampsia and preterm birth complicate pregnancy (Leppävirta, 2017; Terry, 2013). With neurofibromatosis type 2, some evidence suggests a risk for preeclampsia (Terry, 2015). Prenatal genetic diagnosis is available for both types (Merker, 2015; Spits, 2007).

Miscellaneous Conditions

Rosacea fulminans is also known as *pyoderma faciale.* It is rare and characterized by facial pustules and coalescing draining sinuses. Topical or oral antimicrobials are primary treatment, although surgical drainage and corticosteroids have also been used (Fuentelsaz, 2011; Jarrett, 2010).

Hidradenitis suppurativa is said to improve with pregnancy, but in our experiences, it is not appreciably changed. Twice daily topically applied 1-percent clindamycin gel for 12 weeks aims to prevent new lesions. This can be supplemented by 7- to 10-day courses of oral amoxicillin plus clavulanic acid or oral clindamycin to reduce lesion progression (Margesson, 2014). Other options are reviewed by Perng and coworkers (2017).

Other skin conditions that are discussed elsewhere in this book include hirsutism and melanoma (Chap. 63, Malignant Melanoma), cutaneous lupus (Chap. 59, Lupus and Pregnancy), hyperpigmentation (Chap. 4, Breasts), and skin lesions seen with infections (Chaps. 64 and 65).

DERMATOLOGICAL TREATMENT

Local skin care, oral antihistamines, and topical corticosteroids are commonly used for many dermatoses. Oral antihistamines are given for pruritus. Suitable options include first-generation agents such as diphenhydramine (Benadryl), 25 to 50 mg every 6 hours, or chlorpheniramine (Chlor-Trimeton), 4 mg every 6 hours. Second-generation agents—loratadine (Claritin) 10 mg daily or cetirizine (Zyrtec) 5 or 10 mg daily—may produce less sedation and are also pregnancy category B.

Hundreds of topical corticosteroid preparations are available, and in the United States, these are categorized by potency into seven groups. For initial treatment of dermatological disorders, low- or moderate-potency agents are preferred. Low-potency agents include those in groups 6 and 7, such as 1-percent hydrocortisone or 0.05-percent desonide (DesOwen). Moderate-potency drugs are in groups 5, 4, and 3—such as 0.1-percent triamcinolone acetonide (Aristocort) or 0.1-percent mometasone furoate (Elocon). High-potency medications are in group 2, such as 0.05-percent betamethasone dipropionate (Diprolene). Ultrapotent agents in group 1, such as 0.05-percent clobetasol propionate (Temovate), are best reserved for refractory disorders and used for only 2 to 4 weeks on small surface areas.

Mild and moderate strengths are not associated with adverse pregnancy outcomes, whereas high- and ultrapotent agents pose a small risk for fetal-growth restriction with large cumulative doses (Chi, 2013, 2015). Even then, this risk is less than that with systemic corticosteroids. Importantly, with any topical agent, factors that increase systemic absorption include a large surface area treated, compromised epidermal barrier, occlusive dressings, prolonged treatment duration, and coadministration of topical agents that increase absorption.

The list of other agents used for dermatological conditions is extensive. For use in pregnancy and lactation, Murase (2014) and Butler (2014) have compiled tables and evidence-based descriptions of most. Notable therapeutic agents to avoid during pregnancy include methotrexate, psoralen plus ultraviolet A, mycophenolate mofetil, podophyllin, and systemic retinoids. These are discussed in more detail in Chapter 12. Bacterial infections are a potential secondary complication of skin disorders and are treated promptly with oral antimicrobial agents with gram-positive coverage.

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CHAPTER 63: Neoplastic Disorders

Any excessive enlargement of the abdomen or the appearance of pressure symptoms should always lead one to make a careful examination, and in not a few cases a tumour will be found occupying the pelvic cavity. In rare instances malignant tumours of the rectum may so obstruct the pelvic canal as to render caesarean section imperative.

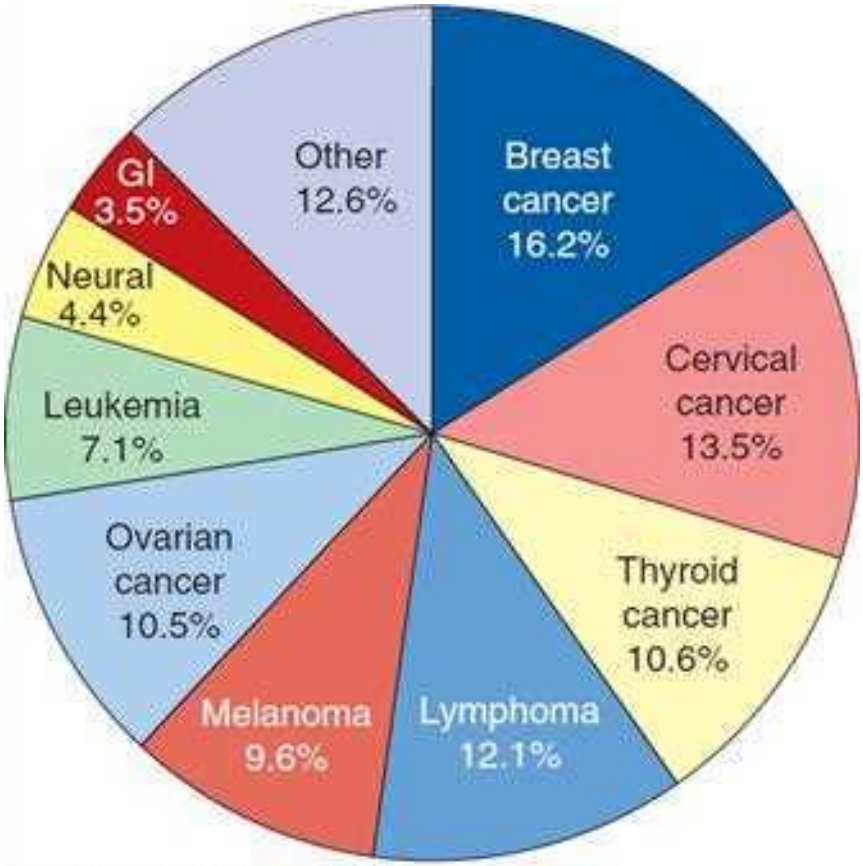
—J. Whitridge Williams (1903)

INTRODUCTION

Any neoplasm can complicate pregnancy, and as written by Williams, physical examination often suggests the diagnosis. Current imaging also allows a greater number of these to be identified antepartum. Most encountered neoplasms are benign, and uterine leiomyomas and ovarian cysts are the most frequent.

Cancer has an incidence approximating 1 per 1000 pregnancies (Parazzini, 2017; Salani, 2014). One third are diagnosed prenatally, and the others within 12 months of delivery. Some of the more frequent ones are shown in Figure 63-1. Breast cancer is found in 1 in 5000 pregnancies, thyroid—1 in 7000, and cervical—1 in 8500 (Smith, 2003). These, along with lymphoma and melanoma, account for 65 percent of malignancy cases in pregnancy (Eibye, 2013). For some cancers—ovary, endometrium, and breast—evidence suggests that high parity is protective (Högnäs, 2014).

FIGURE 63-1
Proportion of malignancies during pregnancy and within 12 months of delivery in 4.85 million women from the California Cancer Registry. GI = gastrointestinal. (Data from Smith, 2003.)



During pregnancy, cancer management poses unique problems related to fetal concerns, and treatment must be individualized. Considerations include the type and stage of malignancy, the desire for pregnancy continuation, and inherent risks associated with modifying or delaying cancer treatment.

CANCER THERAPY IN PREGNANCY

Surgery

Operative procedures indicated for cancer include those for diagnosis, staging, or therapy. Fortunately, most procedures that do not interfere with the reproductive tract are well tolerated by both mother and fetus (Chap. 46, Medications and Surgeries). Although many operations have classically been deferred until after 12 to 14 weeks' gestation to minimize miscarriage risks, this probably is not necessary. We are of the opinion that surgery should be performed regardless of gestational age if maternal well-being is imperiled.

Both pregnancy and malignancy are risk factors for venous thromboembolism (VTE). In one study, Bleau and coworkers (2016) reported a higher risk of VTE in gravidas with myeloid leukemia, Hodgkin disease, cervical cancer, and ovarian cancer compared with that in pregnant women without a malignancy. The risk was not increased in those with brain or thyroid cancer, melanoma, or lymphoid leukemia. That said, current guidelines lack specific recommendations for pregnant women undergoing surgeries for cancer. Thus, depending on the complexity of the planned procedure, it seems reasonable to use prophylactic low-molecular-weight heparin combined with elastic stockings and/or intermittent pneumatic compression as described in Chapter 52 (Thromboprophylaxis).

Diagnostic Imaging

Sonography is a preferred imaging tool during pregnancy. Even so, according to the American College of Obstetricians and Gynecologists (2017a), most diagnostic radiographic procedures deliver very low x-ray doses and should not be delayed if they would directly affect therapy (Chap. 46, X-Ray Dosimetry). Magnetic resonance (MR) imaging can safely be performed in any trimester, but delay until after the first trimester may lower potential risks. Gadolinium should not be used in the first trimester and should be used later in pregnancy only when the benefits overwhelmingly outweigh the risks (American College of Radiology, 2016; Kanal, 2013). Computed tomography (CT) is less often selected due to ionizing radiation, and procedure-related doses are listed in Chapter 46 (Computed Tomography). Accordingly, CT is used in pregnancy most often to evaluate acute concerns that include pulmonary embolism, bowel or renal obstruction, and acute neurological events. To enhance CT, oral and intravenous contrasts may be added. These lack known fetal harm, and postpartum breastfeeding need not be interrupted. Last, some radioisotopes are relatively safe in pregnancy and are listed in Table 46-8.

Radiation Therapy

Therapeutic radiation often results in significant fetal exposure depending on the dose, tumor location, field size, and gestational age. Potential adverse effects include fetal malformation, intellectual disability, growth restriction, sterility, and carcinogenesis (Brent, 1999; Stovall, 1995). In the 2 weeks following fertilization, exposure typically leads to chromosomal damage and embryonic death. The next most susceptible period is during organogenesis in weeks 2 through 8, and exposure can cause malformation. These might develop above a threshold dose of 0.1 to 0.2 Gy. During weeks 8 through 25, the fetal central nervous system is especially vulnerable. The threshold dose for intellectual disability at 8 to 15 weeks' gestation approximates 0.06 Gy, and at 16 to 25 weeks it is about 0.25 Gy (Kal, 2005; Otake, 1996). After 25 weeks' gestation, susceptibility is less, although no gestational age is considered safe for therapeutic radiation exposure. Thus, radiotherapy to the maternal abdomen is contraindicated. With some head and neck cancers, however, radiotherapy to supradiaphragmatic areas can be used relatively safely with abdominal shielding of the fetus (Amant, 2015a).

Chemotherapy

Various antineoplastic drugs may be given for primary treatment or for adjunctive therapy. Although chemotherapy often improves long-term maternal outcomes, many are reluctant to employ it during pregnancy. Concerns for the fetus include malformations, growth restriction, intellectual disability, and the risk of future childhood malignancies. Risks are dependent primarily on fetal age at exposure, and most agents are potentially detrimental in the first trimester during organogenesis. Indeed, in one review, 14 percent of major malformations were attributable to first-trimester exposure to cytotoxic drugs (National Toxicology Program, 2013).

After the first trimester, most antineoplastic drugs are without immediate obvious adverse fetal sequelae (Abdel-Hady, 2012; Vercruysse, 2016). Similarly, late mutagenic effects appear limited (Amant, 2015b; Cardonick, 2015). Although not always practicable, some recommend that chemotherapy be withheld in the 3 weeks before expected delivery because neutropenia or pancytopenia might cause undue risk for maternal infection or hemorrhage. Another concern is that neonatal hepatic and renal clearance of chemotherapy metabolites is limited (Ko, 2011). For these reasons, most cytotoxic chemotherapy agents are contraindicated with breastfeeding (Pistilli, 2013).

Molecular Therapy

Drugs designed to stimulate hemopoiesis are commonly used with cancer treatments. Some of these include the granulocyte colony-stimulating factors filgrastim (Neupogen) and pegfilgrastim (Neulasta). If required in pregnancy, limited data support the safety of these agents (Boxer, 2015). Red blood cells can be stimulated by erythropoietin alfa (Procrit), which from case reports also appears safe in pregnancy (Sienas, 2013). However, maternal hypertension is a known potential risk.

Targeted Therapy

The two main types of targeted therapy are monoclonal antibodies and small molecule inhibitors. Both block the actions of specific enzymes, proteins, or other molecules involved in cancer cell growth. These drugs are designed to treat an ever-expanding list of cancers, and some are described in later discussions of specific tumors. Most of these compounds are labeled by the Food and Drug Administration (FDA) as class D, and data are limited regarding their pregnancy or breastfeeding effects.

Many of these drugs target tyrosine kinase, an important enzyme that regulates signaling pathways involved with cell division, differentiation, and apoptosis. With first-trimester use, embryo toxicity or teratogenicity has been attributed to these. Thus, this specific group of targeted agents is considered for use in pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus (Lodish, 2013).

Of other agents, the monoclonal antibody trastuzumab (Herceptin) inhibits the human epidermal growth factor receptor type 2 (HER2), which some breast cancers express. Although not teratogenic, its use in the second and third trimesters is associated with oligohydramnios, which appears to be reversible upon stopping the drug (Sarno, 2013; Zagouri, 2013b). Because of sparse available data, other HER2 inhibitors are best avoided in pregnancy (Lambertini, 2015).

Fertility and Pregnancy after Cancer Therapy

Fertility may be diminished after chemotherapy or radiotherapy. Counseling ideally takes place before cancer treatment, and guidelines for this have been developed (American Society for Reproductive Medicine, 2013a; Lambertini, 2016; Loren, 2013; Peccatori, 2013). Prior to therapy, cryopreservation of embryos or of oocytes is a recognized fertility-preserving option (American Society for Reproductive Medicine, 2013b,c). Surgical transposition of the ovaries can be considered if pelvic radiation is planned. For this, ovaries and their intact primary blood supply are carried out of the pelvis and fixed to the lateral abdominal wall at a site 3 to 4 cm above the level of the umbilicus. In one review, functional preservation was reported in 65 to 94 percent, depending on radiotherapy type (Gubbala, 2014). Also, such transposition requires transabdominal egg retrieval if later in vitro fertilization is planned (American Society for Reproductive Medicine, 2013a).

Ovarian suppression with gonadotropin-releasing hormone agonists is not beneficial, according to a recent review (Elgindy, 2015). At this time, cryopreservation of ovarian tissue is considered investigational. These methods currently are limited to referral centers.

In counseling cancer survivors, evidence suggests that exposure to most radiotherapy or chemotherapy agents in childhood or adulthood does not significantly increase the risk of congenital anomalies or genetic disease in their offspring (Haggar, 2014; Signorello, 2012; Stensheim, 2013; Winther, 2012). In those treated as children with chemotherapy, studies also do not show a consistent link to adverse obstetrical outcomes (Melin, 2015; Reulen, 2009). Data are limited regarding those with cancer treated as an adult, and some studies have shown slightly higher rates of preterm birth and cesarean delivery (Haggar, 2014; Stensheim, 2013).

Notably, prior abdominopelvic radiation more convincingly affects neonatal outcomes. Adverse effects include elevated rates of abortion, low birthweight, stillbirth, and preterm birth (Signorello, 2006, 2010; Winther, 2008). Radiation may lower reproductive potential by creating reduced uterine volume, a thinned endometrium, and impaired uterine blood flow (Critchley, 1992; Larsen, 2004). Greater effects are seen with direct uterine radiation and with radiotherapy at younger ages (Teh, 2014).

Importantly, many cancer survivors conceive by assisted reproductive technology, which by itself has associated obstetrical risks. This is discussed in Chapter 8 (Reproductive History).

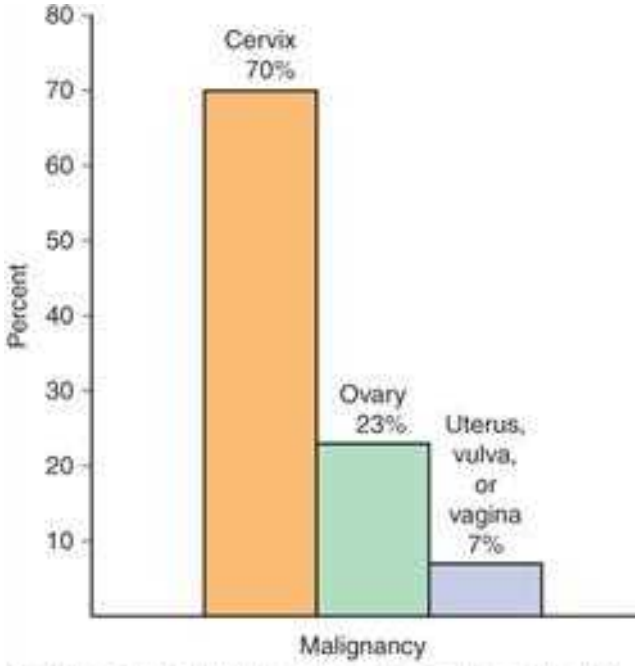
Placental Metastases

Tumors infrequently metastasize to the placenta. As described in Chapter 6 (Amniochorion), the most common types are malignant melanomas, leukemias, lymphomas, and breast cancer (Al-Adnani, 2007). Placentas from pregnancies in these and all other women with a malignancy should be sent for histological evaluation. Because tumor cells are usually confined within the intervillous spaces, fetal metastases are infrequent.

REPRODUCTIVE TRACT NEOPLASMS

Benign neoplasms are common and include leiomyomas, ovarian neoplasms, and endocervical polyps. Cancer in these organs may also complicate pregnancy, and of these, cervical neoplasia makes up the majority (Fig. 63-2).

FIGURE 63-2
Frequency of reproductive-tract malignancies in 844 pregnant women. (Data from Haas, 1984; Lutz, 1977; Smith, 2003.)



Cervix

Endocervical Polyp

These are overgrowths of endocervical stroma covered by epithelium. They typically appear as single, red, elongated fleshy masses of variable size that extend outward from the endocervical canal. Usually benign, they can bleed and can be a source of Pap test results describing *atypical glandular cells of undetermined significance—AGUS*. With removal and histological evaluation of these polyps, dysplasia is diagnosed in up to 0.5 percent, and there is malignant transformation in up to 0.1 percent (Esim Buyukbayrak, 2011; Long, 2013).

Few formal data guide management in pregnancy. Small asymptomatic lesions may be left alone to slough during delivery or puerperal remodeling. Removal and histological evaluation is reasonable if malignancy is suspected or if bleeding is troublesome. For those with a slender stalk, the polyp is grasped with ring forceps and twisted repeatedly about its base to strangulate feeding vessels. With repeated twisting, the base narrows and avulses. Monsel paste, which is ferric subsulfate, can be applied with pressure to the stalk stub for hemostasis. A thick-pedicle polyp may sometimes warrant surgical ligation and excision.

Epithelial Neoplasia

Pregnancy provides an opportune time to screen for cervical intraepithelial neoplasia (CIN), especially in women without regular access to health care. With Pap test screening, pregnancy status is noted on the requisition form because interpretation may be hindered by pregnancy-associated physiological changes. Some of these changes include presence of decidual cells and less often, Arias-Stella reaction. The latter gives an appearance of endocervical gland hyperplasia, which can make differentiating this from truly atypical glandular cells difficult.

Screening guidelines also applicable in pregnant women were updated in 2012 by the American Society for Colposcopy and Cervical Pathology (ASCCP). These include: (1) no screening until age 21, (2) cytology alone every 3 years in those aged 21 to 29 years, and (3) in those older than 30, human papillomavirus (HPV) *and* cytology co-testing every 5 years, or cytology alone every 3 years (Massad, 2013). High-risk conditions for cervical neoplasia include human immunodeficiency virus (HIV) infection, other immunocompromised states, and in utero diethylstilbestrol (DES) exposure. For women with HIV infection, initiation of cervical cancer screening with cytology alone begins within the first year after HIV diagnosis (American College of Obstetricians and Gynecologists, 2016b).

Human Papillomavirus

This virus infects cervical epithelia. In most instances, the infection clears, but in a smaller number, the virus may promote benign, premalignant, or cancerous neoplastic growth. The prevalence of HPV infection in pregnant women approximates 15 percent (Hong, 2013; Liu, 2014). There are more than 100 serotypes, and several are associated with high-grade intraepithelial lesions and invasive cancer. The most prominent of these are serotypes 16 and 18. Cervical cancer screening that combines both cytology and testing for high-risk HPV serotypes is termed *co-testing* and is suitable for women 30 years and older. Notably, as a new paradigm for screening, primary HPV testing alone can be considered an appropriate sole method for women older than 25 years (Huh, 2015). With this, identification of serotypes 16 or 18 prompts colposcopic evaluation.

Serotypes HPV 6 and 11 are linked with benign maternal genital warts. Congenital HPV infection from vertical transmission—mother to fetus or newborn—beyond transient skin colonization is rare. Still, conjunctival, laryngeal, vulvar, or perianal warts present at birth in the neonate or that develop within 1 to 3 years of birth are most likely due to perinatal exposure to these maternal HPV serotypes. This is described further in Chapter 65 (Vaginitis). Importantly, cesarean delivery does not lower the risk of neonatal laryngeal papillomatosis.

The clear link between HPV infection and cervical neoplasia has prompted development of three approved vaccines. These are not administered during pregnancy, are compatible with breastfeeding, and are discussed in Chapter 65 (Vaginitis).

Abnormal Cytology and Histology

The incidence of abnormal cervical cytology during pregnancy is at least as high as that reported for nonpregnant women. Abnormal cytological findings and their suggested management according to consensus guidelines are summarized in Table 63-1. Many of these cytological abnormalities should prompt colposcopy, and the main goal during pregnancy is exclusion of invasive cancer. Accordingly, lesions suspicious for high-grade disease or cancer should undergo biopsy. Unsatisfactory colposcopic evaluation is less common during pregnancy because the transformation zone is better exposed due to cervical eversion. With insufficient visualization of the zone, colposcopy is repeated in 6 to 8 weeks. During this time, the squamocolumnar junction usually will further evert to permit satisfactory examination.

TABLE 63-1

Management of Pap Test Abnormalities in Pregnancy

Abnormality	Women Aged 25+ Years	Women Aged 21 to 34 Years
NILM/HPV positive[a]	Repeat Pap in 1 year; colposcopy if current Pap is 2nd NILM/HPV positive	Not applicable
ASC-US		
HPV positive	Colposcopy preferred; deferral of colposcopy until 6 weeks postpartum acceptable	Repeat Pap in 1 year
HPV negative	Routine screening	Routine screening
HPV unknown	Repeat cytology 1 year; colposcopy if current Pap is 2nd ASC-US	
LSIL	Colposcopy preferred; deferral of colposcopy until 6 weeks postpartum acceptable	Repeat Pap in 1 year
ASC-H HSIL SCCA AGC AIS adenoCA	Colposcopy during pregnancy[b]	

[a]Women aged 30+ years.

[b]Endocervical curettage and endometrial sampling are contraindicated in pregnancy.

adenoCA = adenocarcinoma; AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy; SCCA = squamous cell carcinoma.

Adapted from American Society for Colposcopy and Cervical Pathology (ASCCP) 2012 Consensus Guidelines; Massad, 2013.

Table summarized and used with permission from Dr. Claudia L. Werner.

Women with histologically confirmed CIN during pregnancy may be allowed to deliver vaginally, with further evaluation planned after delivery. For those with CIN 1, the recommended management is reevaluation postpartum. For those with CIN 2 or 3 in which invasive disease has been excluded, deferring reevaluation until at least 6 weeks postpartum is acceptable. Alternatively, repeat colposcopic and cytological evaluations are performed at intervals no more frequent than 12 weeks. Repeat biopsy is recommended only if appearance of the lesion worsens or if cytology suggests invasive cancer (Massad, 2013).

Regression of a CIN lesion is common during pregnancy or postpartum. In a study of 1079 pregnant women with cervical dysplasia in which biopsy correlated with colposcopic findings, 61 percent of lesions reverted to normal postpartum (Fader, 2010). In another study, Yost and colleagues (1999) reported postpartum lesion regression in 70 percent of women with CIN 2 or 3. And, although 7 percent of women had CIN 2 lesions that progressed to CIN 3, no lesion progressed to invasive carcinoma. In another study of 77 women with carcinoma in situ (CIS) diagnosed during pregnancy, a third had postpartum regression of their lesion, two thirds had persistent CIS, and only two women had microinvasive cancer on cone biopsy after delivery (Ackermann, 2006).

Adenocarcinoma in situ (AIS) is managed similarly to CIN 3 (Dunton, 2008). Thus, unless invasive cancer is identified, treatment of AIS is not recommended until 6 weeks postpartum.

Cervical Conization

If invasive epithelial lesions are suspected, conization is indicated and may be done with loop electrosurgical excisional procedure (LEEP) or by cold-knife conization. However, the epithelium and underlying stroma within the endocervical canal cannot be extensively excised without the risk of membrane rupture. Logically, residual disease is common. Of 376 cone biopsies during pregnancy, Hacker and associates (1982) found residual neoplasia in 43 percent of subsequent specimens. In addition, nearly 10 percent of 180 pregnant women required transfusion after conization (Averette, 1970). Thus, if possible, conization is avoided in pregnancy because of its higher risks for abortion, membrane rupture, hemorrhage, and preterm delivery.

Women with CIN treated *before* pregnancy may also encounter pregnancy complications. First, cicatricial cervical stenosis is uncommon but may follow conization, LEEP, or laser surgery. Cervical stenosis almost always yields during labor. A so-called *conglutinated cervix* may undergo almost complete intrapartum effacement without dilation, and the presenting part is separated from the vagina by only a thin layer of cervical tissue. Spontaneous dilation usually promptly follows firm pressure with a fingertip, although instrumented dilation or cruciate incisions may be required.

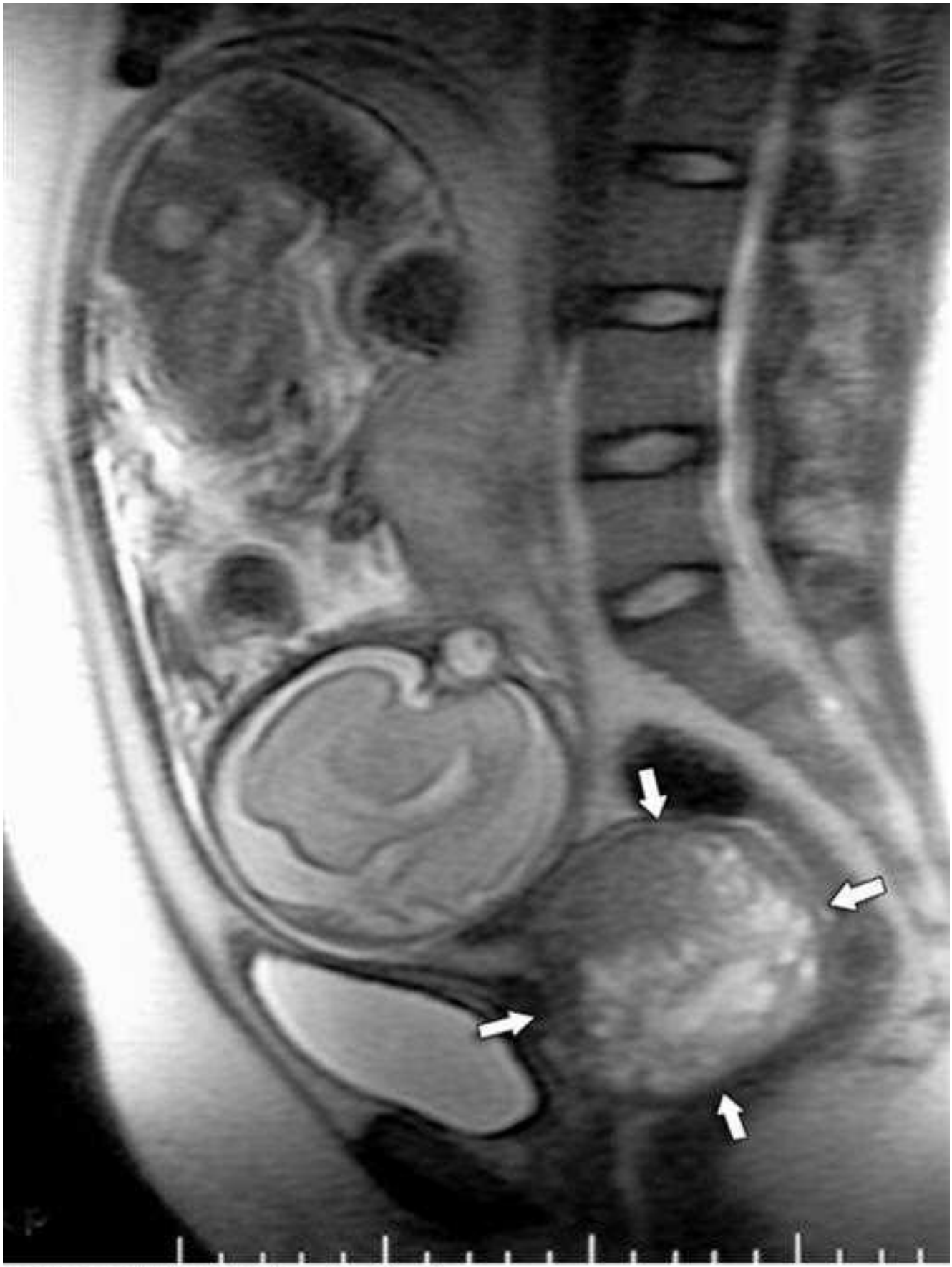
Second, preconceptional cold-knife conization is associated with cervical insufficiency and preterm birth. That said, the relationship between preterm birth and LEEP continues to be debated (Castanon, 2012; Conner, 2014; Stout, 2015; Werner, 2010). The size of tissue excised seems to be directly related to adverse outcomes (Weinmann, 2017).

Invasive Cervical Cancer

The incidence of invasive cervical carcinoma has dramatically declined in the United States as a result of PAP testing (American College of Obstetricians and Gynecologists, 2016b). This cancer is found in approximately 1 in 8500 pregnancies (Bigelow, 2017; Pettersson, 2010). The diagnosis is confirmed with biopsies taken during colposcopy, with conization, or from a grossly abnormal lesion. Of the histological types, squamous cell carcinomas account for 75 percent of all cervical cancers, whereas adenocarcinomas compose the remainder. Cancers may appear as exophytic or endophytic growth; as a polypoid mass, papillary tissue, or barrel-shaped cervix; or as focal ulceration or necrosis. A watery, purulent, foul, or bloody discharge may also be present. Biopsy with Tischler forceps is warranted for suspicious lesions. Abnormal tumor vessels may cause heavier than expected biopsy-site bleeding, which is usually controlled by Monsel paste and pressure.

Cervical cancer is staged clinically, and 70 to 75 percent of cases that are diagnosed in pregnancy are stage I (Bigelow, 2017; Morice, 2012). Physiological pregnancy changes may impede accurate staging, and the extent of cancer is more likely to be underestimated in pregnant women. Specifically, induration of the broad ligament base, which characterizes tumor spread beyond the cervix, may be less prominent due to cervical, paracervical, and parametrial pregnancy-induced softening. Staging in pregnancy typically incorporates findings from pelvic examination and from renal sonography, chest radiography, cystoscopy, proctoscopy, and perhaps cone biopsy. Although MR imaging is not formally considered for clinical staging, it can be used without gadolinium contrast to ascertain involvement of the urinary tract and lymph nodes (Fig. 63-3).

FIGURE 63-3
Sagittal T2-weighted magnetic resonance image of a gravid uterus at 32 weeks' gestation with a large cervical carcinoma (*arrows*).



Management and Prognosis

Cervical cancer treatment in pregnant women is individualized, and factors include the clinical stage, fetal age, and individual desire to continue pregnancy. Stage IA1 is termed *microinvasive disease* and describes lesions with deepest invasion ≤3 mm and widest lateral extension ≤7 mm (FIGO Committee on Gynecologic

Oncology, 2009). If diagnosed by cone biopsy, then treatment follows guidelines similar to those for intraepithelial disease. In general, continuation of pregnancy and vaginal delivery are considered safe, and definitive therapy is reserved until 6 weeks postpartum.

In contrast, invasive cancer demands relatively prompt therapy. During the first half of pregnancy, immediate treatment is advised by most, but this depends on the decision whether to continue pregnancy. During the latter half of pregnancy, most agree that pregnancy can safely be continued until fetal lung maturity is attained (Greer, 1989). In two studies with a total of 40 women past 20 weeks' gestation with either stage I or stage IIA carcinoma, delayed treatment was considered reasonable in women without bulky lesions (Takushi, 2002; van Vliet, 1998). Another option is to complete staging using laparoscopic lymphadenectomy and to delay treatment if metastases are excluded (Alouini, 2008; Favero, 2010). In a metaanalysis, neoadjuvant chemotherapy, that is, prior to surgery, with platinum derivatives was found to be promising for treatment in pregnancy (Zagouri, 2013a).

Although surgical therapy and radiation are equally effective, radical hysterectomy plus pelvic lymphadenectomy is the preferred treatment for invasive cervical cancer in most young women with stage I and early stage IIA lesions. Disadvantageously, radiotherapy for cervical cancer destroys ovarian and possibly sexual function, and frequently causes intestinal and urinary tract injury. In 49 women with pregnancy-associated stage IB cancer, a 30-percent severe complication rate accompanied radiotherapy compared with that of only 7 percent with radical surgery (Nisker, 1983). With surgery before 20 weeks' gestation, radical hysterectomy is usually performed with the fetus in situ. In later pregnancy, however, hysterotomy is often performed first.

Although less commonly selected during pregnancy, other procedures have been investigated for early-stage cervical cancers. Ungár and colleagues (2006) performed abdominal radical trachelectomy before 20 weeks' gestation for stage IB1 cancer in five pregnant women. Yahata and associates (2008) treated four women at 16 to 23 weeks for stage IA1 adenocarcinoma with laser conization, and all delivered at term. Van Calsteren and coworkers (2008) reported similar success.

For more advanced-stage cancer, radiotherapy is given. External beam radiation in early in pregnancy typically leads to spontaneous abortion. If miscarriage does not ensue, curettage is performed. During the second trimester, spontaneous abortion may not promptly occur and may necessitate hysterotomy in up to a fourth of cases. This is selected because labor induction or dilation and evacuation may pose serious hemorrhage risks.

Pregnancy does not have a negative effect on the prognosis of cervical cancer, and survival outcomes are similar for pregnant and nonpregnant women (Amant, 2014; Mogos, 2013). In a case-control study of 44 women with pregnancy-associated cervical cancer, the overall 5-year survival rate approximated 80 percent in both pregnant women and nonpregnant controls (van der Vange, 1995).

Delivery

Any adverse prognostic effects that vaginal delivery through a cancerous cervix might have are unknown. For this reason, the mode of delivery is controversial, especially for small, early-stage lesions. In some cases of bulky or friable tumors, significant hemorrhage from the cancer may complicate vaginal delivery. Also, recurrences have been reported in the episiotomy scar, which result from tumor cells apparently "seeding" the episiotomy (Goldman, 2003). Thus, most favor cesarean delivery.

Pregnancy after Radical Trachelectomy

There is growing experience with pregnancy in women who have undergone fertility-sparing radical trachelectomy for stage IB1 and IB2 cervical cancer before conception. During the typically vaginal procedure, the cervix is amputated at the level of the internal os, and a permanent-suture cerclage is placed around the isthmus for support in future pregnancies. The uterine isthmus is then reconstructed to the vagina. Because of the permanent cerclage, a classical cesarean incision is required for delivery.

Shepherd and colleagues (2006) presented outcomes for 123 such women cared for at their institution. Of 63 women who attempted pregnancy, 19 had 28 live births. All underwent classical cesarean delivery, and one fourth delivered before 32 weeks. Similar findings were reported by Kim (2012) and Park (2014) and their coworkers.

Uterus

Leiomyomas

Also known as myomas and somewhat erroneously called *fibroids*, uterine leiomyomas are common benign smooth-muscle tumors. Their incidence during pregnancy approximates 2 percent, and the cited range depends on the frequency of routine sonography and population characteristics (Qidwai, 2006; Stout, 2010). In one study of 4271 women, the first-trimester leiomyoma prevalence was highest in black women—18 percent—and lowest in whites—8 percent (Laughlin, 2009).

Leiomyomas vary in location and may develop as submucous, subserosal, or intramural growths. Less often, these develop in the cervix or broad ligament. Some become parasitic and their blood supply is derived from adjacent structures such as the highly vascularized omentum. In one rare manifestation–*leiomyomatosis peritonealis disseminata*–numerous, small, benign subperitoneal smooth-muscle tumors appear similar to carcinomatosis. The tumors are likely caused by estrogen stimulation of multicentric subcoelomic mesenchymal cells to become smooth-muscle cells (Bulun, 2015). These growths often regress after pregnancy.

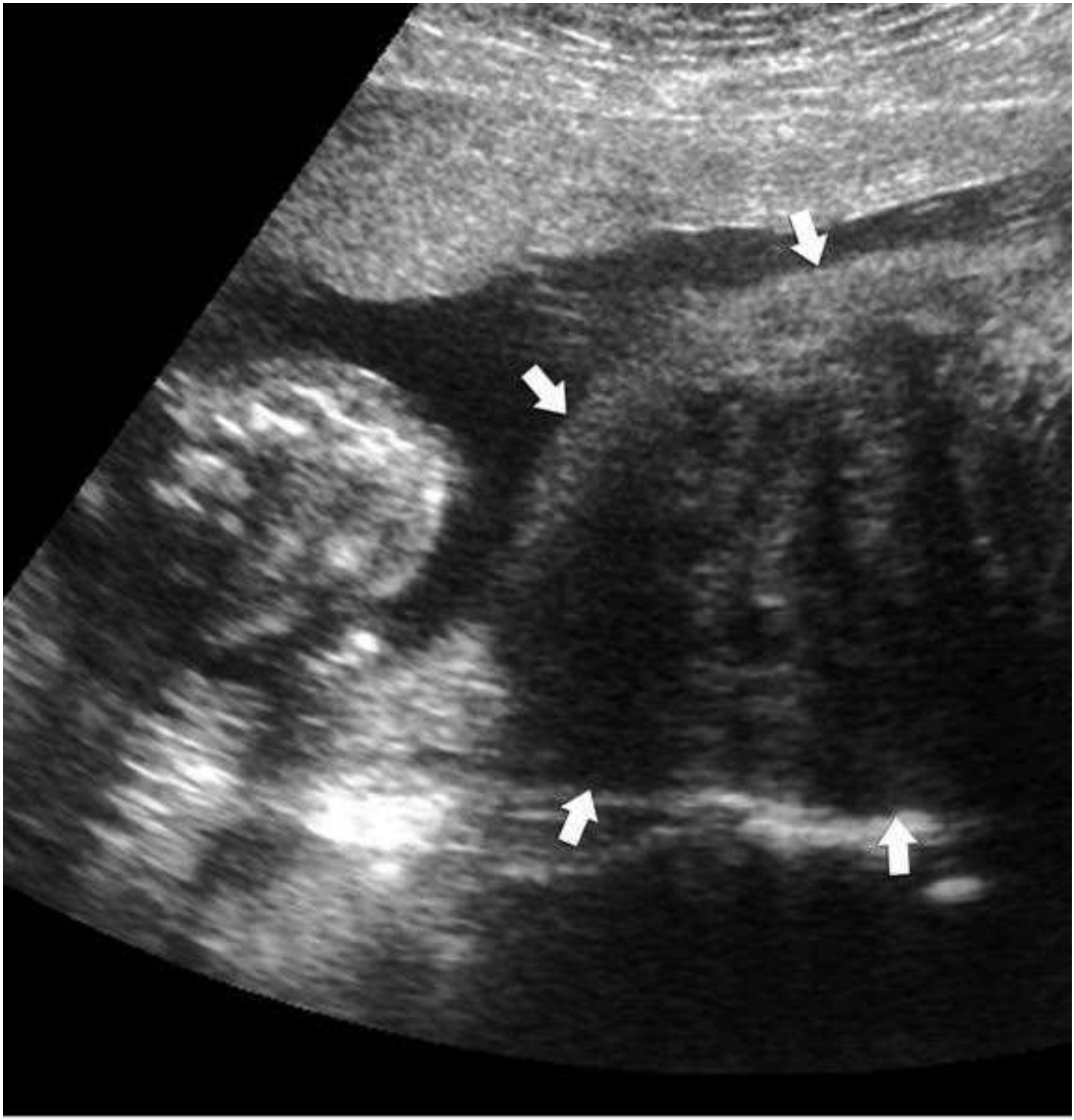
The stimulatory effects of pregnancy progesterone on myoma growth are unpredictable and can be impressive. These tumors respond differently in individual women and may grow, regress, or remain unchanged in size during pregnancy (Laughlin, 2009; Neiger, 2006).

Especially during pregnancy, myomas can be confused with other adnexal masses, and sonographic imaging is indispensable (Fig. 63-4). In women in whom sonographic findings are unclear, MR imaging performed after the first trimester may be necessary. Once diagnosed, leiomyomas do not require surveillance with serial sonography unless associated complications are anticipated.

FIGURE 63-4

Sonogram of a pregnant uterus with a large uterine leiomyoma. The heterogeneous mass (*arrows*) lies beside the fetus (seen in cross section) and has the classic appearance of a leiomyoma in pregnancy. The placenta is located anteriorly, and the mass originates from the posterior lower uterine segment and occupies more

than half of the total uterine volume.



Symptoms

Most leiomyomas are asymptomatic, but acute or chronic pain or pressure may develop. Large myomas more often require admission for pain (Doğan, 2016). For chronic pain secondary to large tumor size, nonnarcotic analgesic drugs usually suffice. More acutely, some myomas can outgrow their blood supply and hemorrhagic infarction follows, which is termed *red* or *carneous degeneration*. Clinically, there is acute focal abdominal pain and tenderness, and sometimes a low-grade fever and leukocytosis. As such, tumor degeneration may be difficult to differentiate from appendicitis, placental abruption, ureteral stone, or pyelonephritis. Sonographic imaging can be helpful, but close observation is requisite because an infarcted myoma is essentially a diagnosis of exclusion. In some women, preterm labor is stimulated by associated inflammation.

Treatment of a degenerated myoma is analgesic medications, and symptoms usually abate within a few days. In severe cases, close observation may be needed to exclude a septic cause. Although surgery is rarely necessary during pregnancy, myomectomy in highly selected cases has resulted in good outcomes. Of 23 reported

cases, women were 14 to 20 weeks' gestation, and in almost half, surgery was performed because of pain (Celik, 2002; De Carolis, 2001). In some, an intramural leiomyoma was in contact with the implantation site. Except for one loss immediately following surgery at 19 weeks, most underwent cesarean delivery later, at term.

Occasionally, a pedunculated subserosal myoma will undergo torsion with subsequent painful necrosis. Laparoscopy or laparotomy can be used to ligate the stalk and resect the necrotic tumor. That said, we believe that surgery should be limited to tumors with a discrete pedicle that can be easily clamped and ligated.

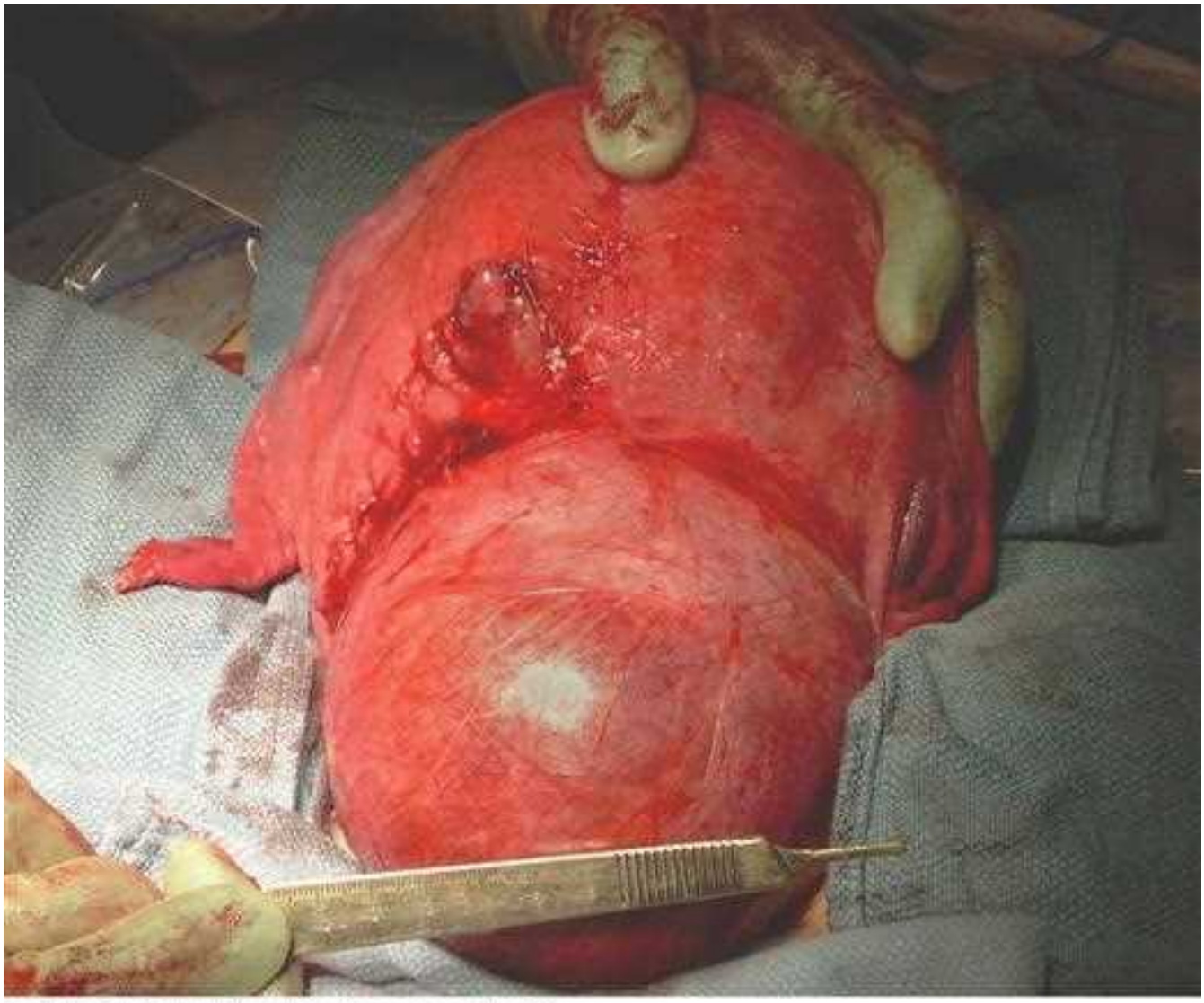
Pregnancy Complications

Myomas are associated with several complications that include preterm labor, placental abruption, fetal malpresentation, obstructed labor, cesarean delivery, and postpartum hemorrhage. In a review of pregnancy outcomes in 2065 women with leiomyomas, Coronado and colleagues (2000) reported that placental abruption and breech presentation were each increased fourfold; first-trimester bleeding and dysfunctional labor, twofold; and cesarean delivery, sixfold. Salvador and associates (2002) reported an eightfold higher second-trimester abortion risk in these women.

Factors most important in determining morbidity in pregnancy are leiomyoma number, size, and location (Ciavattini, 2015; Jenabi, 2018; Lam, 2014). If the placenta is adjacent to or implanted over a leiomyoma, rates of abortion, preterm labor, placental abruption, and postpartum hemorrhage are all increased. Retroplacental myomas are also associated with fetal-growth restriction (Knight, 2016). Tumors in the cervix or lower uterine segment may obstruct labor, as did the one shown in Figure 63-5. Despite these complications, Qidwai and associates (2006) reported a 70-percent vaginal delivery rate in women in whom myomas measured ≥10 cm. These data argue against empirical cesarean delivery for leiomyomas, and we allow a trial of labor unless myomas clearly obstruct the birth canal. If cesarean delivery is indicated, uterine malrotation should be excluded prior to hysterotomy. Myomas are generally left alone unless they cause recalcitrant bleeding. An important caveat is that cesarean hysterectomy may be technically difficult because of lateral ureteral displacement by the masses.

FIGURE 63-5

Cesarean delivery performed because of a large leiomyoma in the lower uterine segment. A classical vertical uterine incision, seen to the left of the myoma, was required for delivery of the fetus.



Bleeding due to myomas may develop during pregnancy from any of several factors. Especially common is bleeding with miscarriage, preterm labor, placenta previa, and placental abruption. Much less often, bleeding may result from a submucous myoma that has prolapsed from the uterus and into the cervix or vagina. In this

unusual circumstance, although heavy or persistent bleeding may require earlier intervention, the stalk, if accessible, can be ligated vaginally near term to avoid tumor avulsion during delivery.

Fortunately, myomas rarely become infected (Genta, 2001). When infection develops, it usually is postpartum, especially if the tumor is located immediately adjacent to the implantation site (Lin, 2002). They also may become infected with an associated septic abortion and myoma perforation by a sound, dilator, or curette.

Fertility Considerations

Despite the relatively high prevalence of myomas in young women, it is not clear whether they diminish fertility, other than by possibly causing miscarriage. In a review of 11 studies, Pritts (2001) concluded that submucous myomas did significantly affect fertility. He also found that hysteroscopic myomectomy improved infertility and early miscarriage rates in these women. If truly implicated in infertility, myomas in other locations may require laparoscopy or laparotomy for excision.

Some of these methods of treatment for infertility may affect subsequent pregnancies. For example, after myomectomy, the gravid uterus can rupture either before or during labor (American College of Obstetricians and Gynecologists, 2016a). Management is individualized, and review of the prior operative report is prudent. If resection resulted in a defect into or immediately adjacent to the endometrial cavity, then cesarean delivery is usually done before labor begins.

Although less effective than surgery, uterine artery embolization of myomas has also been used to treat infertility or symptoms (Mara, 2008). Women so treated have higher rates of miscarriage, cesarean delivery, and postpartum hemorrhage (Homer, 2010). The Society of Interventional Radiology considers myoma embolization relatively contraindicated in women who plan future pregnancies (Stokes, 2010).

Finally, outside the United States, *ulipristal*—a selective progesterone-receptor modulator—can be used for myoma regression. Successful subsequent pregnancies without tumor regrowth have been reported (Luyckx, 2014).

Endometrial Lesions

Occasionally, *endometriosis* can develop after delivery from endometrial tissue implanted within cesarean delivery or episiotomy scars (Bumpers, 2002). Here, they form a palpable mass and can cause cyclic localized pain. Endometriomas within an ovary are discussed in the next section.

Adenomyosis is traditionally found in late reproductive life and beyond. Its acquisition may be at least partially related to disruption of the endometrial-myometrial border during sharp curettage for abortion (Curtis, 2002). In a case-control study, Hashimoto and colleagues (2017) reported significantly higher associated rates of second-trimester abortion, preeclampsia, fetal malposition, and preterm delivery.

Endometrial carcinoma is an estrogen-dependent neoplasia also usually found in women older than 40 years. Thus, it is seen only rarely with pregnancy. Of 27 cases that were identified during pregnancy or within the first 4 months postpartum, most were found in first-trimester curettage specimens (Hannuna, 2009). These are usually early-stage, well-differentiated adenocarcinomas for which treatment consists primarily of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Much less commonly, to preserve future fertility, curettage with or without postprocedural progestational therapy has been used for the rare patient with cancer identified in a miscarriage curettage specimen (Schammel, 1998).

Many more studies describe a conservative approach for well-selected *nonpregnant* women diagnosed with endometrial cancer who wish to preserve fertility. One study followed 13 women treated with progestins for early-stage, well-differentiated adenocarcinoma who then later conceived after apparent remission (Gotlieb, 2003). Nine had liveborn neonates, and four of six women with a recurrence responded to another course of therapy. Similar outcomes were described in 12 women by Niwa (2005) and in 21 women by Signorelli (2009), each with their coworkers. Despite these acceptable pregnancy rates, recurrences and death have been reported, and conservative management is not considered standard (Erkanli, 2010).

Ovary

Ovarian masses found during pregnancy are relatively common. Among studies, incidences vary depending on the frequency of prenatal sonography, the ovarian size threshold used to define a clinically significant “mass,” and whether the study site is tertiary or primary care. Thus, the incidence of ovarian masses not surprisingly ranges from 1 in 100 to 2000 pregnancies (Whitecar, 1999; Zanetta, 2003). Of ovarian malignancies, the absolute incidence in the California Cancer Registry was 1 in 19,000 pregnancies (Smith, 2003).

The most frequent types of ovarian masses are corpus luteum cysts, endometriomas, benign cystadenomas, and mature cystic teratomas. Because pregnant women are usually young, malignant tumors and those of low malignant potential are proportionately uncommon. Our experiences from Parkland Hospital are similar to those of Leiserowitz and associates (2006), who found that 1 percent of 9375 ovarian masses were frankly malignant and that another 1 percent were of low malignant potential. In surgically excised masses, rates of malignancy are higher, vary from 4 to 13 percent, and probably reflect a greater preoperative concern for cancer (Hoffman, 2007; Sherard, 2003).

Most ovarian masses are asymptomatic in pregnant women. Some cause pressure or chronic pain, and acute abdominal pain may be due to torsion, rupture, or hemorrhage. Seldom is blood loss significant enough to cause hypovolemia.

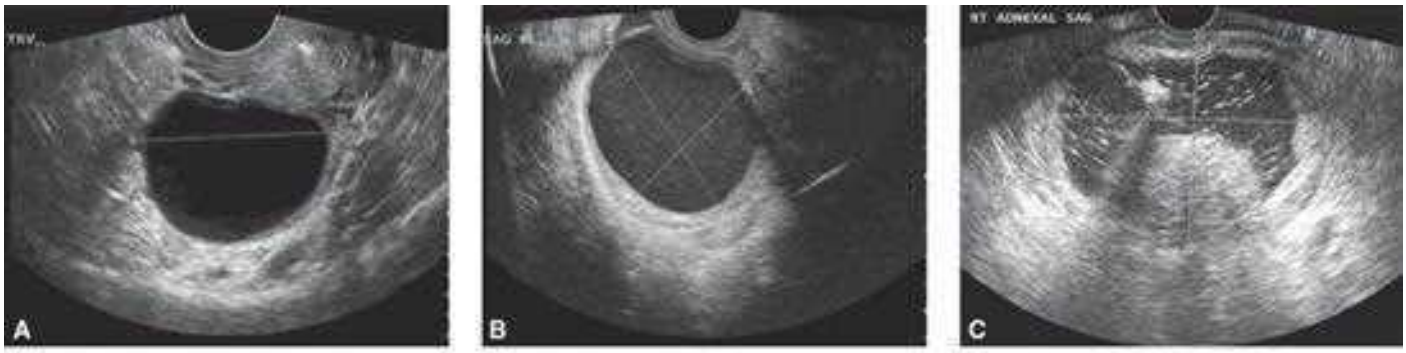
Diagnosis

Many ovarian masses are detected during routine prenatal sonography or during imaging done for other indications, including evaluation of symptoms. The typical sonographic appearance of these masses is shown in Figure 63-6. In some instances, MR imaging can be used to evaluate complicated anatomy.

FIGURE 63-6

Sonographic characteristics of common adnexal masses in pregnancy. **A.** A simple anechoic cyst with smooth walls is characteristic of a physiological corpus luteum cyst or benign cystadenoma. **B.** Cystic structure with diffuse internal low-level echoes suggestive of an endometrioma or hemorrhagic corpus luteum. **C.** Mature

cystic teratoma appears as an adnexal cyst (*marked by calipers*) with accentuated lines and dots that represent hair in both longitudinal and transverse planes. At the central inferior aspect of this cyst, a mural nodule—Rokitansky protuberance—is seen. These typically rounded protuberances range in size from 1 to 4 cm, they are predominantly hyperechoic, and they create an acute angle with the cyst wall. Although not seen here, fat-fluid levels are often identified with cystic teratomas. (Used with permission from Dr. Elysia Moschos.)



Cancer antigen 125 (CA125) serves as a tumor marker, and levels are frequently elevated with ovarian malignancy. Importantly, concentrations of CA125 in early pregnancy and early puerperium are normally elevated, possibly from the decidua (Aslam, 2000; Spitzer, 1998). As shown in the Appendix (Serum and Blood Constituents), from the second trimester until term, levels are not normally higher than those in the nonpregnant woman (Szecsi, 2014). With severe preeclampsia, however, levels are abnormally elevated (Karaman, 2014). Other tumor markers that are not useful for diagnosis or posttreatment surveillance in pregnancy include human chorionic gonadotropin (hCG), alpha-fetoprotein, inhibins A and B, and the multimarker OVA1 test (Liu, 2011).

Complications

The two most common are torsion and hemorrhage. Torsion usually causes acute constant or episodic lower abdominal pain that frequently is accompanied by nausea and vomiting. Sonography often aids the diagnosis. With color Doppler, presence of an ovarian mass with absent flow strongly correlates with torsion. However, minimal or early twisting may compromise only venous flow, thus leaving the arterial supply intact. If torsion is suspected, laparoscopy or laparotomy is warranted. Contrary to prior teaching, adnexectomy is generally unnecessary to avoid clot release, thus, most recommend attempts at untwisting (McGovern, 1999; Zweizig, 1993). With a salvageable ovary, within minutes, congestion is relieved, and ovarian volume and cyanosis diminish. If cyanosis persists, however, then removal of the infarcted adnexum is typically indicated.

If the adnexum is healthy, there are options. First, neoplasms are resected. However, ovarian cystectomy in an ischemic, edematous ovary may be technically difficult, and adnexectomy may be necessary. Second, unilateral or bilateral oophoropexy has been described to minimize the risk of repeated torsion (Djavadian, 2004; Germain, 1996). Techniques described include shortening of the uteroovarian ligament or fixing the uteroovarian ligament to the posterior uterus, the lateral pelvic wall, or the round ligament (Fuchs, 2010; Weitzman, 2008).

The most common cause of ovarian hemorrhage follows rupture of a corpus luteum cyst. If the diagnosis is certain and symptoms abate, then observation and surveillance is usually sufficient. Concern for ongoing bleeding will typically prompt surgical evaluation. If the corpus luteum is removed before 10 weeks' gestation, progestational support is recommended to maintain the pregnancy. Suitable regimens include: (1) micronized progesterone (Prometrium) 200 or 300 mg orally once daily; (2) 8-percent progesterone vaginal gel (Crinone), one premeasured applicator vaginally daily plus micronized progesterone 100 or 200 mg orally once daily; or (3) intramuscular 17-hydroxyprogesterone caproate, 150 mg. The first two regimens are given until 10 completed weeks. For the last, if given between 8 and 10 weeks' gestation, only one injection is required immediately after surgery. If the corpus luteum is excised between 6 and 8 weeks' gestation, then two additional doses should be given 1 and 2 weeks after the first.

Asymptomatic Adnexal Mass During Pregnancy

Because most of these are incidental findings, management considerations include whether resection is necessary and its timing. A cystic benign-appearing mass that is <5 cm often requires no additional antepartum surveillance. Early in pregnancy, this is likely a corpus luteum cyst, which typically resolves by the early second trimester. For cysts ≥10 cm, because of the substantial risk of malignancy, torsion, or labor obstruction, surgical removal is reasonable. Tumors between 5 and 10 cm should be carefully evaluated by sonography along with color Doppler and possibly MR imaging. If they have a simple cystic appearance, these cysts can be managed expectantly with sonographic surveillance (Schmeler, 2005; Zanetta, 2003). Resection is done if cysts grow, begin to display malignant qualities, or become symptomatic. Those with classic findings of endometrioma or mature cystic teratoma may be resected postpartum or during cesarean for obstetrical indications.

On the other hand, if sonographic characteristics suggest cancer—thick septa, nodules, papillary excrescences, or solid components—immediate resection is indicated (Caspi, 2000). In one review of 563 masses, approximately half were simple, and the other half complex (Webb, 2015). Among simple masses, 1 percent were malignant, and of complex masses, 9 percent were cancerous.

Approximately 1 in 1000 pregnant women undergoes surgical exploration for an adnexal mass (Boulay, 1998). In general, we plan resection at 14 to 20 weeks' gestation because most masses that will regress will have done so by this time. As outlined in Chapter 46 (Medications and Surgeries), laparoscopic removal is ideal (Naqvi, 2015; Sisodia, 2015). Importantly, in any instance in which cancer is strongly suspected, the American College of Obstetricians and Gynecologists (2017b) recommends consultation with a gynecologic oncologist.

Pregnancy-Related Ovarian Tumors

Pregnancy Luteoma

One group of ovarian masses results directly from the stimulating effects of various pregnancy hormones on ovarian stroma. These include pregnancy luteoma, hyperreactio luteinalis, and ovarian hyperstimulation syndrome.

Of these, pregnancy luteoma is a rare, benign ovarian neoplasm that arises from luteinized stromal cells and classically causes elevated testosterone levels (Hakim, 2016; Irving, 2011). Up to 25 percent of affected women will be virilized, and of these affected women, nearly half of their female fetuses will have some degree of virilization. However, most mothers and their fetuses are unaffected because the placenta rapidly converts testosterone to estrogen (Kaňová, 2011).

In typical cases, an adnexal mass along with maternal virilization will prompt sonography and measurement of testosterone and CA125 levels. Luteomas range in size from microscopic to >20 cm. They appear as solid tumors, may be multiple or bilateral, and may be complex because of internal hemorrhage (Choi, 2000). Concerns for malignancy may be further investigated with MR imaging (Kao, 2005; Tannus, 2009).

Total testosterone levels are increased, but notably, levels in normal pregnancy can be substantially elevated (Appendix, Serum and Blood Constituents). Differential diagnoses include granulosa cell tumors, thecomas, Sertoli-Leydig cell tumors, Leydig cell tumors, stromal hyperthecosis, and hyperreactio luteinalis.

Generally, luteomas do not require surgical intervention unless there is torsion, rupture, or hemorrhage (Masarie, 2010). These tumors spontaneously regress during the first few months postpartum, and androgen levels drop precipitously during the first 2 weeks following delivery (Wang, 2005). Lactation may be delayed a week or so by hyperandrogenemia (Dahl, 2008). Recurrence in subsequent pregnancies is rare.

Hyperreactio Luteinalis

In this condition, one or both ovaries develop multiple, large theca-lutein cysts, typically after the first trimester. Cysts are caused by luteinization of the follicular theca interna layer, and most are in response to stimulation by exceptionally high hCG levels (Russell, 2009). For this reason, they are more common with gestational trophoblastic disease, twins, fetal hydrops, and other conditions with increased placental mass. Maternal virilization may develop, but fetal virilization has not been reported (Kaňová, 2011; Malinowski, 2015).

As reported by Baxi and coworkers (2014), these ovarian tumors appear sonographically to have a “spoke wheel” pattern (Fig. 20-3). If the diagnosis is confident, and unless complicated by torsion or hemorrhage, surgical intervention is not required. These masses resolve after delivery. Few data allow prediction of risk in a subsequent pregnancy, but in one case report, a woman had hyperreactio with three pregnancies (Bishop, 2016).

Ovarian Hyperstimulation Syndrome

This is typified by multiple ovarian follicular cysts accompanied by increased capillary permeability. It most often is a complication of ovulation-induction therapy for infertility, although it rarely may develop in an otherwise normal pregnancy. It has also been reported with a partial molar pregnancy (Suzuki, 2014). Its etiopathogenesis is thought to involve hCG stimulation of vascular endothelial growth factor (VEGF) expression in granulosa-lutein cells (Soares, 2008). This causes greater vascular permeability that can lead to ascites, pleural or pericardial effusion, hypovolemia with acute kidney injury, and hypercoagulability. Serious complications are renal dysfunction, adult respiratory distress syndrome, ovarian rupture with hemorrhage, and VTE. Unlike hyperreactio lutealis, virilization is absent (Suzuki, 2004).

Detailed guidelines for management are outlined by the American Society for Reproductive Medicine (2016). Treatment is primarily supportive with attention to maintaining vascular volume and thromboprophylaxis. In severe cases, paracentesis can be helpful.

Ovarian Cancer

Malignancies of the ovary are the leading cause of death from genital-tract cancers in all women (American Cancer Society, 2017). Still, it is uncommon in young women, and the incidence of ovarian malignancy ranges from 1 in 20,000 to 1 in 50,000 births (Eibye, 2013; Palmer, 2009). Fortunately, 75 percent of these found in pregnancy are early-stage cancers that carry a 5-year survival rate between 70 and 90 percent (Brewer, 2011). The types of malignancy are also markedly different in pregnant women compared with those in older women. In gravidas, these are, in decreasing order of frequency, germ cell and sex cord-stromal tumors, low-malignant-potential tumors, and epithelial tumors (Morice, 2012).

Pregnancy apparently does not alter the prognosis of most ovarian malignancies. Management is similar to that for nonpregnant women, with the usual proviso that it may be modified depending on gestational age. Thus, if frozen section histopathological analysis verifies malignancy, surgical staging is done with careful inspection of all accessible peritoneal and visceral surfaces (Giuntoli, 2006). Peritoneal washings are taken for cytology, biopsies are obtained from the diaphragmatic surface and peritoneum, omentectomy is completed, and pelvic and infrarenal paraaortic lymph nodes are sampled, if accessible.

If there is advanced disease, bilateral adnexectomy and omentectomy will decrease most tumor burden. In early pregnancy, hysterectomy and aggressive surgical debulking procedures may be elected. In other cases, minimal debulking as described in the previous paragraph is done and the operation terminated. In some cases of aggressive or large-volume disease, chemotherapy can be given during pregnancy while awaiting pulmonary maturation. Monitoring maternal CA125 serum levels during chemotherapy is not accurate in pregnancy (Aslam, 2000; Morice, 2012).

Adnexal Cysts

Paratubal and paroovarian cysts are either distended remnants of the paramesonephric ducts or are mesothelial inclusion cysts. Although most measure ≤3 cm, they occasionally attain worrisome dimensions. Their reported incidence is influenced by size, but one autopsy series in nonpregnant women cited this to be 5 percent (Dorum, 2005). The most common paramesonephric cyst is the hydatid of Morgagni, which is pedunculated and typically dangles from one of the fimbria. These cysts infrequently cause complications and are most often identified at the time of cesarean delivery or puerperal sterilization. In these instances, they can simply be

excised or drained by creating a large window in the cyst wall. Neoplastic paraovarian cysts are rare, sonographically and histologically resemble tumors of ovarian origin, and rarely are of borderline potential or frankly malignant (Korbin, 1998).

Vulva and Vagina

Preinvasive disease in young women—vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN)— are seen more often than invasive disease and are commonly associated with HPV infection. As with cervical neoplasia, these premalignant conditions are treated after delivery.

Cancer of the vulva or vagina is generally a malignancy of older women, and thus, these are rarely associated with pregnancy. Even so, any suspicious lesions should be biopsied. Treatment is individualized according to the clinical stage and depth of invasion. In a review of 23 cases, investigators concluded that radical surgery for stage I disease was feasible during pregnancy—including in the last trimester (Heller, 2000).

We and others question the necessity of resection in late pregnancy because definitive therapy can often be delayed due to these cancers' typically slow progression (Anderson, 2001). It appears that vaginal delivery is not contraindicated if vulvar and inguinal incisions are well healed. Vulvar sarcoma, vulvar melanoma, and vaginal malignancies are rare in pregnancy and are the subjects of case reports (Alexander, 2004; Kuller, 1990; Matsuo, 2009).

BREAST CARCINOMA

Breast cancer rates rise most acutely between ages 40 and 80 years. However, because of its overall high frequency, breast cancer is relatively common even in younger women and is the most frequent cancer found in gravidas. From the Nationwide Inpatient Sample of 11.8 million births, the incidence approximated 1 in 15,000 (Maor, 2017). And, as more women choose to delay childbearing, the frequency of associated breast cancer is certain to grow. Postponed childbearing was considered partially responsible for the increase in pregnancy-associated breast cancer in Sweden and Denmark (Andersson, 2015; Eibye, 2013).

Some studies suggest that women with a family history of breast cancer—especially those with *BRCA1* and *BRCA2* breast cancer gene mutations—are more likely to develop breast malignancy during pregnancy (Wohlfahrt, 2002). However, it may be that it is parity that modifies this risk. Namely, parous women older than 40 years with these mutations have a significantly lower cancer risk than nulliparas with these mutated genes (Andrieu, 2006; Antoniou, 2006). Women with *BRCA1* and *BRCA2* gene mutations who undergo induced abortion or those who breastfeed do not have an increased breast cancer risk (Friedman, 2006). Moreover, Jernström and associates (2004) found that breastfeeding conveyed a protective effect against this cancer in those with *BRCA1* gene mutation, but not in those with *BRCA2* mutations. Of other congenital factors, it is controversial whether DES exposure raises breast cancer risks (Hoover, 2011; Titus-Ernstoff, 2006).

Diagnosis

More than 90 percent of gravidas with breast cancer have a palpable mass, and greater than 80 percent of cases are self-reported (Brewer, 2011). In pregnancy, clinical assessment, diagnostic procedures, and treatment of women with breast tumors are often slightly delayed (Berry, 1999). This can be partially attributed to pregnancy-induced breast tissue that obscures masses.

The evaluation of pregnant women with a breast mass does not differ from that for nonpregnant women (Loibl, 2015). Thus, any suspicious breast mass should be pursued to diagnosis. Pragmatically, a palpable discrete mass can be biopsied or excised. If imaging is desirable to distinguish between a solid mass and a cystic lesion, sonography has high sensitivity and specificity (Navrozoglou, 2008). Mammography is appropriate if indicated, and the fetal radiation risk is negligible—0.04 mGy—with appropriate shielding (Krishna, 2013). But, because breast tissue is denser in pregnancy, mammography has a false-negative rate of 35 to 40 percent (Woo, 2003). If the decision to biopsy is uncertain, then MR imaging may be used. With such techniques, masses can usually be described as either solid or cystic.

Cystic breast lesions are simple, complicated, or complex (Berg, 2003). Simple cysts do not require special management or monitoring, but they may be aspirated if symptomatic. Complicated cysts show internal echoes during sonography, and they sometimes are indistinguishable from solid masses. These are typically aspirated, and if the sonographic abnormality does not resolve completely, a core-needle biopsy is usually performed. Complex cysts have septa or intracystic masses seen sonographically. Because some breast cancer may form complex cysts, excision is usually recommended.

For solid breast masses, evaluation is with the triple test, that is, clinical examination, imaging, and core needle biopsy. If all three suggest a benign lesion or if all three suggest a breast cancer, the test is said to be concordant. A concordant benign triple test is ≥99-percent accurate, and breast lumps in this category can be followed by clinical examination alone. Fortunately, most masses in pregnancy have these three reassuring features. In contrast, if any of the three assessments suggests malignancy, the mass should be excised.

Management

Once breast cancer is diagnosed, a limited search of the most common metastatic sites is completed. For most women, this includes a chest radiograph, liver sonography, and skeletal MR imaging (Becker, 2016; Krishna, 2013).

Treatment of breast cancer is multidisciplinary and includes an obstetrician, breast surgeon, and medical oncologist. Initially, desires for pregnancy continuation are addressed, and data indicate that pregnancy interruption does not influence the course or prognosis of breast cancer (Cardonick, 2010). With pregnancy continuation, treatment in general mirrors that for nonpregnant women. Important caveats are that chemotherapy and surgery are postponed to the second trimester, and adjuvant radiotherapy is withheld until after delivery (Brewer, 2011).

Surgical treatment may be definitive. In the absence of metastatic disease, either a wide excision or a modified or total mastectomy—each with axillary node staging—can be performed (Rosenkranz, 2006). Staging by sentinel lymph node biopsy and lymphoscintigraphy with technetium-99m is safe. Breast reconstruction, if

desired, is typically delayed until after delivery (Viswanathan, 2011). That said, Caragacianu and coworkers (2016) described good results in 10 pregnant women who underwent immediate reconstruction after mastectomy.

Chemotherapy is usually given with both positive- and negative-node breast cancers. In premenopausal women, survival rates with this approach are improved, even if lymph nodes are cancer free. For node-positive disease, multiagent chemotherapy is begun if delivery is not anticipated within several weeks. Cyclophosphamide, doxorubicin, and cisplatin are currently used (Euhus, 2016). If an anthracycline-based agent such as doxorubicin is used, pretherapy maternal echocardiography is performed because of associated cardiotoxicity (Brewer, 2011). Good maternal and perinatal results have been reported (Berry, 1999; Hahn, 2006).

Immunotherapy for breast cancers is now commonplace. Trastuzumab (Herceptin) is a monoclonal antibody to the HER2/neu receptor, which is found in approximately a third of invasive breast cancers (Hudis, 2007). The drug is not recommended in pregnancy. This is because HER2/neu is strongly expressed in fetal renal epithelium, and trastuzumab has been linked with miscarriage, fetal renal failure and related oligohydramnios, and preterm birth (Amant, 2010; Azim, 2010).

The effects of pregnancy on the course of breast cancer and its prognosis are complex. Breast cancer is more aggressive in younger women, but whether it is more aggressive during pregnancy in these same women is debatable (Azim, 2014). Clinically, most studies indicate little difference in overall survival rates with pregnancy-associated breast cancer compared with similarly aged and staged nonpregnant women (Beadle, 2009). Other reports note worse overall survival rates with pregnancy-associated breast cancer (Rodriguez, 2008). These investigators do conclude, however, that later disease stages are more prevalent in pregnant women.

Indeed, breast cancer is usually found at a more advanced stage in pregnant women, and thus overall prognosis is diminished (Andersson, 2015). The aggregate of studies published after 1990 indicate that up to 60 percent of pregnant women have concomitant axillary node involvement at diagnosis. And although, stage for stage, the 5-year survival rate is comparable in pregnant and nonpregnant women, the more advanced stages that are typical of pregnant women worsen their prognosis (Kuo, 2017; Zemlickis, 1992).

Pregnancy Following Breast Cancer

After breast cancer treatment, chemotherapy will render some women infertile, and options for childbearing are limited (Kim, 2011). For those who become pregnant, long-term maternal survival rates are not adversely affected (Averette, 1999; Velentgas, 1999). One metaanalysis of 10 studies found that for women with early breast cancer, pregnancy that occurs 10 months after diagnosis may, in fact, confer a survival benefit (Valachis, 2010). Data do not indicate that breastfeeding adversely alters the course.

In women successfully treated for breast cancer, recurrence is a concern. Because recurrences are more common soon after treatment, it seems reasonable to delay conception for 2 to 3 years. Hormonal contraceptive methods are contraindicated, and a copper-containing intrauterine device is an excellent long-acting reversible method for many. That said, women who conceive do not appear to have diminished survival rates (Ives, 2006). Notably, women treated with tamoxifen are at risk for several months after its discontinuation to have a newborn with congenital anomalies. This drug has an extremely long half-life, and thus delaying conception is recommended for at least 2 months after tamoxifen completion (Braems, 2011).

THYROID CANCER

Palpable thyroid nodules are detected in 4 to 7 percent of the population, and approximately 10 percent are malignant (Burman, 2015). Clinical nodules are typically evaluated with sonography and measurement of serum thyroid-stimulating hormone (TSH) and free thyroxine levels. Fine-needle aspiration is indicated for a suspicious nodule (Alexander, 2017; Gharib, 2016).

With a diagnosis of thyroid malignancy, pregnancy termination is not necessary. Primary therapy is thyroidectomy performed ideally during the second trimester. Postoperatively, replacement thyroxine is given. Most thyroid cancers are well differentiated and follow an indolent course. Thus, delayed surgical treatment does not usually alter outcome (Yazbeck, 2012; Yu, 2016).

In some types of thyroid cancer, radioiodine is used for primary or postoperative treatment. This is contraindicated in both pregnancy and lactation for several reasons. First, transplacental ^{131}I is avidly trapped by the fetal thyroid gland to cause hypothyroidism. Second, during lactation, the breast also concentrates a substantial amount of iodide. This may pose neonatal risk due to radioiodine-contaminated milk ingestion and maternal risk from significant breast irradiation. To limit maternal exposure, a delay of 3 months between lactation and thyroid ablation will more reliably ensure complete breast involution (Sisson, 2011). In women with thyroid cancer who ultimately receive ^{131}I doses, pregnancy should be avoided for 6 months to 1 year. This time ensures thyroid function stability and permits confirmation of cancer remission (Abalovich, 2007).

LYMPHOMAS

Hodgkin Disease

This lymphoma is probably B-cell derived and is cytologically distinguished from other lymphomas by Reed–Sternberg cells. Of cancers in pregnancy, lymphomas are common, and gestational rates are rising because of delayed childbearing (Horowitz, 2016). In pregnant women, Hodgkin lymphomas are more frequent than non–Hodgkin lymphomas. In one population-based review of 7.9 million births from the Nationwide Inpatient Sample, El-Messidi and colleagues (2015) reported its incidence to be 1 in 12,400.

In more than 70 percent of Hodgkin disease cases, lymph nodes painlessly enlarge at sites above the diaphragm, that is, in the axillary, cervical, or submandibular chains. Approximately one third of patients have symptoms such as fever, night sweats, malaise, weight loss, and pruritus. Diagnosis is by histological examination of involved nodes (Longo, 2015).

The Ann Arbor staging system, shown in Table 63-2, is applied to Hodgkin and other lymphomas. For staging, pregnancy limits the use of some radiographic studies, but at minimum, chest radiography, abdominal imaging with sonography or MR imaging, and bone marrow biopsy are completed (Williams, 2001). MR imaging is excellent for evaluating thoracic and abdominal paraaortic lymph nodes (Brenner, 2012). Staging laparotomy is seldom done today (Longo, 2015).

TABLE 63-2

Ann Arbor Staging System for Hodgkin and Other Lymphomas

Stage	Findings
I	Involvement in a single lymph node region or lymphoid site—e.g., spleen or thymus
II	Involvement of two or more lymph node groups on the same side of the diaphragm—the mediastinum is a single site
III	Involvement of lymph nodes on both sides of the diaphragm 1. Limited to spleen or splenic hilar, celiac, or portal nodes 2. Includes paraaortic, iliac, or mesenteric nodes plus those in III
IV	Extralymphatic involvement—e.g., liver or bone marrow

Substage A = no symptoms; substage B = fever, sweats, or weight loss; substage E = extralymphatic involvement excluding liver and bone marrow.

The current trend for nonpregnant individuals is to administer chemotherapy for all stages of Hodgkin disease. In pregnancy, for early-stage disease in the first trimester, options include observation until after 12 weeks' gestation, single-agent vinblastine until the second trimester, pregnancy termination followed by multiagent chemotherapy, or radiotherapy alone for isolated neck or axillary sites (El-Hemaidi, 2012; Eyre, 2015).

For advanced-stage disease, chemotherapy is recommended regardless of gestational age. Before 20 weeks, therapeutic abortion is a consideration, but if termination is unacceptable, then treatment with vinblastine followed by multiagent therapy in the second trimester can be used (Eyre, 2015). For most advanced-stage disease after the first trimester, cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine are given, and radiotherapy can be added postpartum (Cohen, 2011). In general, postponement of therapy until fetal maturity is achieved seems justifiable only when the diagnosis is made late in pregnancy.

Women with Hodgkin lymphoma have a higher incidence of VTE (El-Messidi, 2015; Horowitz, 2016). Also, in our experiences, pregnant women with Hodgkin disease —even after they are "cured"—are inordinately susceptible to infection and sepsis. Active antineoplastic therapy only increases this vulnerability.

The overall prognosis with Hodgkin lymphoma is good, and survival rates exceed 70 percent. Pregnancy does not adversely affect the cancer course or pregnancy outcomes in women with this lymphoma. Specifically, neither chemotherapy after the first trimester nor mediastinal and neck irradiation has adverse fetal effects (Brenner, 2012; El-Messidi, 2015; Pinnix, 2016). For women with disease in remission, pregnancy does not stimulate a relapse (Weibull, 2016).

Non-Hodgkin Lymphomas

Although usually B-cell tumors, non-Hodgkin lymphomas can also be T-cell or natural-killer-cell neoplasms. Their biology, classification, and treatment are complex (Longo, 2015; O'Gara, 2009). They are associated with viral infections, and indeed, their incidence has risen sharply at least partly because 5 to 10 percent of HIV-infected persons develop lymphoma. Other associated viruses include Epstein-Barr virus, hepatitis C virus, and human herpes virus 8. Some of these lymphomas are aggressive, and survival rates vary with the type of cell line involved (Longo, 2015).

Non-Hodgkin lymphomas are infrequent during pregnancy (Brenner, 2012; Pinnix, 2016). They are also staged according to the Ann Arbor system. If diagnosed in the first trimester, pregnancy termination followed by multiagent chemotherapy is recommended for all but indolent or very early disease. These less aggressive forms may either be observed or be temporized with focal supradiaphragmatic radiotherapy and then full treatment in the second trimester. If one of these lymphomas is diagnosed after the first trimester, chemotherapy and immunotherapy with rituximab are given (Cohen, 2011; Rizack, 2009). In one follow-up of 55 individuals at 6 to 29 years after exposure to chemotherapy in utero during maternal lymphoma treatment, no congenital, neurological, or psychological abnormalities were noted (Avilés, 2001).

Burkitt lymphoma is an aggressive B-cell tumor associated with Epstein-Barr virus infection. Prognosis is poor, and treatment is given with multiagent chemotherapy. In a review of 19 women whose pregnancies were complicated by this lymphoma, 17 died within a year of diagnosis (Barnes, 1998).

Leukemias

In general, these malignancies arise either from lymphoid tissues—lymphoblastic or lymphocytic leukemias, or from bone marrow—myeloid leukemias. They can be acute or chronic. Although adult leukemias are more prevalent after age 40, they still are among the most common malignancies of young women (see Fig. 63-1).

Leukemia was diagnosed in 1 in 40,000 pregnancies reported to the California Cancer Registry (Smith, 2003). In a review of 72 pregnancies complicated by leukemia from 1975 until 1988, 44 had acute myelogenous leukemia; 20 had acute lymphocytic leukemia; and eight had one of the chronic leukemias (Caligiuri, 1989).

Acute leukemias almost always cause marked peripheral blood count abnormalities, and often the white blood cell count is elevated with readily recognizable circulating blast cells. The diagnosis is made from bone marrow biopsy.

With current multiagent chemotherapy, remission during pregnancy is common, compared with an almost 100-percent mortality rate before 1970. Pregnancy termination does not further improve the prognosis, however, abortion is a consideration in early pregnancy to avoid potential chemotherapy teratogenesis. One example of the latter is treatment of acute promyelocytic leukemia with all-*trans*-retinoic acid, also known as tretinoin (Carradice, 2002; Sanz, 2015). This potent teratogen causes retinoic acid syndrome (Chap. 12, Retinoids). In another example, acute myeloid leukemia is treated with tyrosine kinase inhibitors, another teratogen group (Palani, 2015). In other cases, pregnancy termination before viability may simplify management of an acutely ill woman.

Other than these caveats, treatment of gravidas with leukemia is similar to that for nonpregnant women. Acute myeloid leukemia is treated without delay (Ali, 2015). After induction chemotherapy, postremission maintenance therapy is mandatory to prevent a relapse, which is then usually treated with stem-cell transplantation. If allogeneic stem-cell transplantation is indicated, early delivery is considered. With some chronic leukemias, it may be possible to delay therapy until after delivery (Fey, 2008). As with lymphoma, infection and hemorrhage are significant complications that should be anticipated in women with active disease.

Most descriptions of leukemia treatment in pregnancy are single cases or small series (Routledge, 2016; Sanz, 2015). In an earlier review of 58 cases, 75 percent were diagnosed after the first trimester (Reynoso, 1987). Half were acute myelogenous leukemia, which had a remission rate of 75 percent with chemotherapy. Only 40 percent of these pregnancies resulted in liveborn neonates (Caligiuri, 1989).

MALIGNANT MELANOMA

These most frequently originate from a preexisting skin nevus and its pigment-producing melanocytes. Melanomas should be suspected in pigmented lesions that show changes in contour, surface elevation, discoloration, bleeding, or ulceration, which should prompt biopsy (Richtig, 2017). They are most common in light-skinned whites and develop relatively frequently in women of childbearing age.

In some population studies, melanoma is the most frequent malignancy complicating pregnancy (Andersson, 2015; Bannister-Tyrrell, 2015). Still, the reported incidence ranges widely from 0.03 to 2.8 per 1000 live births (Eibye, 2013; Smith, 2003). One explanation is that many are treated as outpatients and thus are not entered into tumor registries. As noted earlier (Reproductive Tract Neoplasms), malignant melanoma is one of the tumors that is known to metastasize to the placenta and fetus. Placental evaluation for metastases should be performed after delivery.

Staging is clinical. Stage I is a melanoma with no palpable lymph nodes; in stage II, lymph nodes are palpable; and in stage III, there are distant metastases. For patients with stage I, tumor thickness is the single most important predictor of survival. The Clark classification includes five levels of involvement by depth into the epidermis, dermis, and subcutaneous fat. The Breslow scale measures tumor thickness and size, in addition to depth of invasion.

Primary surgical treatment for melanoma is determined by the stage and includes wide local resection, sometimes with extensive regional lymph node dissection. Schwartz and associates (2003) recommend sentinel lymph node mapping and biopsy using ^{99m}Tc-sulfur colloid, which has a calculated fetal dose of 0.014 mSv or 0.014 mGy. Routine regional node dissection reportedly improves survival rates in nonpregnant patients with microscopic metastases (Cascinelli, 1998). For pregnant patients, an algorithm has been proposed that begins with resection of the primary tumor under local anesthesia but postpones sentinel lymph node biopsy until after delivery (Broer, 2012). Although prophylactic chemotherapy or immunotherapy is usually avoided during pregnancy, it may be given if indicated by tumor stage and maternal prognosis. In most cases of distant metastatic melanoma, treatment is at best palliative. Currently, the role of estrogen receptor-β in melanoma progression is under investigation, and it may be a target for future therapeutic intervention (de Giorgi, 2011).

Stage-for-stage, survival is equivalent between pregnant and nonpregnant women (Driscoll, 2016; Johansson, 2014). In one study, half of pregnant women had stage III or IV lesions (de Haan, 2017). Therapeutic abortion does not improve maternal survival rates. Clinical stage is the strongest determinant of survival, and women with deep cutaneous invasion or regional node involvement have the worst prognosis. Approximately 60 percent of recurrences will manifest within 2 years, and 90 percent by 5 years. Thus, most recommend that pregnancy be avoided for 3 to 5 years after surgical resection. Interim contraception can include combination oral contraceptives, as they do not appear to have adverse cancer effects (Gandini, 2011). Related, subsequent pregnancies in women with localized melanoma do not lower cancer survival rates (Driscoll, 2009).

GASTROINTESTINAL TRACT CANCER

Carcinomas of the colon and rectum are the third most frequent in women of all age groups in the United States (American Cancer Society, 2016). Their incidence in pregnancy is rising because of delayed childbearing (Rogers, 2016). Even so, colorectal tumors are uncommon before age 40. Smith and colleagues (2003) reported an approximate incidence of 1 per 150,000 deliveries in the California Cancer Registry. The incidence approximated 1 per 35,000 births in a Danish Registry (Eibye, 2013). Most—80 percent—of colorectal carcinomas in pregnant women arise from the rectum. In one review, only 41 cases in pregnancy were colon cancers above the peritoneal reflection (Chan, 1999).

The most frequent symptoms of colorectal cancer are abdominal pain, distention, nausea, constipation, and rectal bleeding. If symptoms of colon disease persist, digital rectal examination, stool tests for occult blood, and flexible sigmoidoscopy or colonoscopy are done. Some malignancies of the gastrointestinal tract are discovered because of metastases to the ovary. *Kruckenberg tumors* are tumor-laden ovaries from another primary, often gastrointestinal, and have a bleak prognosis (Glišić, 2006; Kodama, 2016).

Treatment of colon cancer in pregnant women mirrors the same general guidelines as for nonpregnant women. Without evidence of metastatic disease, surgical resection is preferred, but most gravidas have advanced lesions (Al-Ibrahim, 2014). During the first half of pregnancy, hysterectomy is not necessary to perform colon or rectal resection, and thus, therapeutic abortion is not mandated. During later pregnancy, therapy may be delayed until fetal maturation, however, bowel hemorrhage, obstruction, or perforation may force surgical intervention (Minter, 2005).

Gastric cancer is rarely associated with pregnancy, and most reported cases are from Japan. Hirabayashi and coworkers (1987) reviewed outcomes in 60 pregnant women during a 70-year period from 1916 to 1985. Delayed diagnosis during pregnancy is common, and the prognosis is consistently poor (Lee, 2009). Esophageal cancer has similar symptoms, but it is rare (Sahin, 2015). It is axiomatic that persistent unexplained upper gastrointestinal symptoms should be evaluated by endoscopy.

MISCELLANEOUS TUMORS

Various other neoplasms have been reported in pregnancy and are usually the subject of case reports. Examples include carcinoid tumors, which are usually of gastrointestinal origin (Durkin, 1983). Both pancreatic and hepatocellular cancer are rare during pregnancy (Kakoza, 2009; Marinoni, 2006; Papoutsis, 2012; Perera, 2011). Another report described a massive intrahepatic cholangiocarcinoma masquerading as HELLP syndrome (Bladerston, 1998). Except for thyroid cancer, malignant tumors of the head and neck are rare (Cheng, 2015). Lung cancer is also uncommon (Boussios, 2013). Central nervous system neoplasms had a reported frequency of 1 in 10,000 to 28,000 births (Eibye, 2013; Smith, 2003). Bladder and urachal duct carcinoma are rarely coincident with pregnancy (McNally, 2013; Yeaton-Massey, 2013). Last, bone tumors have been described (Kathiresan, 2011).

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CHAPTER 64: Infectious Diseases

According to many authorities, influenza exerts a very pernicious influence upon pregnancy. It would appear that the effects of influenza must vary with the severity of the epidemic, and more particularly with the frequency of pneumonic complications. As a rule, any septic condition offers a worse prognosis in pregnancy. Several instances have been reported of transmission of the offending bacteria to the foetus.

—J. Whitridge Williams (1903)

INTRODUCTION

Infections have historically been a major cause of maternal and fetal morbidity and mortality worldwide, and they remain so in the 21st century. The unique maternal–fetal vascular connection in some cases serves to protect the fetus from infectious agents, whereas in other instances it provides a conduit for their transmission to the fetus. Maternal serological status, gestational age at the time infection is acquired, the mode of acquisition, and the immunological status of both the mother and her fetus all influence disease outcome.

MATERNAL AND FETAL IMMUNOLOGY

Pregnancy-Induced Immunological Changes

Even after intensive study, many of the maternal immunological adaptations to pregnancy are not well elucidated. It is known that pregnancy is associated with an increase in the CD4+ T cells that secrete Th2-type cytokines—for example interleukins (Fragiadakis, 2016). Th1-type cytokine production—for example, interferon gamma and interleukin 2—appears to be somewhat suppressed, leading to a *Th2 bias* in pregnancy. This bias affects the ability to rapidly eliminate certain intracellular pathogens during pregnancy, although the clinical implications of this suppression are unknown (Kourtis, 2014; Svensson-Arvelund, 2014). Importantly, the Th2 humoral immune response remains intact. It also appears that human leukocyte antigen (HLA)-C expressed by extravillous trophoblasts elicits responses from decidual natural killer (dNK) and decidual CD8+ T cells (Crespo, 2017).

In describing infections, *horizontal transmission* is the spread of an infectious agent from one individual to another. *Vertical transmission* refers to passage from the mother to her fetus of an infectious agent through the placenta, during labor or delivery, or by breastfeeding. Thus, preterm rupture of membranes, prolonged labor, and obstetrical manipulations may enhance the risk of neonatal infection (Centers for Disease Control and Prevention, 2010). Table 64-1 details specific infections by mode and timing of acquisition. A final term, the *secondary attack rate*, is the probability that infection develops in a susceptible individual following known contact with an infectious person.

TABLE 64-1

Specific Causes of Some Fetal and Neonatal Infections

Intrauterine
Transplacental
Viruses: varicella-zoster, coxsackie, human parvovirus B19, rubella, CMV, HIV, Zika
Bacteria: *Listeria*, syphilis, *Borrelia*
Protozoa: toxoplasmosis, malaria
Ascending infection
Bacteria: group B *streptococcus*, coliforms
Viruses: HIV
Intrapartum
Maternal exposure
Bacteria: gonorrhea, chlamydia, group B *streptococcus*, tuberculosis, mycoplasmas
Viruses: HSV, HPV, HIV, hepatitis B, hepatitis C, Zika
External contamination
Bacteria: staphylococcus, coliforms
Viruses: HSV, varicella zoster
Neonatal
Human transmission: staphylococcus, HSV
Respirators and catheters: staphylococcus, coliforms

CMV = cytomegalovirus; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus.

Fetal and Newborn Immunology

The active immunological capacity of the fetus and neonate is compromised compared with that of older children and adults. That said, fetal cell-mediated and humoral immunity begin to develop by 9 to 15 weeks' gestation (Warner, 2010). The primary fetal response to infection is immunoglobulin M (IgM). Passive immunity is provided by IgG transferred across the placenta. By 16 weeks, this transfer begins to rise rapidly, and by 26 weeks, fetal concentrations are equivalent to those of the mother. After birth, breastfeeding is protective against some infections, although this protection begins to decline at 2 months of age. Current World Health Organization (2013) recommendations are to exclusively breastfeed for the first 6 months of life with partial breastfeeding until 2 years of age.

Neonatal infection, especially in its early stages, may be difficult to diagnose because these newborns often fail to express classic clinical signs. If the fetus was infected in utero, there may be depression and acidosis at birth for no apparent reason. The neonate may suck poorly, vomit, or show abdominal distention. Respiratory insufficiency can develop, which may present similarly to idiopathic respiratory distress syndrome. The neonate may be lethargic or jittery. The response to sepsis may be hypothermia rather than hyperthermia, and the total leukocyte and neutrophil counts may be depressed.

VIRAL INFECTIONS

Cytomegalovirus

Several viruses cause severe maternal infections, and some can also cause devastating fetal infections. Of these, cytomegalovirus (CMV) is a ubiquitous DNA herpes virus that eventually infects most humans. CMV is also the most common perinatal infection in the developed world. Specifically, some evidence of fetal infection is found in 0.2 to 2.2 percent of all neonates (American College of Obstetricians and Gynecologists, 2017). The virus is secreted into all body fluids, and person-to-person contact with viral-laden saliva, semen, urine, blood, and nasopharyngeal and cervical secretions can transmit infection. The fetus may become infected by transplacental viremia, or the neonate is infected at delivery or during breastfeeding. Moreover, acquisition continues to accrue. Day-care centers, for example, are a frequent source. Revello and coworkers (2008) reported that amniocentesis in women whose blood is positive for CMV DNA does not result in iatrogenic fetal transmission.

Up to 85 percent of women from lower socioeconomic backgrounds are seropositive by the time of pregnancy, whereas only half of women in higher income groups are immune. Following primary CMV infection, and in a manner similar to other herpesvirus infections, the virus becomes latent with periodic reactivation characterized by viral shedding. This occurs despite high serum levels of anti-CMV IgG antibody. These antibodies do not prevent maternal recurrence, reactivation, or reinfection, nor do they totally mitigate fetal or neonatal infection.

Maternal Infection

Women who are seronegative before pregnancy, but who develop primary CMV infection during pregnancy, are at greatest risk to have an infected fetus. It is estimated that 25 percent of congenital CMV infections in the United States are from primary maternal infection (Wang, 2011). Most CMV infections are clinically silent, but they can be detected by seroconversion, and this may be as high as 1 to 7 percent annually (Hyde, 2010). Conversely, diagnosis of CMV nonprimary infection is a challenge (Picone, 2017).

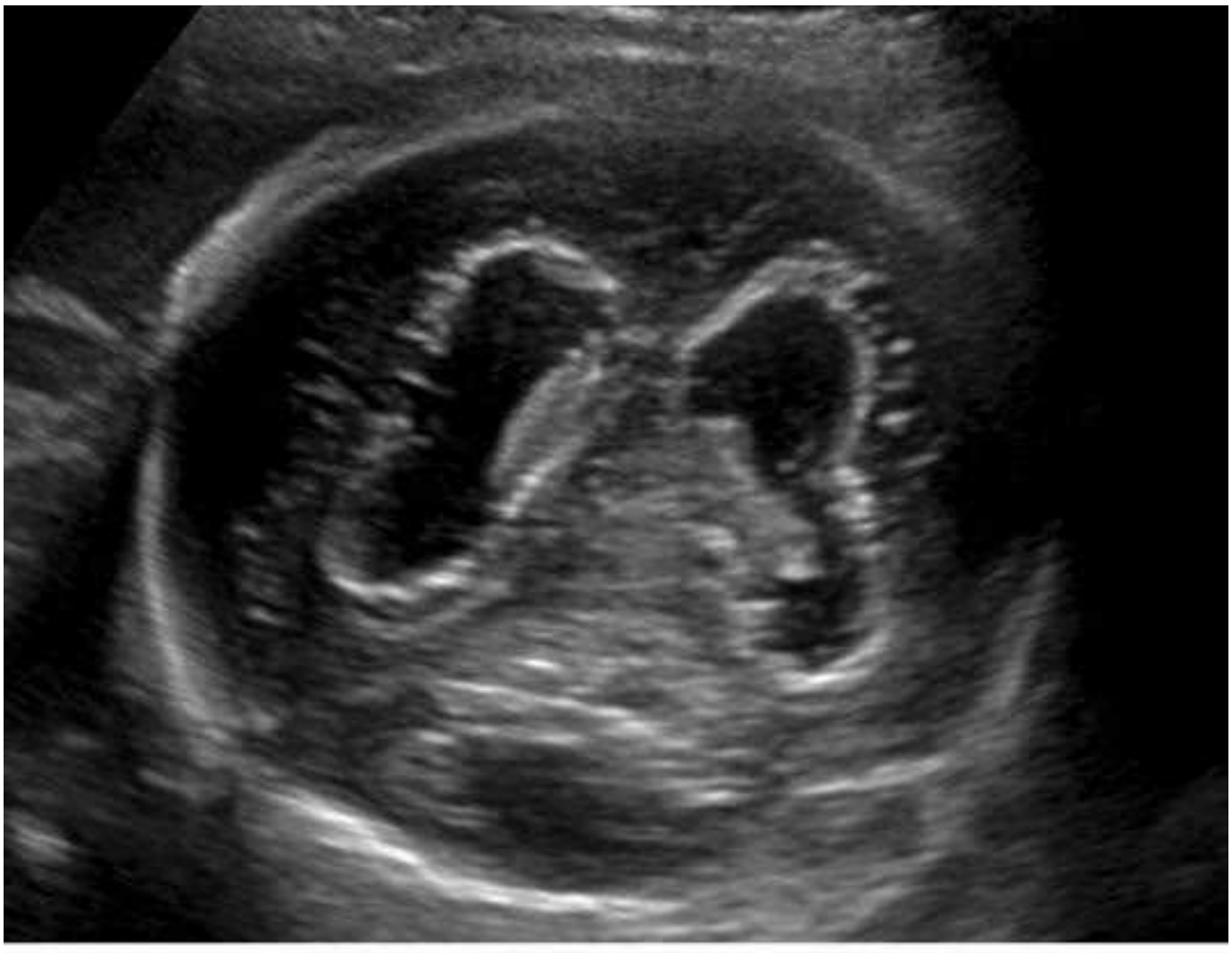
Pregnancy does not increase the risk or severity of maternal CMV infection. Most infections are asymptomatic, but 10 to 15 percent of infected adults have a mononucleosis-like syndrome characterized by fever, pharyngitis, lymphadenopathy, and polyarthritis. Immunocompromised women may develop myocarditis, pneumonitis, hepatitis, retinitis, gastroenteritis, or meningoencephalitis. Nigro and associates (2003) reported that most women in a cohort with primary infection had elevated serum aminotransferases or lymphocytosis. Reactivation disease usually is asymptomatic, although viral shedding is common.

Transmission rates for primary infection are 30 to 36 percent in the first trimester, 34 to 40 percent in the second, and 40 to 72 percent in the third trimester (American College of Obstetricians and Gynecologists, 2017; Picone, 2017). In contrast, recurrent maternal infection infects the fetus in only 0.15 to 1 percent of cases. Naturally acquired immunity during pregnancy results in a 70-percent risk reduction of congenital CMV infection in future pregnancies (Fowler, 2003; Leruez-Ville, 2017). However, as noted earlier, maternal immunity does not prevent recurrences, and maternal antibodies do not prevent fetal infection (Ross, 2011).

Fetal Infection

Newborns with apparent sequelae of in-utero-acquired CMV infection are described as having *symptomatic CMV infection*. Congenital infection is a syndrome that may include growth restriction, microcephaly, intracranial calcifications, chorioretinitis, mental and motor retardation, sensorineural deficits, hepatosplenomegaly, jaundice, hemolytic anemia, and thrombocytopenic purpura (Cheeran, 2009). An example of periventricular calcifications is shown in Figure 64-1. Of the estimated 40,000 infected neonates born each year, only 5 to 10 percent demonstrate this syndrome (Fowler, 1992). Thus, most infected infants are asymptomatic at birth, but some develop late-onset sequelae. Complications may include hearing loss, neurological deficits, chorioretinitis, psychomotor retardation, and learning disabilities. Infections in dichorionic twins most likely are nonconcordant (Egaña-Ugrinovic, 2016).

FIGURE 64-1
Coronal view of cranial sonogram from a neonate with congenital cytomegalovirus infection showing multiple periventricular calcifications.

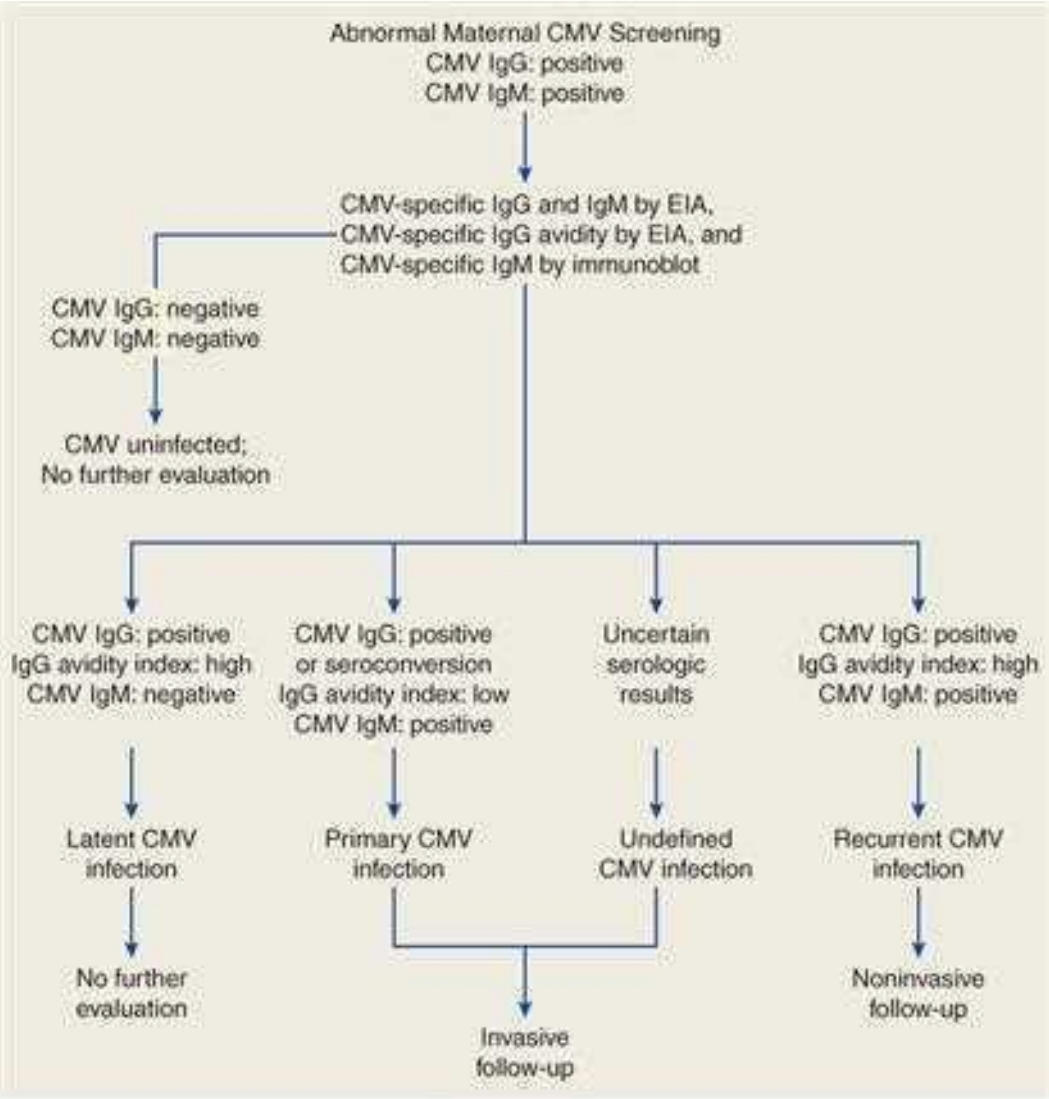


Prenatal Diagnosis

Routine prenatal CMV serological screening is currently not recommended by the Society for Maternal–Fetal Medicine (2016). An algorithm for management is shown in Figure 64-2. Pregnant women should be tested for CMV if they present with a mononucleosis-like illness or if congenital infection is suspected based on abnormal sonographic findings. Primary infection is diagnosed using CMV-specific IgG testing of paired acute and convalescent sera. CMV IgM does not accurately reflect timing

of seroconversion because IgM antibody levels may be elevated for more than a year (Stagno, 1985). Moreover, CMV IgM may be found with reactivation disease or reinfection with a new strain. Thus, specific CMV IgG avidity testing is valuable in confirming primary CMV infection. High anti-CMV IgG avidity indicates primary maternal infection >6 months before testing (Kanengisser-Pines, 2009). Finally, viral culture may be useful, although a minimum of 21 days is required before findings are considered negative.

FIGURE 64-2
Algorithm for evaluation of suspected maternal primary cytomegalovirus (CMV) infection in pregnancy. EIA = enzyme immunoassay; IgG = immunoglobulin G; IgM = immunoglobulin M.



Several fetal abnormalities associated with CMV infection may be seen with sonography, computed tomography, or magnetic resonance imaging. In some cases, they are found at the time of routine prenatal sonographic screening, but in others they are part of a specific evaluation in women with CMV infection. Findings include microcephaly, ventriculomegaly, and cerebral calcifications; ascites, hepatomegaly, splenomegaly, and hyperechoic bowel; hydrops; and oligohydramnios (Society for Maternal-Fetal Medicine, 2016). Abnormal sonographic findings seen in combination with positive findings in fetal blood or amniotic fluid are predictive of an approximate 75-percent risk of symptomatic congenital infection (Enders, 2001).

CMV nucleic acid amplification testing (NAAT) of amniotic fluid is considered the gold standard for the diagnosis of fetal infection. Sensitivities range from 70 to 99 percent and depend on amniocentesis timing. Sensitivity is highest when amniocentesis is performed at least 6 weeks after maternal infection and after 21 weeks' gestation (Azam, 2001; Guerra, 2000). A negative result from amniotic fluid polymerase chain reaction (PCR) testing does not exclude fetal infection and may need to be repeated if suspicion for fetal infection is high.

Management and Prevention

The management of the immunocompetent pregnant woman with primary or recurrent CMV is limited to symptomatic treatment. If recent primary CMV infection is confirmed, amniotic fluid analysis should be offered. Counseling regarding fetal outcome depends on the gestational age during which primary infection is documented. Despite the high infection rate with primary infection in the first half of pregnancy, most fetuses develop normally. However, pregnancy termination may be an option for some.

Currently, no proven treatments are available for CMV infection (Society for Maternal–Fetal Medicine, 2016). Leruez-Ville and associates (2016) recently reported that oral treatment with valacyclovir, 8 g daily, apparently mitigated adverse outcomes in eight of 11 affected fetuses treated beginning at median of 25.9 weeks' gestation. Kimberlin and colleagues (2015) previously showed that intravenous valganciclovir administered for 6 weeks to neonates with symptomatic central nervous system (CNS) disease prevented hearing deterioration at 6 months and possibly later. Passive immunization with CMV-specific hyperimmune globulin may lower the risk of congenital CMV infection when given to pregnant women with primary disease (Nigro, 2005, 2012; Visentin, 2012). The Maternal–Fetal Medicine Units Network currently is conducting a randomized trial designed to address this.

There is no CMV vaccine, although several clinical trials are underway (Arvin, 2004; Schleiss, 2016). Prevention of congenital infection relies on avoiding maternal primary infection, especially in early pregnancy. Basic measures such as good hygiene and hand washing have been promoted, particularly for women with toddlers in day-care settings (Fowler, 2000). CMV may be sexually transmitted among infected partners, but no data address the efficacy of preventive strategies.

Varicella-Zoster Virus

Maternal Infection

Varicella–zoster virus (VZV) is a double-stranded DNA herpesvirus acquired predominately during childhood, and 90 percent of adults have serological evidence of immunity (Whitley, 2015). The incidence of adult varicella declined by 82 percent after the introduction of varicella vaccination, and this has resulted in a drop in maternal and fetal varicella rates (American College of Obstetricians and Gynecologists, 2017). In the United States between 2003 and 2010, the incidence of maternal varicella among 7.7 million pregnancy admissions was 1.21 per 10,000 (Zhang, 2015).

Primary infection—*varicella* or *chickenpox*—is transmitted by direct contact with an infected individual, although respiratory transmission has been reported. The incubation period is 10 to 21 days, and a nonimmune woman has a 60- to 95-percent risk of becoming infected after exposure (Whitley, 2015). Primary varicella presents with a 1- to 2-day flulike prodrome, which is followed by pruritic vesicular lesions that crust after 3 to 7 days. Infection tends to be more severe in adults (Marin, 2007). Affected patients are then contagious from 1 day before the onset of the rash until the lesions become crusted.

Mortality is predominately due to VZV pneumonia, which is thought to be more severe during adulthood and particularly in pregnancy. Although the incidence was once thought to be higher, only 2 to 5 percent of infected pregnant women develop pneumonitis (Marin, 2007; Zhang, 2015). Risk factors for VZV pneumonia include smoking and having more than 100 cutaneous lesions. Maternal mortality rates with pneumonia have decreased to 1 to 2 percent (Chandra, 1998).

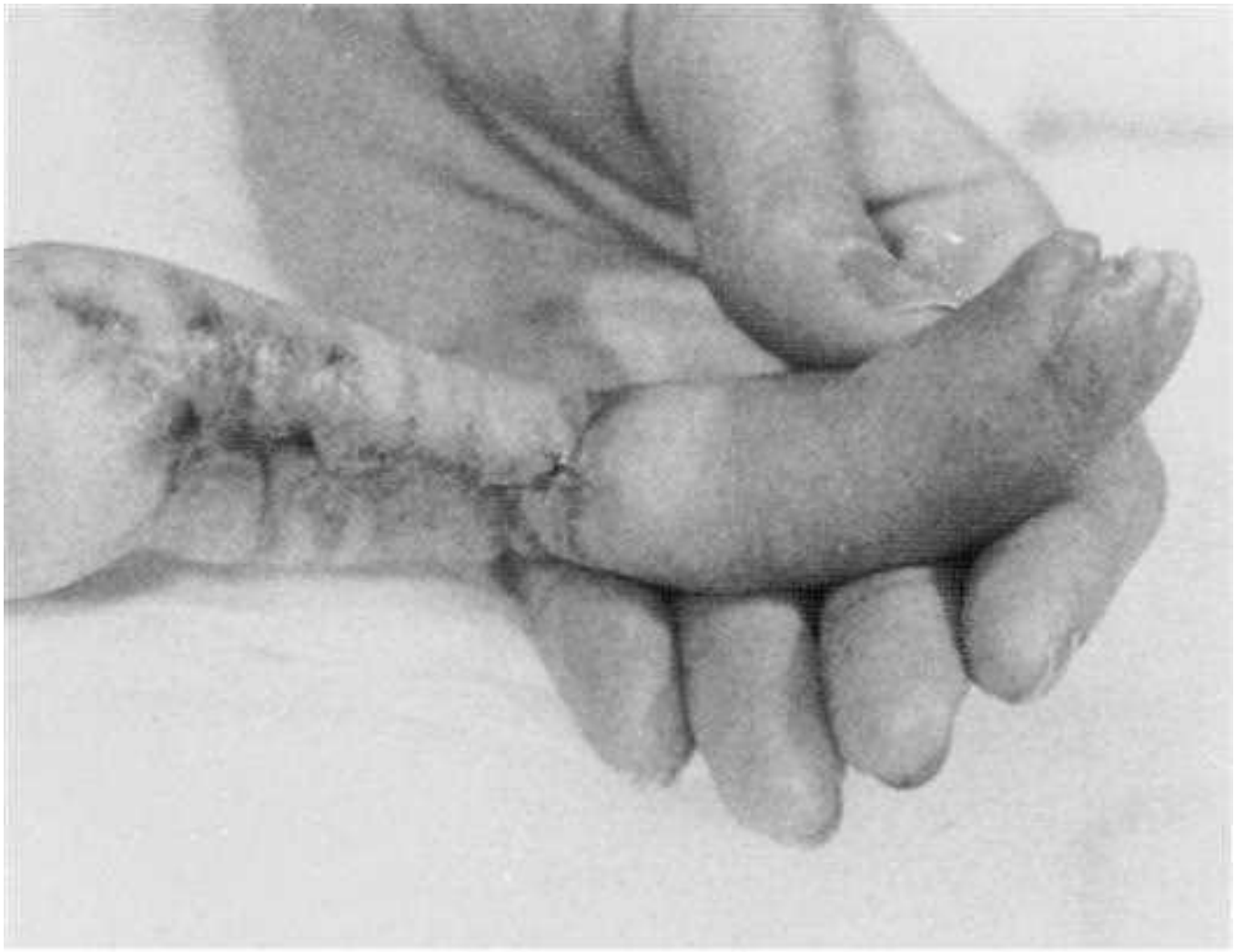
Symptoms of VZV pneumonia usually appear 3 to 5 days into the course of illness. Fever, tachypnea, dry cough, dyspnea, and pleuritic pain are characteristic. Nodular infiltrates are similar to other viral pneumonias (Chap. 51, Influenza Pneumonia). Although resolution of pneumonitis parallels that of skin lesions, fever and compromised pulmonary function may persist for weeks.

If primary varicella is reactivated years later, it causes *herpes zoster* or *shingles* (Whitley, 2015). This presents as a unilateral dermatomal vesicular eruption associated with severe pain. Zoster does not appear to be more frequent or severe in pregnant women. Congenital varicella syndrome rarely develops in cases of maternal herpes zoster (Ahn, 2016; Enders, 1994). Zoster is contagious if blisters are broken, although less so than with primary varicella.

Fetal and Neonatal Infection

In women with varicella during the first half of pregnancy, the fetus may develop *congenital varicella syndrome*. Some features include chorioretinitis, microphthalmia, cerebral cortical atrophy, growth restriction, hydronephrosis, limb hypoplasia, and cicatricial skin lesions as shown in Figure 64-3 (Ahn, 2016; Auriti, 2009). Enders and coworkers (1994) evaluated 1373 pregnant women with varicella. When maternal infection developed before 13 weeks, only two of 472 pregnancies—0.4 percent—had neonates with congenital varicella syndrome. The highest risk was between 13 and 20 weeks, during which time seven of 351 exposed fetuses—2 percent—had evidence of congenital varicella. After 20 weeks' gestation, the researchers found no clinical evidence of congenital infection. Ahn and colleagues (2016) recently described similar findings. That said, sporadic reports have described CNS abnormalities and skin lesions in fetuses who developed congenital varicella in weeks 21 to 28 of gestation (Lamont, 2011a; Marin, 2007).

FIGURE 64-3
Atrophy of the lower extremity with bony defects and scarring in a fetus infected during the first trimester by varicella. (Reproduced with permission from Paryani SG, Arvin AM: Intrauterine infection with varicella zoster virus after maternal varicella, N Engl J Med. 1986 Jun 12;314(24):1542–1546.)



If the fetus or neonate is exposed to active infection just before or during delivery, and therefore before maternal antibody has been formed, the newborn faces a serious threat. Attack rates range from 25 to 50 percent, and mortality rates approach 30 percent. In some instances, neonates develop disseminated visceral and CNS disease, which is commonly fatal. For this reason, *varicella-zoster immune globulin* (VZIG) should be administered to neonates born to mothers who have clinical evidence of varicella 5 days before and up to 2 days after delivery.

Diagnosis

Maternal varicella is usually diagnosed clinically. Infection may be confirmed by NAAT of vesicular fluid, which is very sensitive. The virus may also be isolated by scraping the vesicle base during primary infection and performing a Tzanck smear, tissue culture, or direct fluorescent antibody testing. Congenital varicella may be diagnosed using NAAT analysis of amnionic fluid, although a positive result does not correlate well with the development of congenital infection (Mendelson, 2006). A detailed anatomical sonographic evaluation performed at least 5 weeks after maternal infection may disclose abnormalities, but the sensitivity is low (Mandelbrot, 2012).

Management

Maternal Viral Exposure

Several aspects of maternal VZV exposure and infection in pregnancy affect management. Exposed gravidas with a negative history for chickenpox should undergo VZV serological testing. At least 70 percent of these women will be seropositive, and thus immune. Exposed pregnant women who are susceptible (seronegative) should be given varicella-zoster immune globulin (VariZIG). Although best given within 96 hours of exposure, its use is approved for up to 10 days to prevent or attenuate varicella infection (Centers for Disease Control and Prevention, 2012, 2013d). Passive immunization appears to be highly effective (Jespersen, 2016). In women with known history of varicella, VariZIG is not indicated.

Maternal Infection

Any patient diagnosed with primary varicella infection or herpes zoster should be isolated from pregnant women. Because VZV pneumonia often presents with few symptoms, a chest radiograph is recommended by many. Most women require only supportive care, but those who require intravenous (IV) fluids and especially those with pneumonia are hospitalized. IV acyclovir therapy is given to women requiring hospitalization—500 mg/m^2 or 10 to 15 mg/kg every 8 hours.

Vaccination

An attenuated live-virus vaccine is recommended for nonpregnant adolescents and adults with no history of varicella. Two doses of *Varivax* are given 4 to 8 weeks apart, and the seroconversion rate is 98 percent (Marin, 2007). Importantly, vaccine-induced immunity diminishes over time, and the breakthrough infection rate approximates 5 percent at 10 years (Chaves, 2007).

The vaccine is not recommended for pregnant women or for those who may become pregnant within a month following each vaccine dose. That said, a registry of more than 1000 vaccine-exposed pregnancies reports no cases of congenital varicella syndrome or other associated congenital malformations (Marin, 2014; Wilson, 2008). The attenuated vaccine virus is not secreted in breast milk. Thus, postpartum vaccination should not be delayed because of breastfeeding (American College of Obstetricians and Gynecologists, 2016c).

Influenza Virus

These respiratory infections are caused by members of the family Orthomyxoviridae. *Influenza A* and *B* form one genus of these RNA viruses, and both cause epidemic human disease (Cohen, 2015b). Influenza A viruses are subclassified further by hemagglutinin (H) and neuraminidase (N) surface antigens. Influenza outbreaks occur annually, and the most recent epidemic was in 2016 to 2017 caused by an influenza A/H_3N_2 strain (Shang, 2016).

Maternal and Fetal Infection

Fever, dry cough, and systemic symptoms characterize this infection, which usually is not life-threatening in otherwise healthy adults. However, pregnant women appear to be more susceptible to serious complications, particularly pulmonary involvement (Cohen, 2015b; Mertz, 2017; Rasmussen, 2012). Severe infection has a maternal mortality rate of 1 percent (Duryea, 2015). And from 2009 to 2010, widespread influenza A infection affected pregnant women and caused 12 percent of pregnancy-related deaths (Callaghan, 2015).

No firm evidence links influenza A virus and congenital malformations (Irving, 2000; Zerbo, 2017). Conversely, Lynberg and colleagues (1994) reported higher rates of neural-tube defects in neonates born to women with influenza early in pregnancy. This was possibly associated with hyperthermia. Viremia is infrequent, and transplacental passage is rare (Rasmussen, 2012). Stillbirth, preterm delivery, and first-trimester abortion have all been reported, but usually correlate with the severity of maternal infection (Centers for Disease Control and Prevention, 2011; Fell, 2017; Meijer, 2015).

Influenza may be detected in nasopharyngeal swabs using viral antigen rapid detection assays (Table 64-2). Reverse transcriptase–polymerase chain reaction (RT-PCR) is the more sensitive and specific test, although not widely available (Cohen, 2015b). In contrast, rapid influenza diagnostic tests (RIDTs) are least indicative, with sensitivities of 40 to 70 percent. *Decisions to administer antiviral medications for influenza treatment or chemoprophylaxis should be based on clinical symptoms and epidemiological factors.* Specifically, the start of therapy should not be delayed pending testing results (Centers for Disease Control and Prevention, 2017e).

TABLE 64-2

Outpatient Influenza A and B Virus Testing Methods

Method[a]	Test Time
Viral cell culture	3–10 d
Rapid cell culture	1–3 d
Direct (DFA) or indirect (IFA) fluorescent antibody assay	1–4 hr
RT-PCR and other molecular assays	1–6 hr
Rapid influenza diagnostic tests (RIDT)	<30 min

[a]Nasopharyngeal or throat swab.

RT-PCR = reverse transcription-polymerase chain reaction.

Data from Centers for Disease Control and Prevention, 2017e.

Management

Two classes of antiviral medications are currently available. *Neuraminidase inhibitors* are highly effective for the treatment of early influenza A and B. These include *oseltamivir* (Tamiflu), which is taken orally for treatment and for chemoprophylaxis; z*anamivir* (Relenza), which is inhaled for treatment; and *peramivir* (Rapivab), which is administered intravenously.

The *adamantanes* include amantadine and rimantadine, which were used for years for treatment and chemoprophylaxis of influenza A. In 2005, influenza A resistance to adamantine was reported to exceed 90 percent in the United States. Thus, its use is not currently recommended. It is possible that these drugs may again be effective for subsequently mutated strains. Patterns of resistance are available at cdc.gov/flu.

Experience with all of these antiviral agents in pregnant women is limited (Beau, 2014; Beigi, 2014; Dunstan, 2014). They are Food and Drug Administration category C drugs and thus used when potential benefits outweigh risks. At Parkland Hospital, we start oral oseltamivir treatment within 48 hours of symptom onset—75 mg twice daily for 5 days. Early administration may reduce length of hospital stays (Meijer, 2015; Oboho, 2016). Prophylaxis with oseltamivir, 75 mg orally once daily for 7 days, is also recommended for significant exposures. Antibacterial medications are added when a secondary bacterial pneumonia is suspected (Chap. 51, Pregnancy Outcome).

Vaccination

Effective vaccines are formulated annually. Vaccination against influenza throughout the influenza season, but optimally in October or November, is recommended by the Centers for Disease Control and Prevention (CDC) (2013a) and the American College of Obstetricians and Gynecologists (2016b) for all women who will be pregnant during the influenza season. This is especially important for those affected by chronic medical disorders such as diabetes, heart disease, asthma, or human immunodeficiency virus (HIV) infection. Inactivated vaccine prevents clinical illness in 70 to 90 percent of healthy adults. Importantly, there is no evidence of teratogenicity or other adverse maternal or fetal events (Chambers, 2016; Fell, 2017; Kharbanda, 2017; Polyzos, 2015; Sukumaran, 2015). Moreover, for mothers vaccinated during pregnancy, several studies found lower rates of influenza in their infants up to 6 months of age (Nunes, 2017; Steinhoff, 2012; Zaman, 2008). Immunogenicity of the trivalent inactivated seasonal influenza vaccine in pregnant women is similar to that in the nonpregnant individual. A live attenuated influenza virus vaccine is available for intranasal use but is not recommended for pregnant women (Cohen, 2015b).

Mumps Virus

This uncommon adult infection is caused by an RNA paramyxovirus. Because of childhood immunization, up to 90 percent of adults are seropositive (Rubin, 2012). The virus primarily infects the salivary glands but also may involve the gonads, meninges, pancreas, and other organs. It is transmitted by direct contact with respiratory secretions, saliva, or through fomites. Most transmission occurs before and within 5 days of parotitis onset, and droplet isolation is recommended during this time (Kutty, 2010). Treatment is symptomatic, and mumps during pregnancy is no more severe than in nonpregnant adults.

Women who develop mumps in the first trimester may have a greater risk of spontaneous abortion. Infection in pregnancy is not associated with congenital malformations, and fetal infection is rare (McLean, 2013).

The live attenuated Jeryl-Lynn vaccine strain is part of the MMR vaccine—measles, mumps, and rubella. This vaccine is contraindicated in pregnancy according to the CDC (McLean, 2013). No malformations attributable to MMR vaccination in pregnancy have been reported, but pregnancy should be avoided for 30 days after mumps vaccination. The vaccine may be given to susceptible women postpartum, and breastfeeding is not a contraindication.

Measles Virus

This is a highly contagious RNA virus of the family Paramyxoviridae that only infects humans. In endemic areas, annual outbreaks of measles, also called rubeola, occur in late winter and early spring, transmission is primarily by respiratory droplets, and the secondary attack rate among contacts exceeds 90 percent (Rainwater-Lovett, 2015). Resurgences in measles have been linked to clusters of vaccine-eligible but unvaccinated individuals (Fiebelkorn, 2010; Phadke, 2016). Fever, coryza, conjunctivitis, and cough are typical symptoms. The characteristic erythematous maculopapular rash develops on the face and neck and then spreads to the back, trunk, and extremities. *Koplik spots* are small white lesions with surrounding erythema found within the oral cavity. Immediate or delayed neurological sequelae of measles may manifest in several forms, making diagnosis difficult (Buchanan, 2012; Chiu, 2016). Diagnosis of acute infection is most commonly performed by serological evidence of IgM antibodies, although RT-PCR tests are available. Treatment is supportive.

Pregnant women without evidence of measles immunity should be administered passive immunoprophylaxis with immune globulin, 400 mg/kg intravenously (Centers for Disease Control and Prevention, 2017d). Active vaccination is not performed during pregnancy, however, susceptible women can be vaccinated routinely postpartum, and breastfeeding is not contraindicated (Ohji, 2009).

The virus does not appear to be teratogenic (Siegel, 1973). However, rates of spontaneous abortion, preterm delivery, and low-birthweight neonates are increased with maternal measles (Rasmussen, 2015). If a woman develops measles shortly before birth, risk of serious infection developing in the neonate is considerable, especially in a preterm neonate.

Rubella Virus

This RNA togavirus causes rubella, also called German measles, which is of minor importance in the absence of pregnancy. *Rubella infection in the first trimester, however, poses significant risk for abortion and severe congenital malformations.* Transmission occurs via nasopharyngeal secretions, and the transmission rate is 80 percent to susceptible individuals. The peak incidence is late winter and spring in endemic areas (Lambert, 2015).

Maternal rubella is usually a mild febrile illness with a generalized maculopapular rash beginning on the face and spreading to the trunk and extremities. That said, 25 to 50 percent of infections are asymptomatic. Other symptoms may include arthralgias or arthritis, head and neck lymphadenopathy, and conjunctivitis. The incubation period is 12 to 23 days. Viremia usually precedes clinical signs by about a week, and adults are infectious during viremia and through 7 days after the rash appears. Up to half of maternal infections are subclinical despite viremia that may cause devastating fetal infection (McLean, 2013).

Diagnosis

Rubella virus may be isolated from the urine, blood, nasopharynx, and cerebrospinal fluid for up to 2 weeks after rash onset. The diagnosis is usually made, however, with serological analysis. In one study, 6 percent of nonimmune women seroconverted to rubella virus during pregnancy (Hutton, 2014). Specific IgM antibody can

be detected using enzyme-linked immunoassay for 4 to 5 days after onset of clinical disease, but antibody can persist for up to 6 weeks after appearance of the rash. Importantly, rubella virus reinfection can give rise to transient low levels of IgM. With this, fetal infection can rarely occur, but no adverse fetal effects have been described. Serum IgG antibody titers peak 1 to 2 weeks after rash onset. This rapid antibody response may complicate serodiagnosis unless samples are initially collected within a few days after the onset of the rash. If, for example, the first specimen was obtained 10 days after the rash, detection of IgG antibodies would fail to differentiate between very recent disease and preexisting immunity to rubella. IgG avidity testing is performed concomitant with the serological tests above. High-avidity IgG antibodies indicate an infection at least 2 months in the past.

Fetal Effects

The rubella virus is one of the most complete teratogens, and effects of fetal infection are worst during organogenesis (Adams Waldorf, 2013). Pregnant women with rubella and a rash during the first 12 weeks of gestation have an affected fetus with congenital infection in up to 90 percent of cases (Miller, 1982). At 13 to 14 weeks' gestation, this incidence is 50 percent, and by the end of the second trimester, it is 25 percent. Defects are rare after 20 weeks' gestation. Features of congenital rubella syndrome amenable to prenatal diagnosis are cardiac septal defects, pulmonary stenosis, microcephaly, cataracts, microphthalmia, and hepatosplenomegaly (Yazigi, 2017). Other abnormalities include sensorineural deafness, intellectual disability, neonatal purpura, and radiolucent bone disease. *Neonates born with congenital rubella may shed the virus for many months and thus be a threat to other infants and to susceptible adults who contact them.* Reports of delayed morbidities associated with congenital rubella syndrome may include a rare, progressive panencephalitis, insulin-dependent diabetes mellitus, and thyroid disorders (Sever, 1985; Webster, 1998).

Management and Prevention

There is no specific treatment for rubella. Droplet precautions for 7 days after the onset of the rash are recommended. Postexposure passive immunization with polyclonal immunoglobulin may be of benefit if given within 5 days of exposure (Young, 2015).

Although large epidemics of rubella have virtually disappeared in the United States because of immunization, up to 10 percent of women in the United States are susceptible. Cluster outbreaks during the 1990s mainly involved persons born outside the United States, as congenital rubella is still common in developing nations (Centers for Disease Control and Prevention, 2013f). To eradicate rubella and prevent congenital rubella syndrome completely, a comprehensive approach is recommended for immunizing the adult population (Grant, 2015).

MMR vaccine should be offered to nonpregnant women of childbearing age who do not have evidence of immunity whenever they make contact with the health-care system. Vaccination of all susceptible hospital personnel who might be exposed to patients with rubella or who might have contact with pregnant women is important. Rubella vaccination should be avoided 1 month before or during pregnancy because the vaccine contains attenuated live virus. No observed evidence links the vaccine and induced malformations, although the overall theoretical risk is up to 2.6 percent (McLean, 2013; Swamy, 2015). MMR vaccination is not an indication for pregnancy termination.

Prenatal serological screening for rubella is indicated for all pregnant women. Women found to be nonimmune are offered the MMR vaccine postpartum.

Respiratory Viruses

More than 200 antigenically distinct respiratory viruses cause the common cold, pharyngitis, laryngitis, bronchitis, and pneumonia. Rhinovirus, coronavirus, and adenovirus are major causes of the common cold. The RNA-containing rhinovirus and coronavirus usually produce a trivial, self-limited illness characterized by rhinorrhea, sneezing, and congestion. The DNA-containing adenovirus is more likely to produce cough and lower respiratory tract involvement, including pneumonia.

The potential teratogenic effects of respiratory viruses are controversial. In a case-control study using data from the Finnish Register of Congenital Malformations, 393 gravidas with a common cold had a four- to fivefold greater risk of fetal anencephaly (Kurppa, 1991). In another population study of California births from 1989 to 1991, low attributable risks for neural-tube defects were associated with many illnesses in early pregnancy (Shaw, 1998). Adams and colleagues (2012) performed amnionic fluid viral PCR studies in 1191 women undergoing amniocentesis for fetal karyotyping. Viral PCR was positive in 6.5 percent, with adenovirus being the virus most frequently identified. There was an association with fetal-growth restriction, nonimmune hydrops, foot/hand abnormalities, and neural-tube defects. Adenoviral infection is a known cause of childhood myocarditis. Towbin (1994) and Forsnes (1998) and their associates used PCR tests to identify and link adenovirus to fetal myocarditis and nonimmune hydrops.

Hantaviruses

These RNA viruses are members of the family Bunyaviridae. They are associated with a rodent reservoir, and transmission involves inhalation of virus excreted in rodent urine and feces. Outbreaks of hantaviruses including Sin Nombre virus and Seoul virus have been reported in the United States, the most recent in early 2017 (Centers for Disease Control and Prevention, 2017b). Hantaviruses are a heterogenous group of viruses with low and variable rates of transplacental transmission. Howard and associates (1999) reported the *Hantavirus pulmonary syndrome* to cause maternal death, fetal demise, and preterm birth. They found no evidence of vertical transmission of the causative Sin Nombre virus.

Enteroviruses

These viruses are a major subgroup of RNA picornaviruses that include coxsackievirus, poliovirus, and echovirus. They are trophic for intestinal epithelium but can also cause widespread maternal, fetal, and neonatal infections that may include the CNS, skin, heart, and lungs. Most maternal infections are subclinical yet can be fatal to the fetus–neonate (Tassin, 2014). Hepatitis A is an enterovirus that is discussed in Chapter 55 (Chronic Viral Hepatitis).

Coxsackievirus infections with group A and B are usually asymptomatic. Symptomatic infections—usually with group B—include aseptic meningitis, polio-like illness, hand foot and mouth disease, rashes, respiratory disease, pleuritis, pericarditis, and myocarditis. No treatment or vaccination is available (Cohen, 2015a). Coxsackievirus may be transmitted by maternal secretions to the fetus at delivery in up to half of mothers who seroconverted during pregnancy (Modlin, 1988). Transplacental passage has also been reported (Ornoy, 2006).

Congenital malformation rates may be slightly increased in fetuses of pregnant women who had serological evidence of coxsackievirus (Brown, 1972). Viremia can cause fetal hepatitis, skin lesions, myocarditis, and encephalomyelitis, all of which may be fatal. Some have reported higher rates of cardiac anomalies and of low-birthweight, preterm, and small-for-gestational-age newborns (Chen, 2010; Koro'lkova, 1989). Maternal–fetal infection has been associated with massive perivillous fibrin deposition and fetal death (Yu, 2015). Finally, a rare association between maternal coxsackievirus infection and insulin-dependent diabetes in offspring has been described (Viskari, 2012).

Polioviruses cause highly contagious infections that are subclinical or mild. The virus is trophic for the CNS, and it can cause paralytic poliomyelitis (Cohen, 2015a). Siegel (1955) demonstrated that pregnant women not only were more susceptible to polio but also had a higher death rate. Perinatal transmission has been observed, especially when maternal infection developed in the third trimester (Bates, 1955). Inactivated subcutaneous polio vaccine is recommended for susceptible pregnant women who must travel to endemic areas or are placed in other high-risk situations. Live oral polio vaccine has been used for mass vaccination during pregnancy without harmful fetal effects (Harjulehto, 1989).

Parvovirus

This B19 virus causes *erythema infectiosum*, or *fifth disease*. It is a small, single-stranded DNA virus that replicates in rapidly proliferating cells such as erythroblast precursors (Brown, 2015). This can lead to anemia, which is its primary fetal effect. Only individuals with the erythrocyte globoside membrane P antigen are susceptible. In women with severe hemolytic anemia—for example, sickle-cell disease—parvovirus infection may cause an aplastic crisis.

The main mode of parvovirus transmission is respiratory or hand-to-mouth contact, and the infection is common in spring months. The maternal infection rate is highest in women with school-aged children and in day-care workers, but not in schoolteachers. An infected person develops viremia 4 to 14 days after exposure, and an otherwise immunocompetent individual is no longer infectious at the onset of the rash. By adulthood, only 40 percent of women are susceptible. The annual seroconversion rate is 1 to 2 percent but is >10 percent during epidemic periods (Brown, 2015). The secondary attack rate approaches 50 percent.

Maternal Infection

In 20 to 30 percent of adults, infection is asymptomatic. Fever, headache, and flulike symptoms may begin in the last few days of the viremic phase. Several days later, a bright red rash with erythroderma affects the face and gives a slapped-cheek appearance. The rash becomes lacelike and spreads to the trunk and extremities. Adults often have milder rashes and develop symmetrical polyarthralgia that may persist several weeks. Mayama and associates (2014) described a pregnant woman in whom B19 infection was associated with hemophagocytic lymphohistiocytosis. No evidence suggests that parvovirus infection is altered by pregnancy. With recovery, IgM antibody is generated 7 to 10 days postinfection, and production persists for 3 to 4 months. Several days after IgM is produced, IgG antibody is detectable and persists for life with natural immunity (American College of Obstetricians and Gynecologists, 2017).

Fetal Infection

There is vertical transmission to the fetus in up to a third of maternal parvovirus infections (de Jong, 2011; Lamont, 2011b). Fetal infection has been associated with abortion, nonimmune hydrops, and stillbirth (Lassen, 2012; Mace, 2014; McClure, 2009). According to the American College of Obstetricians and Gynecologists (2017), the rate of fetal loss with serologically proven parvovirus infection is 8 to 17 percent before 20 weeks' gestation, and 2 to 6 percent after midpregnancy. Currently, no data support evaluating asymptomatic mothers and stillborn fetuses for parvovirus infection.

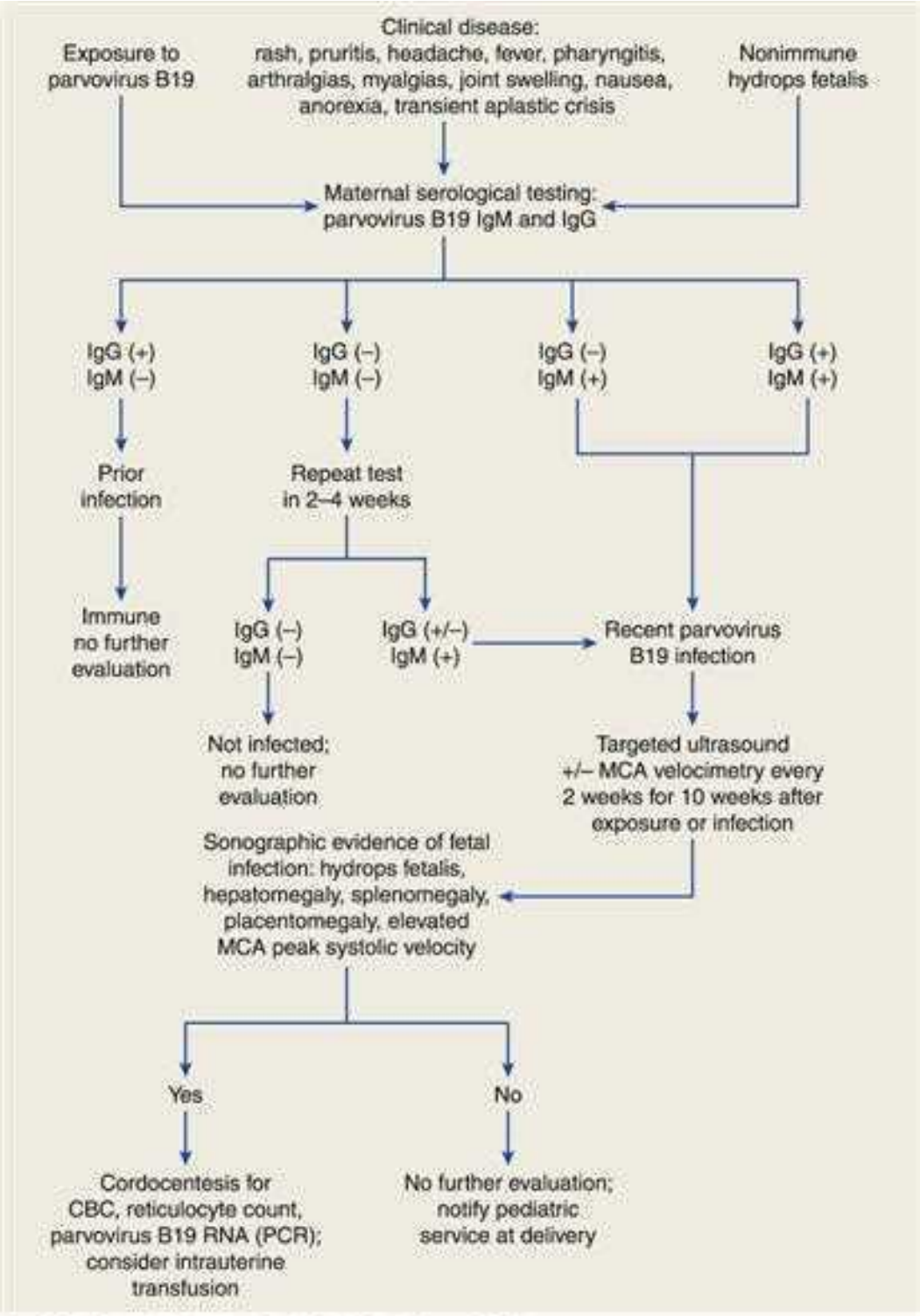
Hydrops develops in only approximately 1 percent of fetuses of women infected with parvovirus (American College of Obstetricians and Gynecologists, 2017; Pasquini, 2016; Puccetti, 2012). Still, it is the most frequent infectious agent of nonimmune hydrops in autopsied fetuses (Rogers, 1999). Hydrops usually stems from infection in the first half of gestation. In one report, more than 80 percent of hydrops cases were found in the second trimester, with a mean gestational age of 22 to 23 weeks (Yaegashi, 2000). At least 85 percent of cases of fetal infection developed within 10 weeks of maternal infection, and the mean interval was 6 to 7 weeks. The critical period for maternal infection leading to fetal hydrops was estimated to be between 13 and 16 weeks' gestation, which coincided with the period in which fetal hepatic hemopoiesis is greatest.

Diagnosis and Management

An algorithm for diagnosis of maternal parvoviral infection is illustrated in Figure 64-4. Diagnosis is generally made by maternal serological testing for specific IgG and IgM antibodies (Bonvicini, 2011; Brown, 2015). Viral DNA may be detectable by PCR in maternal serum during the prodrome and persist for months to years after infection. Fetal infection is diagnosed by detection of B19 viral DNA in amnionic fluid or IgM antibodies in fetal serum obtained by cordocentesis (de Jong, 2011; Weiffenbach, 2012). Fetal and maternal viral loads do not predict fetal morbidity and mortality (de Haan, 2007).

FIGURE 64-4

Algorithm for evaluation and management of human parvovirus B19 infection in pregnancy. CBC = complete blood count; IgG = immunoglobulin G; IgM = immunoglobulin M; MCA = middle cerebral artery; PCR = polymerase chain reaction; RNA = ribonucleic acid.



Most cases of parvovirus-associated hydrops develop in the first 10 weeks after infection. Thus, serial sonography every 2 weeks should be performed in women with recent infection (see Fig. 64-4). As discussed in Chapter 10 (Ductus Arteriosus), middle cerebral artery (MCA) Doppler interrogation can also be used to predict fetal anemia (Chauvet, 2011). Fetal blood sampling is warranted with hydrops to assess the degree of fetal anemia. Comorbid fetal myocarditis may induce hydrops with lesser degrees of anemia.

Depending on gestational age, fetal transfusion for hydrops may improve outcome in some cases (Enders, 2004). Mortality rates as high as 30 percent have been reported in hydropic fetuses without transfusions. With transfusion, 94 percent of hydrops cases resolve within 6 to 12 weeks, and the overall mortality rate is <10 percent. Most fetuses require only one transfusion because hemopoiesis resumes as infection resolves. Concurrent fetal thrombocytopenia worsens the prognosis (Melamed, 2015).

Long-Term Prognosis

Reports describing neurodevelopmental outcomes in fetuses transfused for B19 infection-induced anemia are conflicting. In one review of 24 transfused hydropic fetuses, abnormal neurodevelopment was noted in five of 16 survivors—32 percent—at 6 months to 8 years (Nagel, 2007). Outcomes were not related to severity of fetal anemia or acidemia, and these investigators hypothesized that the infection itself induced cerebral damage. In another study of 28 children treated with intrauterine transfusion, 11 percent had neurodevelopmental impairment during evaluation at a median age of 5 years (de Jong, 2012). Conversely, Dembinski (2003) found no significant neurodevelopmental delay despite severe fetal anemia.

Prevention

Currently, no parvovirus vaccine is available, and no evidence suggests that antiviral treatment prevents maternal or fetal infection. Decisions to avoid higher-risk work settings are complex and require assessment of exposure risks. Pregnant women should be counseled that risks for infection approximate 5 percent for casual, infrequent contact; 20 percent for intense, prolonged work exposure such as for teachers; and 50 percent for close, frequent interaction such as in the home. Workers at day-care centers and schools need not avoid infected children because infectivity is greatest before clinical illness. Finally, infected children do not require isolation.

West Nile Virus

This mosquito-borne RNA flavivirus is a human neuropathogen. It has become the most common cause of arthropod-borne viral encephalitis in the United States (Centers for Disease Control and Prevention, 2017f; Krow-Lucal, 2017). West Nile viral infections are typically acquired through mosquito bites in late summer or perhaps through blood transfusion. The incubation period is 2 to 14 days, and most persons have mild or no symptoms. Fewer than 1 percent of infected adults develop meningoencephalitis or acute flaccid paralysis (Granwehr, 2004). Presenting symptoms may include fever, mental status changes, muscle weakness, and coma (Stewart, 2013).

Diagnosis of West Nile infection is based on clinical symptoms and the detection of viral IgG and IgM in serum and IgM in cerebrospinal fluid. There is no known effective antiviral treatment, and management is supportive. The primary strategy for preventing exposure in pregnancy is the use of insect repellant containing *N,N*-diethyl-*m*-toluamide (DEET). This is considered safe for use among pregnant women (Wylie, 2016). Avoiding outdoor activity and stagnant water and wearing protective clothing are also recommended.

Adverse effects of West Nile viremia on pregnancy are unclear. Animal data suggest that embryos are susceptible, and a case report of human fetal infection at 27 weeks' gestation described chorioretinitis and severe temporal and occipital lobe leukomalacia (Alpert, 2003; Julander, 2006). In 77 maternal infections initially reported to the West Nile Virus Pregnancy Registry, there were four miscarriages, two elective abortions, and 72 live births, 6 percent of which were preterm (O'Leary, 2006). Three of these 72 newborns were shown to have West Nile infection, and it could not be established conclusively that infection was acquired congenitally. Of three major malformations *possibly* associated with viral infection, none was definitively confirmed. Similar conclusions were reached by Pridjian and colleagues (2016), who analyzed data from the CDC West Nile Virus Registry. Transmission of West Nile virus through breastfeeding is rare.

Coronavirus Infections

These are single-stranded RNA viruses that are prevalent worldwide. In 2002, an especially virulent strain of coronavirus—*severe acute respiratory syndrome (SARS–CoV)* was first noted in China. It rapidly spread throughout Asia, Europe, and North and South America. The case-fatality rate approached 10 percent in the nonpregnant population and was as high as 25 percent in pregnant women (Lam, 2004; Wong, 2004). Although no additional cases have been confirmed since 2004, the CDC (2013b) now lists SARS-CoV as a "select agent" that has the potential to pose a severe threat to public health and safety.

Another novel regional coronavirus with a high case-fatality rate was detected in 2012—Middle East respiratory syndrome coronavirus (MERS-CoV) (Arabi, 2017). Although experience with MERS-CoV is sparse in pregnancy, infection has been reported to cause maternal and perinatal deaths (Assiri, 2016).

Ebola Virus

A member of the RNA Filoviridae family, the Ebola virus is transmitted by direct person-to-person contact (Kuhn, 2015). Infection produces a severe hemorrhagic fever with pronounced immunosuppression and disseminated intravascular coagulopathy. Treatment is supportive, and the mortality rate approaches 50 percent.

Data are few concerning Ebola viral infection in pregnancy (Beigi, 2017; Money, 2015; Oduyebo, 2015). The CDC concludes that pregnant women are at increased risk for severe illness and death (Jamieson, 2014). That said, no evidence suggests that pregnant women are more susceptible to Ebola virus infection. One report described trophoblast infection (Muehlenbachs, 2017).

Zika Virus

This RNA virus of the Flavivirdae family has recently been recognized as the first major mosquito-borne teratogen (Rasmussen, 2016). Although Zika virus is primarily transmitted by mosquito bite, sexual transmission is also possible, and the virus may be detected in body fluids for months following acute infection (Hills, 2016; Joguet, 2017; Paz-Bailey, 2017).

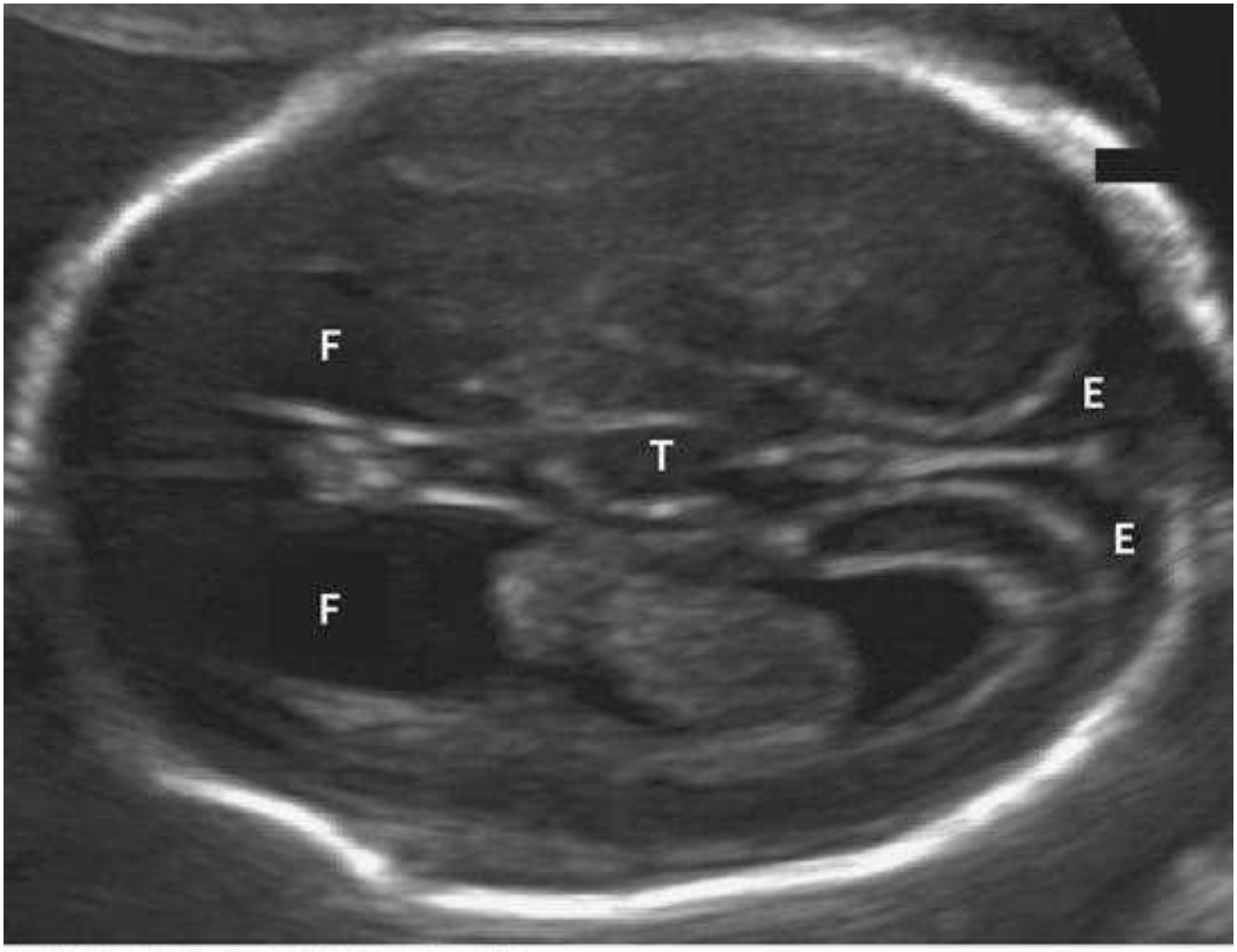
Maternal–Fetal Infection

Reminiscent of the rubella epidemic in the 1960s, in adults Zika infection may be asymptomatic or cause mild symptoms of rash, fever, headache, arthralgia, and conjunctivitis lasting a few days. Virus is typically detectable in blood around the time of symptom onset and may persist days to months in pregnant women (Driggers, 2016; Meaney-Delman, 2016). Serum IgM antibodies typically become detectable within the first two weeks after symptom onset and remain a median of four months (Oduyebo, 2017). Rarely, Guillain-Barré syndrome may develop following infection (da Silva, 2017; Parra, 2016).

The fetus can be severely infected whether or not the mother is symptomatic. Honein and coworkers (2017) describe a 6-percent overall fetal infection rate. In one report of 134 women with positive RT-PCR results, fetal mortality was 7 percent (Brasil, 2016). Among live births, the rate of fetal birth defects ranges from 5 percent—among women with possible Zika infection—to 15 percent among pregnant women with laboratory-confirmed infection in the first trimester (Reynolds, 2017). In the most severely affected fetuses, a congenital Zika syndrome has been described that includes microcephaly, lissencephaly, ventriculomegaly, intracranial calcifications, ocular abnormalities, and congenital contractures (Honein, 2017; Moore, 2017; Soares de Oliveira-Szejnfeld, 2016). Sonographic findings from a Zika-infected fetus are shown in Figure 64-5.

FIGURE 64-5

Sonographic transverse view of the cranium from a fetus with congenital Zika infection. Findings shown include a thin cerebral cortex, increased extraaxial space (*E*), dilated ventricles (*F,T*), and absent cavum septum pellucidum. (Reproduced with permission from Driggers RW, Ho CY, Korhonen EM, et al: Zika virus infection with prolonged maternal viremia and fetal brain abnormalities, N Engl J Med. 2016 Jun 2;374(22):2142–2151.)



Diagnosis and Management

Diagnosis of this infection in pregnant women is made with detection of Zika virus RNA in blood or urine or by serological testing. Detection of Zika virus RNA by PCR confirms infection. Serological assays for Zika IgM antibodies may cross react with other flaviviruses. Thus, a positive assay result is followed by another assay containing virus-specific neutralizing antibodies (Oduyebo, 2017). Testing recommendations and interpretation have evolved for pregnant women who are symptomatic and those who are asymptomatic but have ongoing exposure risk. This risk includes living in or traveling to an area with active local transmission. Large-scale screening programs have been described to identify women at high risk for travel-associated Zika infection (Adhikari, 2017).

Currently, no specific treatment or vaccine is available for Zika infection, although several vaccine candidates are in development (Beigi, 2017; World Health Organization, 2017). Prophylaxis includes protective netting and insect spray to control the vector mosquito and avoidance of sexual contact with partners recently exposed. The CDC has established a pregnancy hotline (770–488–7100) and U.S. Zika Pregnancy Registry (ZikaPregnancy@cdc.gov) for clinicians with concerns related to management of women with Zika infection or exposure.

BACTERIAL INFECTIONS

Group A *Streptococcus*

Infections caused by *Streptococcus pyogenes* are important in pregnant women. This organism is the most frequent bacterial cause of acute pharyngitis and is associated with several systemic and cutaneous infections. *S pyogenes* produces numerous toxins and enzymes responsible for its local and systemic toxicity. Pyrogenic exotoxin-producing strains are usually associated with severe disease (Shinar, 2016; Wessels, 2015). In most cases, streptococcal pharyngitis, scarlet fever, and erysipelas are not life threatening. Treatment, usually with penicillin, is similar in pregnant and nonpregnant women.

In the United States, *S pyogenes* infrequently causes puerperal infection. Still, it remains the most common cause of severe maternal postpartum infection and death worldwide, and the incidence of these infections is rising (Deutscher, 2011; Hamilton, 2013; Wessels, 2015). Puerperal infections are discussed in detail in Chapter 37. The early 1990s saw the emergence of streptococcal toxic shock syndrome, manifested by hypotension, fever, and evidence of multiorgan failure with associated bacteremia. Group A puerperal sepsis is seriously complicated in 20 percent of cases (Shinar, 2016). The case-fatality rate approximates 30 percent, and morbidity and mortality rates are improved with early recognition. Treatment includes clindamycin plus penicillin therapy and often surgical debridement (Chapter 47, Management). No vaccine for group A streptococcus is commercially available.

Group B *Streptococcus*

Streptococcus agalactiae is a group B organism that can be found to colonize the gastrointestinal and genitourinary tract in 10 to 25 percent of pregnant women (Kwatra, 2016). Throughout pregnancy, group B *Streptococcus* (GBS) is isolated in a transient, intermittent, or chronic fashion. Although the organism is most likely always present in these same women, their isolation is not always homologous.

Maternal and Perinatal Infection

The spectrum of maternal and fetal GBS effects ranges from asymptomatic colonization to septicemia. *S agalactiae* has been implicated in adverse pregnancy outcomes that include preterm labor, prematurely ruptured membranes, clinical and subclinical chorioamnionitis, and fetal infections (Randis, 2014). GBS can also cause maternal bacteriuria, pyelonephritis, osteomyelitis, postpartum mastitis, and puerperal infections. It remains the leading infectious cause of morbidity and mortality among infants in the United States (Centers for Disease Control and Prevention, 2010; Schrag, 2016).

Neonatal sepsis has received the most attention due to its devastating consequences and available effective preventative measures. Infection <7 days after birth is defined as *early-onset disease* and is seen in 0.21/1000 live births (Centers for Disease Control and Prevention, 2015). Many investigators use a threshold of <72 hours of life as most compatible with intrapartum acquisition of disease (Stoll, 2011). We and others have also encountered unexpected intrapartum stillbirths from GBS infections (Nan, 2015). Tudela and associates (2012) reported that newborns with early-onset GBS infection often had clinical evidence of fetal infection during labor or at delivery.

In many neonates, septicemia involves signs of serious illness that usually develop within 6 to 12 hours of birth. These include respiratory distress, apnea, and hypotension. At the outset, therefore, neonatal infection must be differentiated from respiratory distress syndrome caused by insufficient surfactant production (Chap. 34, Respiratory Distress Syndrome). The mortality rate with early-onset disease has declined to approximately 4 percent, and preterm newborns are disparately affected.

Late-onset disease caused by GBS is noted in 0.32 per 1000 live births and usually manifests as meningitis 1 week to 3 months after birth (Centers for Disease Control and Prevention, 2015). The mortality rate, although appreciable, is less for late-onset meningitis than for early-onset sepsis. Unfortunately, it is not uncommon for surviving infants of both early- and late-onset disease to exhibit devastating neurological sequelae.

Prophylaxis for Perinatal Infections

As GBS neonatal infections evolved beginning in the 1970s and before widespread intrapartum chemoprophylaxis, rates of early-onset sepsis ranged from 2 to 3 per 1000 live births. By 2010, these outcomes led to a policy of universal rectovaginal culture screening for GBS at 35 to 37 weeks' gestation followed by intrapartum antibiotic prophylaxis for women identified to be carriers. These outcomes stimulated development of expanded laboratory identification criteria for GBS; updated algorithms for screening and intrapartum chemoprophylaxis for women with preterm prematurely ruptured membranes, preterm labor, or penicillin allergy; and described new dosing for penicillin G chemoprophylaxis. Following these changes, the incidence of early-onset GBS neonatal sepsis decreased to 0.21 cases per 1000 live births by 2015 (Centers for Disease Control and Prevention, 2015).

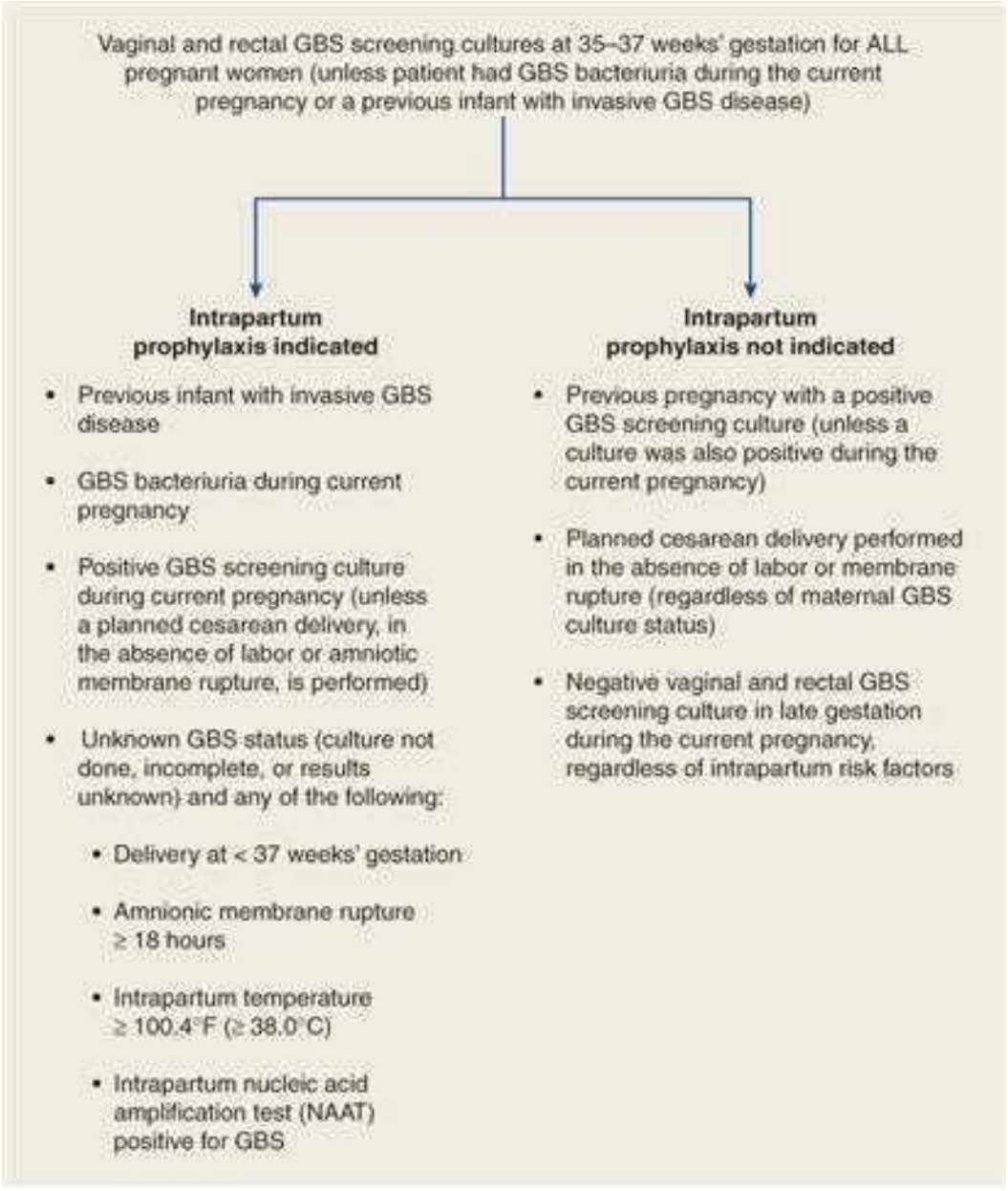
Thus, during the past three decades, several strategies have been proposed to prevent perinatal acquisition of GBS infections. These strategies have not been compared in randomized trials and are either culture-based or risk-based guidelines (Ohlsson, 2014). These methods have been adopted in the United States, but not all European countries have guidelines (Di Renzo, 2015).

Culture-Based Prevention

The CDC (2010) GBS guidelines recommend a culture-based approach, which was also adopted by the American College of Obstetricians and Gynecologists (2016e). Shown in Figure 64-6, this strategy is designed to identify women who should be given intrapartum antimicrobial prophylaxis. Women are screened for GBS colonization at 35 to 37 weeks' gestation, and intrapartum antimicrobials are given to women with rectovaginal GBS-positive cultures. Selective enrichment broth followed by subculture improves detection. In addition, more rapid techniques such as DNA probes and NAATs are being developed (Helali, 2012). A previous sibling with GBS invasive disease and identification of GBS bacteriuria in the current pregnancy are also considered indications for prophylaxis.

FIGURE 64-6

Indications for intrapartum prophylaxis to prevent perinatal group B streptococcal (GBS) disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures obtained at 35 to 37 weeks' gestation. (From Centers for Disease Control and Prevention, 2010.)



Risk-Based Prevention

This approach is recommended for women in labor and whose GBS culture results are not known. It relies on risk factors associated with intrapartum GBS transmission. Intrapartum chemoprophylaxis is given to women who have any of the following: delivery <37 weeks, ruptured membranes ≥18 hours, or intrapartum temperature ≥100.4°F (≥38.0°C). Women with GBS during the current pregnancy and women with a prior infant with invasive early-onset GBS disease are also given chemoprophylaxis.

At Parkland Hospital in 1995—and prior to consensus guidelines—we adopted and continue to use the risk-based approach for intrapartum treatment of women at high risk. Importantly, in addition, all term neonates who were not given intrapartum prophylaxis were treated in the delivery room with aqueous penicillin G, 50,000 to 60,000 units intramuscularly. Rates of early-onset GBS sepsis decreased to 0.4 to 0.66 per 1000 live births (Stafford, 2012; Wendel, 2002). Non-GBS early-onset sepsis decreased from 0.66 to 0.24 per 1000 live births (Stafford, 2012). Thus, this approach has results similar to those reported by the CDC (2010) for culture-based prevention.

GBS Vaccine

Serotype-specific capsular antibody concentrations clinically correlate with GBS neonatal disease. Antibody-producing vaccines have been tested, but none are clinically available (Donders, 2016; Kobayashi, 2016; Madhi, 2016).

Intrapartum Antimicrobial Prophylaxis

Preventive antimicrobials administered 4 or more hours before delivery are highly effective (Fairlie, 2013). Regardless of screening method, penicillin remains the first-line agent for prophylaxis, and ampicillin is an acceptable alternative (Table 64-3). Women with a penicillin allergy and no history of anaphylaxis are given cefazolin (Briody, 2016). Those at high risk for anaphylaxis should have antimicrobial susceptibility testing performed to exclude clindamycin resistance.

Clindamycin-sensitive but erythromycin-resistant isolates should have a D-zone test performed to assess for inducible clindamycin resistance. If clindamycin resistance is confirmed, vancomycin should be administered. *Erythromycin is no longer used for penicillin-allergic patients.*

TABLE 64-3

Regimens for Intrapartum Antimicrobial Prophylaxis for Perinatal GBS Disease

Regimen	Treatment
Recommended	Penicillin G, 5 million units IV initial dose, then 2.5 to 3.0 million units IV every 4 hours until delivery
Alternative	Ampicillin, 2 g IV initial dose, then 1 g IV every 4 hours or 2 g every 6 hours until delivery
Penicillin allergic Patients not at high risk for anaphylaxis Patients at high risk for anaphylaxis and with GBS susceptible to clindamycin Patients at high risk for anaphylaxis and with GBS resistant to clindamycin or susceptibility unknown	 Cefazolin, 2 g IV initial dose, then 1 g IV every 8 hours until delivery Clindamycin, 900 mg IV every 8 hours until delivery Vancomycin, 1 g IV every 12 hours until delivery

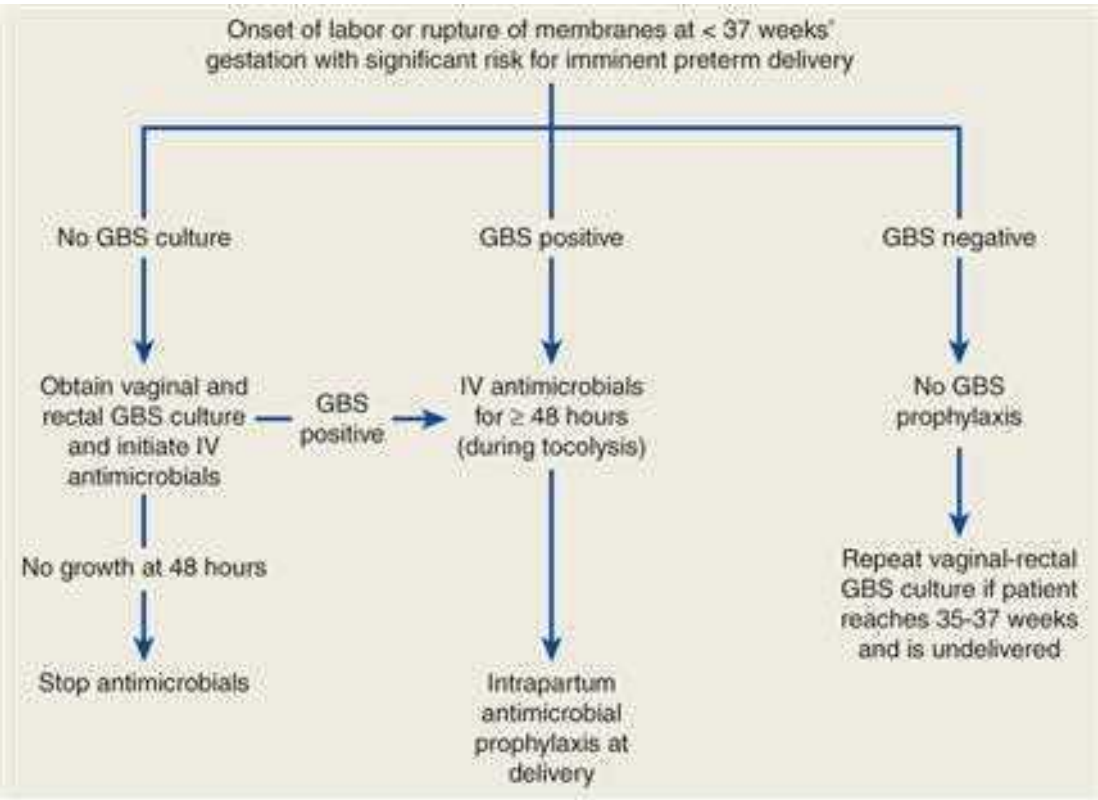
GBS = group B *Streptococcus*; IV = intravenous.

Data from the Verani, 2010

Further recommendations for management of spontaneous preterm labor, threatened preterm delivery, or preterm prematurely ruptured membranes are shown in Figure 64-7. Women undergoing cesarean delivery before labor onset with intact membranes do not need intrapartum GBS chemoprophylaxis, regardless of GBS colonization status or gestational age.

FIGURE 64-7

Sample algorithm for prophylaxis for women with group B streptococcal (GBS) disease and threatened preterm delivery. This algorithm is not an exclusive course of management, and variations that incorporate individual circumstances or institutional preferences may be appropriate. IV = intravenous. (Adapted from Centers for Disease Control and Prevention, 2016a.)



Methicillin-Resistant *Staphylococcus aureus*

Staphylococcus aureus is a pyogenic gram-positive organism and is considered the most virulent of the staphylococcal species. It primarily colonizes the nares, skin, genital tissues, and oropharynx. Approximately 20 percent of normal individuals are persistent carriers, 30 to 60 percent are intermittent carriers, and 20 to 50 percent are noncarriers (Gorwitz, 2008). Colonization is considered the greatest risk factor for infection (Marzec, 2016; Sheffield, 2013). Methicillin-resistant *S aureus* (MRSA) colonizes only 2 percent of adults but is a significant contributor to the health-care burden (Gorwitz, 2008). MRSA infections are associated with increased cost and higher mortality rates compared with those by methicillin-sensitive *S aureus* (MSSA) (Beigi, 2009; Butterly, 2010).

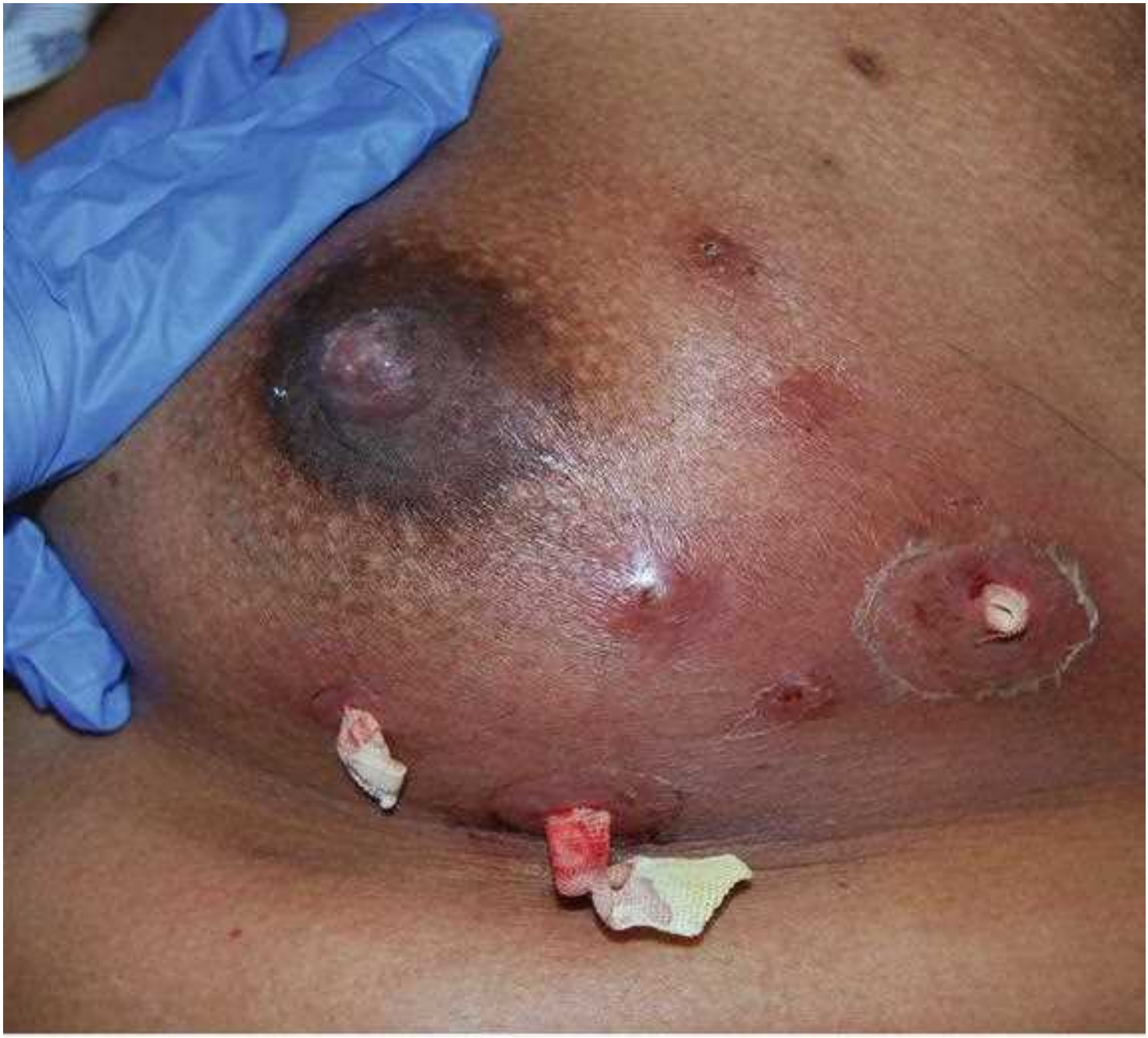
Community-acquired MRSA (CA-MRSA) is diagnosed when identified in an outpatient setting or within 48 hours of hospitalization in a person without traditional risk factors. Such risk factors include prior MRSA infection, hospitalization, dialysis or surgery within the past year, and indwelling catheters or devices (Dantes, 2013). Hospital-associated MRSA (HA-MRSA) infections are nosocomial. Most cases of MRSA in pregnant women are CA-MRSA.

MRSA and Pregnancy

Anovaginal colonization with *S aureus* is identified in 10 to 25 percent of obstetrical patients (Top, 2010). Skin and soft tissue infections are the most common presentation of MRSA in pregnant women (Fig. 64-8). Mastitis and breast abscesses have been reported in up to a fourth of cases of MRSA complicating pregnancy (Laibl, 2005; Lee, 2010). Perineal abscesses, wound infections at sites such as abdominal and episiotomy incisions, and chorioamnionitis are also associated with MRSA (Pimentel, 2009; Thurman, 2008). Finally, osteomyelitis has been reported (Nguyen, 2015; Tanamai, 2016).

FIGURE 64-8

This antepartum patient presented with multiple small microabscesses for which culture identified methicillin-resistant *Staphylococcus aureus*. (Reproduced with permission from Dr. Stephan Shivvers.)



A rise in CA-MRSA infections has been reported in neonatal intensive care units and newborn nurseries. In these settings, infection is frequently associated with maternal and health-care worker skin infections and infected breast milk. Vertical transmission is rare (Jimenez-Truque, 2012; Pinter, 2009).

Management

The Infectious Diseases Society of America has published guidelines for the treatment of MRSA infections (Liu, 2011). Uncomplicated superficial infections are primarily managed by drainage and local wound care. Although historically de-emphasized, recent evidence suggests benefit from antibiotic therapy in addition to incision and drainage of smaller abscesses (Daum, 2017; Forcade, 2012). Severe superficial infections, especially those that fail to respond to local care or those in patients with medical comorbidities, are treated with MRSA-appropriate antibiotics. Purulent cellulitis should be treated empirically for CA-MRSA until culture results are available.

Most CA-MRSA strains are sensitive to trimethoprim-sulfamethoxazole and clindamycin (Miller, 2015; Talan, 2016). Rifampin rapidly develops resistance and should not be used for monotherapy. Linezolid, although effective against MRSA, is expensive, and there is little information regarding its use in pregnancy. Doxycycline, minocycline, and tetracycline, although effective for MRSA infections, should not be used in pregnancy. Vancomycin remains the first-line therapy for inpatient serious MRSA infections.

The control and prevention of HA-MRSA and CA-MRSA rely on appropriate hand hygiene and prevention of skin-to-skin contact or contact with wound dressings. Decolonization should be considered only in cases in which a patient develops recurrent superficial infections despite optimal hygiene measures or if ongoing

transmission occurs among household or close contacts (Liu, 2011). Decolonization measures include nasal treatment with mupirocin, chlorhexidine gluconate baths, and oral rifampin therapy if previous measures have failed. Routine decolonization is not effective in the general obstetrical population. For women with culture-proven CA-MRSA infection during pregnancy, we add single-dose vancomycin to routine beta-lactam perioperative prophylaxis for cesarean deliveries and higher-order perineal lacerations. Breastfeeding in these women is not prohibited, but optimal hygiene and attention to minor skin breaks is encouraged.

Listeriosis

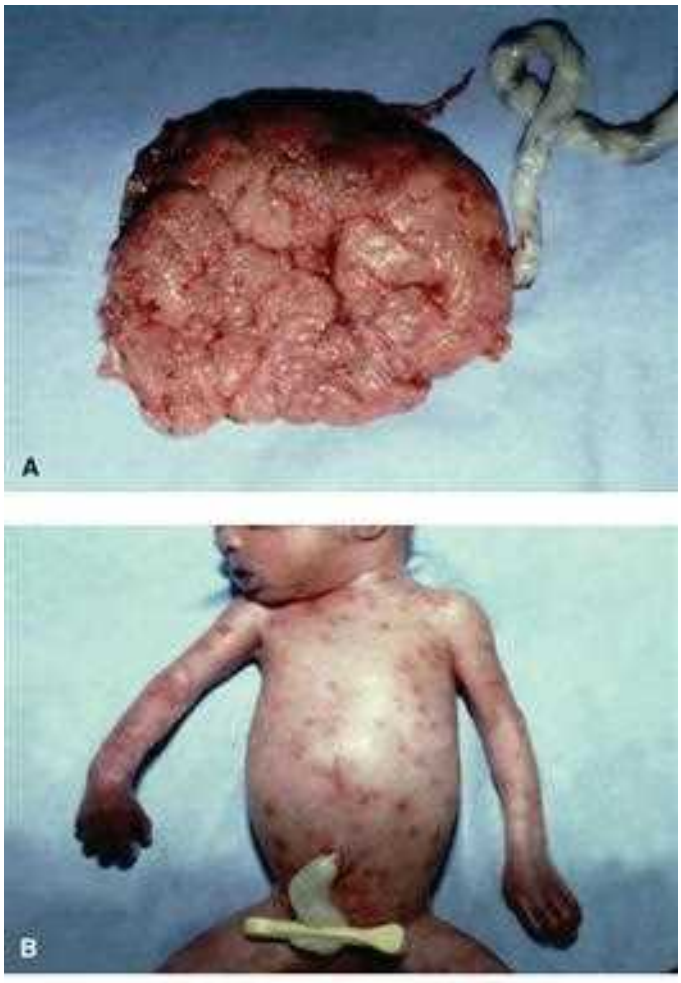
Listeria monocytogenes is an uncommon but probably underdiagnosed cause of neonatal sepsis (Kylat, 2016). This facultative intracellular gram-positive bacillus can be isolated from the feces of 1 to 5 percent of adults. Nearly all cases of listeriosis are thought to be foodborne. Outbreaks have been caused by raw vegetables, coleslaw, apple cider, melons, milk, fresh Mexican-style cheese, smoked fish, and processed foods such as pâté, hummus, wieners, and sliced deli meats (Centers for Disease Control and Prevention, 2013e).

Listerial infections are more common in pregnant women, immunocompromised patients, and the very old or young. The incidence of such infections in pregnancy is estimated to be up to 100 times that in the general population (Kourtis, 2014; Rouse, 2016). In 1651 cases reported in 2009 to 2011, the CDC found that 14 percent were in pregnant women (Silk, 2013). It is unclear why pregnant women still account for a significant number of these reported cases. One hypothesis is that pregnant women are susceptible because of decreased cell-mediated immunity (Baud, 2011).

Maternal and Fetal Infection

Listeriosis during pregnancy may be asymptomatic or may cause a febrile illness that is confused with influenza, pyelonephritis, or meningitis (Centers for Disease Control and Prevention, 2013e). The diagnosis usually is not apparent until blood cultures are reported as positive. Occult or clinical infection also may stimulate labor. Discolored, brownish, or meconium-stained amnionic fluid is common with fetal infection, even in preterm gestations. Maternal listeriosis causes fetal infection that characteristically produces disseminated granulomatous lesions with *microabscesses* (Fig. 64-9). Chorioamnionitis is common, and placental lesions include multiple, well-demarcated macroabscesses. Early- and late-onset neonatal infections are similar to group B streptococcal sepsis. In a review of 222 cases, infection resulted in abortion or stillbirth in 20 percent, and neonatal sepsis developed in 68 percent of surviving newborns (Mylonakis, 2002). In one large, prospective cohort study, 24 percent of mothers experienced fetal loss, but none after 29 weeks' gestation (Charlier, 2017). However, a neonatal-case fatality rate of 21 percent has been reported (Sapuan, 2017).

FIGURE 64-9
The pale placenta **(A)** and stillborn infant **(B)** resulted from maternal listeriosis.



Treatment with ampicillin plus gentamicin is usually recommended because of synergism against *Listeria* species (Rouse, 2016). Trimethoprim-sulfamethoxazole can be given to penicillin-allergic women. Maternal treatment in most cases is also effective for fetal infection (Chan, 2013). No vaccine is available. Prevention is by washing raw vegetables, cooking all raw food, and avoiding the implicated foods listed previously (American College of Obstetricians and Gynecologists, 2016d).

Salmonellosis

Infections from *Salmonella* species continue to be a major cause of foodborne illness (Peques, 2012). Six serotypes, including *Salmonella* subtypes *typhimurium* and *enteritidis,* account for most cases in the United States. Nontyphoid *Salmonella* gastroenteritis is contracted through contaminated food. Symptoms that include nonbloody diarrhea, abdominal pain, fever, chills, nausea, and vomiting begin 6 to 48 hours after exposure. Diagnosis is made by stool studies (Chap. 54, Inflammatory Bowel Disease). Intravenous crystalloid solutions are given for rehydration. Antimicrobials are not given in uncomplicated infections because they do not commonly shorten illness and may prolong the convalescent carrier state. If gastroenteritis is complicated by bacteremia, antimicrobials are given as discussed below. Rare case reports have linked *Salmonella* bacteremia with abortion (Coughlin, 2002).

Typhoid fever caused by *Salmonella typhi* remains a global health problem, although it is uncommon in the United States. Infection is spread by oral ingestion of contaminated food, water, or milk. In pregnant women, the disease is more likely to be encountered during epidemics or in those with HIV infection (Hedriana, 1995). In former years, antepartum typhoid fever resulted in abortion, preterm labor, and maternal or fetal death (Dildy, 1990).

Fluoroquinolones and third-generation cephalosporins are the preferred treatment. For enteric (typhoid) fever, antimicrobial susceptibility testing is important because of the development of drug-resistant strains (Crump, 2015). Typhoid vaccines appear to exert no harmful effects when administered to pregnant women and are given in an epidemic or before travel to endemic areas.

Shigellosis

Bacillary dysentery caused by *Shigella* is a relatively common, highly contagious cause of inflammatory exudative diarrhea in adults. Shigellosis is more common in children attending day-care centers and is transmitted via the fecal-oral route. Clinical manifestations range from mild diarrhea to severe dysentery, bloody stools, abdominal cramping, tenesmus, fever, and systemic toxicity. Although shigellosis may be self-limited, careful attention to treatment of dehydration is essential in severe cases. We have cared for pregnant women in whom secretory diarrhea exceeded 10 L/day! Antimicrobial therapy is imperative, and effective treatment during pregnancy includes fluoroquinolones, ceftriaxone, or azithromycin. Antimicrobial resistance is rapidly emerging, and antibiotic susceptibility testing can help guide appropriate therapy (Centers for Disease Control and Prevention, 2016). Shigellosis can stimulate uterine contractions and cause preterm birth (Parisot, 2016).

Hansen Disease

Also known as leprosy, this chronic infection is caused by *Mycobacterium leprae* and is rare in this country. Diagnosis is confirmed by PCR. Multidrug therapy with dapsone, rifampin, and clofazimine is recommended for treatment and is generally safe during pregnancy (Gimovsky, 2013; Ozturk, 2017). Duncan (1980) reported an excessive incidence of low-birthweight newborns among infected women. The placenta is not involved, and neonatal infection apparently is acquired from skin-to-skin or droplet transmission (Duncan, 1984). Vertical transmission is common in untreated mothers (Moschella, 2004).

Lyme Disease

Caused by the spirochete *Borrelia burgdorferi*, Lyme disease is the most commonly reported vectorborne illness in the United States (Centers for Disease Control and Prevention, 2017c). Lyme borreliosis follows tick bites of the genus *Ixodes*. There are three stages (Steere, 2015). Early infection—stage 1—causes a distinctive local skin lesion, *erythema migrans*, which may be accompanied by a flulike syndrome and regional adenopathy. If untreated, disseminated infection—stage 2—follows in days to weeks. Multisystem involvement is frequent, but skin lesions, arthralgia, myalgia, carditis, and meningitis predominate. If still untreated after several weeks to months, late or persistent infection—stage 3—manifests in perhaps half of patients. Native immunity is acquired, and the disease enters a chronic phase in about 10 percent. Some patients remain asymptomatic, but others in the chronic phase develop various skin, joint, or neurological manifestations (Shapiro, 2014).

Clinical diagnosis is important because serological and PCR testing has many pitfalls (Steere, 2015). IgM and IgG serological testing is recommended in early infection and is followed by Western blotting for confirmation. Ideally, acute and convalescent serological evaluation is completed if possible, however, false-positive and -negative rates are high.

Optimal treatment of Lyme disease was published by the Infectious Diseases Society of America (Sanchez, 2016). For early infection, treatment with doxycycline, amoxicillin, or cefuroxime is recommended for 14 days, although doxycycline is usually avoided in pregnancy. A 14- to 28-day course of IV ceftriaxone, cefotaxime, or penicillin G is given for complicated early infections that include meningitis, carditis, or disseminated infections. Chronic arthritis and post-Lyme disease syndrome are treated with prolonged oral or IV regimens, however, symptoms respond poorly to treatment (Steere, 2015).

No vaccine is commercially available. Avoiding areas with endemic Lyme disease and improving tick control in those areas is the most effective prevention. Self-examination with removal of unengorged ticks within 36 hours of attachment reduces infection risk (Hayes, 2003). For tick bites recognized within 72 hours, a single 200-mg oral dose of doxycycline may reduce infection development.

Several reports describe Lyme disease in pregnancy, although large series are lacking. Transplacental transmission has been confirmed, but no congenital effects of maternal borreliosis have been conclusively identified (Shapiro, 2014; Walsh, 2006). Prompt treatment of maternal early infection should prevent most adverse pregnancy outcomes (Mylonas, 2011).

Tuberculosis

Diagnosis and management of tuberculosis during pregnancy is discussed in detail in Chapter 51 (Tuberculosis).

PROTOZOAL INFECTIONS

Toxoplasmosis

The obligate intracellular parasite *Toxoplasma gondii* has a life cycle with two distinct stages (Kim, 2015). The *feline* stage takes place in the cat—the definitive host—and its prey. Unsporulated oocysts are excreted in feces. In the *nonfeline* stage, tissue cysts containing bradyzoites or oocysts are ingested by the intermediate host, including humans. Gastric acid digests the cysts to release bradyzoites, which infect small-intestinal epithelium. Here, they are transformed into rapidly dividing tachyzoites, which can infect all cells within the host mammal. Humoral and cell-mediated immune defenses eliminate most of these, but tissue cysts develop. Their lifelong persistence is the chronic form of toxoplasmosis.

Human infection is acquired by eating raw or undercooked meat infected with tissue cysts or by contact with oocysts from cat feces in contaminated litter, soil, or water. Prior infection is confirmed by serological testing, and its prevalence depends on geographic locale and parasite genotype. In the United States, seroprevalence in persons aged 10 to 19 years is 5 to 30 percent, and this can exceed 60 percent in those older than 50 (Kim, 2015). Thus, a significant segment of pregnant women in this country are susceptible to infection. The incidence of prenatal infection resulting in birth of a newborn with congenital toxoplasmosis varies from 0.8 per 10,000 live births in the United States to 10 per 10,000 in France (Cook, 2000). Between 400 and 4000 cases of congenital toxoplasmosis are diagnosed annually in the United States (Jones, 2014).

Maternal and Fetal Infection

Most acute maternal infections are subclinical and are detected only by prenatal or newborn serological screening. In some cases, maternal symptoms may include fatigue, fever, headache, muscle pain, and sometimes a maculopapular rash and posterior cervical lymphadenopathy. In immunocompetent adults, initial infection confers immunity, and prepregnancy infection nearly eliminates any risk of vertical transmission. Infection in immunocompromised women, however, may be severe, and reactivation may cause encephalitis, retinochoroiditis, or mass lesions. Maternal infection is associated with a fourfold increased preterm delivery rate before 37 weeks (Freeman, 2005).

The incidence and severity of fetal toxoplasmosis depend on gestational age at the time of maternal infection. Risks for fetal infection rise with gestational age. A metaanalysis estimated the risk to be 15 percent at 13 weeks, 44 percent at 26 weeks, and 71 percent at 36 weeks (SYROCOT Study Group, 2007). Conversely, the severity of fetal infection is much greater in early pregnancy, and these fetuses are much more likely to have clinical findings of infection (American College of Obstetricians and Gynecologists, 2017).

Importantly, most infected fetuses are born without obvious stigmata of toxoplasmosis. Clinically affected neonates usually have generalized disease expressed as low birthweight, hepatosplenomegaly, jaundice, and anemia. Some primarily have neurological disease with intracranial calcifications and with hydrocephaly or microcephaly (Dhombres, 2017). Many eventually develop chorioretinitis and exhibit learning disabilities. This classic triad—chorioretinitis, intracranial calcifications, and hydrocephalus—is often accompanied by convulsions. Infected neonates with clinical signs are at risk for long-term complications (Abdoli, 2014; Wallon, 2014).

Screening and Diagnosis

With IgG antibody confirmed before pregnancy, there is no risk for a congenitally infected fetus. The American College of Obstetricians and Gynecologists (2017) does not recommend prenatal screening for toxoplasmosis in areas of low prevalence, including the United States. Screening should be performed in immunocompromised pregnant women, including those with HIV infection. In areas of high toxoplasmosis prevalence—for example, France and Austria—routine screening has resulted in diminished congenital disease (Kim, 2015; Wallon, 2013).

Pregnant women with suspected toxoplasmosis should be tested. The parasite is rarely detected in tissue or body fluids. Antitoxoplasma IgG develops within 2 to 3 weeks after infection, peaks at 1 to 2 months, and usually persists for life—sometimes in high titers. Although IgM antibodies appear by 10 days after infection and usually become negative within 3 to 4 months, they may remain detectable for years. Thus, IgM antibodies are not used alone to diagnose acute toxoplasmosis (Dhakal, 2015). Best results are obtained with the Toxoplasma Serologic Profile performed at the Palo Alto Medical Foundation Research Institute (www.toxolab@pamf.org). Toxoplasma IgG avidity increases with time. Thus, if a high-avidity IgG result is found, infection in the preceding 3 to 5 months is excluded. Multiple tests are available that allow high avidity results to confirm latent infection with a 100-percent positive-predictive value (Villard, 2013).

Congenital toxoplasmosis is suspected when sonography reveals findings such as hydrocephaly, intracranial or hepatic calcifications, ascites, placental thickening, hyperechoic bowel, and growth restriction. Prenatal diagnosis of congenital toxoplasmosis is performed using PCR amplification of toxoplasma DNA in amnionic fluid (Filisetti, 2015; Montoya, 2008). The sensitivity of PCR varies with gestational age and is lowest before 18 weeks (Romand, 2001).

Management

No randomized clinical trials have assessed the benefit and efficacy of treatment to decrease the risk for congenital infection. A systematic review of data from 1438 treated pregnancies found weak evidence for early treatment to reduce congenital toxoplasmosis risks (SYROCOT Study Group, 2007). Treatment has been associated with a reduction in rates of serious neurological sequelae and neonatal demise (Cortina-Borja, 2010).

Prenatal treatment is based on two regimens—spiramycin alone or a pyrimethamine–sulfonamide combination given with folinic acid (American College of Obstetricians and Gynecologists, 2017). These two regimens have also been used consecutively (Hotop, 2012). Little evidence supports the use of a specific regimen

(Montazeri, 2017; Valentini, 2015). That said, most experts will use spiramycin in women with acute infection early in pregnancy to reduce vertical transmission. Because it does not cross the placenta, spiramycin may not be used to treat fetal infection. Pyrimethamine–sulfadiazine with folinic acid is selected for maternal infection after 18 weeks' gestation or if fetal infection is suspected.

Prevention

There is no vaccine for toxoplasmosis, so avoidance of infection is necessary if congenital infection is to be prevented. Efforts include: (1) cooking meat to safe temperatures; (2) peeling or thoroughly washing fruits and vegetables; (3) cleaning all food preparation surfaces and utensils that have contacted raw meat, poultry, seafood, or unwashed fruits and vegetables; (4) wearing gloves when changing cat litter, or else delegating this duty; and (5) avoiding feeding cats raw or undercooked meat and keeping cats indoors. Although these preventive steps are recommended, no data support their effectiveness (American College of Obstetricians and Gynecologists, 2017; Di Mario, 2015).

Malaria

This protozoan infection remains a global health crisis and causes 2000 deaths per day worldwide (White, 2015). Malaria has been effectively eradicated in Europe and in most of North America, and worldwide mortality rates have fallen more than 25 percent. In the United States, most cases of malaria are imported—some in returning military personnel (Mace, 2017). Transmitted by infected *Anopheles* mosquitoes, six species of *Plasmodium* cause human disease—*falciparum, vivax,* two species of *ovale, malariae,* and *knowlesi*.

Malaria and Pregnancy

Pregnant women have increased susceptibility to malarial infections (Kourtis, 2014). Antibodies to the parasite surface antigen VAR2CSA mediate placental accumulation of infected erythrocytes and lead to the harmful effects of malaria (Mayor, 2015). Through this mechanism, some immunity accrues with parity and is called *pregnancy-specific antimalarial immunity.* Ironically, malaria treatment dampens this immunity, and resurgence in pregnancy has been documented in Mozambique (Mayor, 2015).

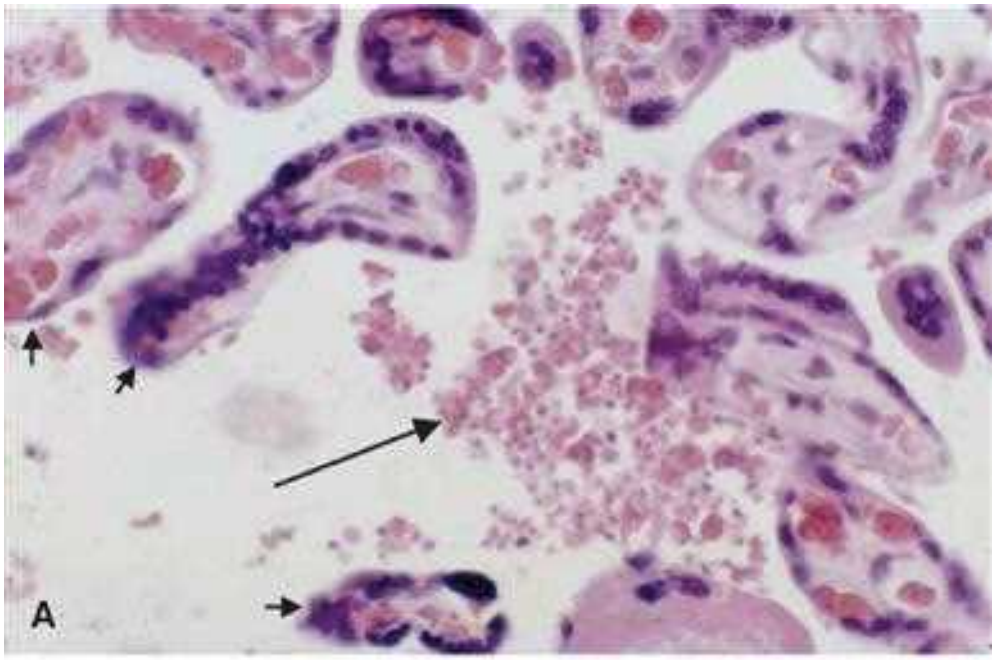
Maternal and Fetal Infection

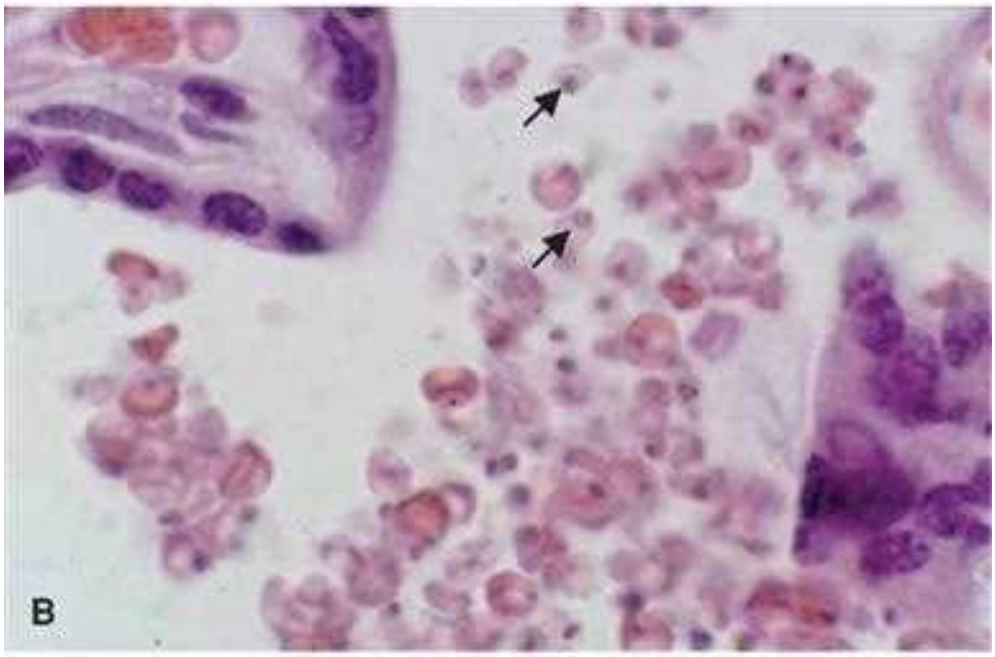
Clinical findings are fever, chills, and flulike symptoms including headaches, myalgia, and malaise, which may occur at intervals. Symptoms are less severe with recurrences. Malaria may be associated with anemia and jaundice, and *falciparum* infections may cause kidney failure, coma, and death. That said, many otherwise healthy but infected adults in endemic areas are asymptomatic because of partial immunity. Pregnant women, although often asymptomatic, are said to be more likely to develop traditional symptoms (Desai, 2007).

Malarial infections during pregnancy—whether symptomatic or asymptomatic—are associated with higher rates of perinatal morbidity and mortality (Menéndez, 2007; Nosten, 2007). Adverse outcomes include stillbirth, preterm birth, low birthweight, and maternal anemia. The latter two are documented most frequently (Machado Filho, 2014; McClure, 2013). Maternal infection is associated with a 14-percent rate of low-birthweight newborns worldwide (Eisele, 2012). These adverse perinatal outcomes correlate with high levels of placental parasitemia (Rogerson, 2007). The latter occurs when parasitized erythrocytes, monocytes, and macrophages accumulate in the vascular areas of the placenta (Fig. 64-10). Infections with *P falciparum* are the worst, and early infection raises the risk for abortion. The incidence of malaria increases significantly in the latter two trimesters and postpartum (Diagne, 2000). Despite this, congenital malaria occurs in <5 percent of neonates born to infected mothers.

FIGURE 64-10

Photomicrograph of placental malaria. **A.** Multiple infected red blood cells (*long black arrow*) are seen in the intervillous space of this placenta. Multiple villi cut in cross section are shown, and three are highlighted (*short arrows*). **B.** Increased magnification of image **(A).** Multiple infected erythrocytes are seen, and two are identified (*arrows).*





Diagnosis and Management

Identification of parasites by microscopical evaluation of a thick and thin blood smear remains the gold standard for diagnosis. In women with low parasite densities, however, the sensitivity of microscopy is poor. Malaria-specific antigens are now being used for rapid diagnostic testing. Not only is their sensitivity still an issue in pregnancy, but these tests are not routinely available (Kashif, 2013; White, 2015).

For treatment, the most frequently used antimalarial drugs are not contraindicated in pregnancy. The World Health Organization recommends that all infected patients living in or traveling from endemic areas be treated with an artemisinin-based regimen for uncomplicated falciparum malaria (Tarning, 2016). The CDC (2013c) recommends using atovaquone-proguanil or artemether-lumefantrine only if other treatment options are not available or tolerated.

The CDC (2013c) recommends that pregnant women diagnosed with uncomplicated malaria caused by *P vivax, malariae, ovale,* and chloroquine-sensitive *P falciparum* should be treated with chloroquine or hydroxychloroquine. For women infected with multidrug-resistant *P falciparum*, one first-line agent for nonpregnant persons is artemether-lumefantrine. Another primary option is artesunate plus mefloquine or artesunate plus dihydroartemisinin-piperaquine (White, 2015). The PREGACT Study Group (2016) recently compared four artemisinin-based drugs in 3428 pregnant women with falciparum malaria and reported no serious maternal or perinatal adverse effects. Second-line treatment regimens are artesunate; quinine plus either tetracycline, doxycycline, or clindamycin; or atovaquone-proguanil. Chloroquine-resistant *P vivax* should be treated with mefloquine. Chloroquine-sensitive *P vivax* or *P ovale* should be treated with chloroquine throughout

pregnancy and then primaquine postpartum. Resistance to all the antimalarial drugs has been reported, including the recently added artemisinin-based compounds.

Treatment regimens for uncomplicated and severe malarial infections in pregnancy are detailed at: www.cdc.gov/malaria/diagnosis_treatment. The CDC also maintains a malaria hotline for treatment recommendations (855–856–4713).

Prevention and Chemoprophylaxis

Malaria control and prevention relies on chemoprophylaxis when traveling to or living in endemic areas. Vector control is also important. Insecticide-treated netting, pyrethroid insecticides, and DEET-based insect repellent lower malarial rates in endemic areas. These are well tolerated in pregnancy (Menéndez, 2007). If travel is necessary, chemoprophylaxis is recommended.

Chloroquine and hydroxychloroquine prophylaxis is safe and well tolerated in pregnancy. Prophylaxis lowers placental infection rates from 20 percent to 4 percent in asymptomatic infected women in areas without chloroquine resistance (Cot, 1992). For travelers to areas with chloroquine-resistant *P falciparum*, mefloquine prophylaxis is recommended (Freedman, 2016). One evaluation compared prophylaxis during pregnancy with either sulfadoxine-pyrimethamine or dihydroartemisinin-piperaquine and found the latter to be more effective (Kakuru, 2016). Primaquine and doxycycline are contraindicated in pregnancy, and data are insufficient for atovaquone/proguanil use. The latest chemoprophylaxis regimens for pregnancy can be obtained from the CDC *Travelers' Health* website at: www.cdc.gov/malaria/travelers/drugs.html. The CDC also publishes *Health Information for International Travel* (The Yellow Book) at: www.cdc.gov/yellowbook. For women living in endemic areas, intermittent preventive treatment was found to be superior to intermittent screening with treatment (Desai, 2015).

Amebiasis

Approximately 10 percent of the world population is infected with *Entamoeba histolytica*, and most are asymptomatic (Andrade, 2015). Amebic dysentery, however, may take a fulminant course during pregnancy, with fever, abdominal pain, and bloody stools. Prognosis is worse if complicated by a hepatic abscess. Diagnosis is made by identifying *E histolytica* cysts or trophozoites within a stool sample. Therapy is similar to that for the nonpregnant woman, and metronidazole or tinidazole are the preferred drugs for amebic colitis and invasive disease. Noninvasive infections may be treated with iodoquinol or paromomycin.

MYCOTIC INFECTIONS

Disseminated fungal infection—usually pneumonitis—during pregnancy is uncommon with coccidiomycosis, blastomycosis, cryptococcosis, or histoplasmosis. Their identification and management are considered in Chapter 51 (Tuberculosis).

TRAVEL PRECAUTIONS DURING PREGNANCY

Pregnant travelers face general medical, obstetrical, and potentially hazardous destination risks. Several sources provide travel information (Freedman, 2016). The International Federation for Tropical Medicine has comprehensive information available at www.iftm-hp.org, and the International Society of Travel Medicine publishes information at www.istm.org/bodyofknowledge. Also, *The Yellow Book*, mentioned earlier, by the CDC has extensive travel information regarding pregnancy and breastfeeding.

BIOTERRORISM

The concept of bioterrorism involves the deliberate release of bacteria, viruses, or other infectious agents to cause illness or death. These natural agents are often altered to increase their infectivity or their resistance to medical therapy. Health-care providers should be alert for significant increases in the number of persons with febrile illnesses accompanied by respiratory symptoms or with rashes not easily associated with common illnesses. Clinicians are urged to contact their state health department or the CDC for current information and recommendations. The American College of Obstetricians and Gynecologists (2016a) has addressed disaster preparedness for obstetricians. It provides both general considerations and recommendations for hospital readiness and obstetrics-specific issues.

Smallpox

The variola virus causes smallpox and is considered a serious weapon. The virus is highly transmissible and carries an overall 30-percent case-fatality rate. The last case of smallpox in the United States was reported in 1949, and worldwide it was reported in Somalia in 1977. Nishiura (2006) has reviewed the severe perinatal and maternal morbidity and mortality caused by smallpox. The case-fatality rate of smallpox in pregnancy is 61 percent if the pregnant woman is unvaccinated. Rates of stillbirth, abortion, preterm labor and delivery, and neonatal demise rise significantly in pregnancies complicated by this infection.

Because the smallpox vaccine currently available is made with live vaccinia virus, pregnancy should be delayed for 4 weeks in recipients. It is generally not given to pregnant women because of the risk of fetal vaccinia, a rare but serious complication. Inadvertent smallpox vaccination during pregnancy has not, however, been convincingly associated with fetal malformations or preterm birth (Badell, 2015). Moreover, no cases of fetal vaccinia have been reported with second-generation smallpox vaccine exposure. The Smallpox Vaccine in Pregnancy Registry remains active, and vaccinated women are still being enrolled: DOD.NHRC-birthregistry@mail.mil.

Anthrax

Bacillus anthracis is a gram-positive, spore-forming, aerobic bacterium. It can cause three main types of clinical anthrax: inhalational, cutaneous, and gastrointestinal (Centers for Disease Control and Prevention, 2017a). The bioterrorist anthrax attacks of 2001 involved inhalational anthrax (Inglesby, 2002). Spores

are inhaled and deposited in the alveoli. They are engulfed by macrophages and germinate in mediastinal lymph nodes. The incubation period is usually less than 1 week but may be as long as 2 months. Within 1 to 5 days of symptom onset, the second stage is heralded by the abrupt onset of severe respiratory distress and high fevers. Mediastinitis and hemorrhagic thoracic lymphadenitis are common. Chest radiographs show a widened mediastinum. Case-fatality rates with inhalational anthrax are high, even with aggressive antibiotic and supportive therapy (Holty, 2006).

Anthrax affecting pregnant women and its treatment were reviewed by Meaney-Delman and coworkers (2012, 2013). They reported data on 20 pregnant and postpartum women. The overall mortality rate was 80 percent, with a 60-percent fetal or neonatal loss rate. Of note, most cases were published before the advent of antibiotics.

Regimens for postexposure anthrax prophylaxis are given for 2 months. The CDC recommend that asymptomatic pregnant and lactating women with documented exposure to *B anthracis* be given postexposure prophylaxis with ciprofloxacin, 500 mg orally twice daily for 60 days (Hendricks, 2014; Meaney-Delman, 2013). Amoxicillin, 500 mg orally three times daily, can be substituted if the strain is proven sensitive. In the case of ciprofloxacin allergy and either penicillin allergy or resistance, doxycycline, 100 mg orally twice daily, is given for 60 days. Risks from anthrax far outweigh any fetal risks from doxycycline (Meaney-Delman, 2013).

The anthrax vaccine is an inactivated, cell-free product that requires three injections over 28 days. Vaccination is generally avoided in pregnancy because safety data are limited. Inadvertent vaccination of pregnant women with the vaccine has not been linked with a significant increase in fetal malformation or miscarriage rates (Conlin, 2015; Ryan, 2008). The anthrax vaccine is an essential adjunct to postexposure antimicrobial prophylaxis, even in pregnancy.

Other Bioterrorism Agents

Other category A bioterrorism agents include *Francisella tularensis*—tularemia, *Clostridium botulinum*—botulism, *Yersinia pestis*—plague, and viral hemorrhagic fevers—for example, Ebola, Marburg, Lassa, and Machupo. The guidelines for these biological agents are evolving and are detailed at the CDC Bioterrorism website: emergency.cdc.gov/bioterrorism/index.asp.

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CHAPTER 65: Sexually Transmitted Infections

Syphilis is one of the most important complications of pregnancy, as it is one of the most frequent causes of abortion or premature labour. Syphilis is the most common cause of foetal death in the later months of pregnancy, and may be maternal or paternal in origin.

—J. Whitridge Williams (1903)

INTRODUCTION

Syphilis and gonorrhea were prominently mentioned in the first edition of this book, with special consideration for their harmful effects on fetal development. Although Williams confined his discussion to these two infections, today, sexually transmitted diseases (STDs) include chlamydial and trichomonal infections and viral STDs such as hepatitis B, human immunodeficiency virus (HIV), herpes simplex virus (HSV), and human papillomavirus (HPV) infections. In some form, all can be injurious to the mother or fetus and thus should be aggressively sought and treated. In many instances, recommended therapies are provided in guidelines from the Centers for Disease Control and Prevention (CDC) and listed throughout the chapter.

Vertical transmission refers to passage from the mother to her fetus of an infectious agent through the placenta, during labor or delivery, or by breastfeeding. Treatment of most STDs is clearly associated with improved pregnancy outcome and prevention of perinatal morbidity. Logically, education, screening, treatment, and prevention are essential components of prenatal care.

SYPHILIS

Despite the availability of adequate therapy for decades, syphilis remains a major issue for both mother and fetus. From 2001 through 2015, the primary and secondary syphilis rates have risen almost yearly (Centers for Disease Control and Prevention, 2016c). In the United States in 2015, the combined rate for both of these among women was 1.8 cases per 100,000 persons (de Voux, 2017). For congenital syphilis, after a nadir in 2012, rates have also risen yearly to reach 12.4 cases per 100,000 live births in 2015. Of risks, higher congenital syphilis rates are linked to inadequate prenatal care, black or Hispanic race, and lack of treatment (Su, 2016). Similarly, syphilis remains a significant global health problem, with many countries reporting high numbers of new infections (Newman, 2015; World Health Organization, 2012).

Pathogenesis and Transmission

Syphilis is caused by the spirochetal bacterium *Treponema pallidum.* Minute abrasions on the vaginal mucosa provide an entry portal, and cervical eversion, hyperemia, and friability raise transmission risk. Spirochetes replicate and then disseminate through lymphatic channels within hours to days. The incubation period is 3 to 4 weeks depending on host factors and inoculum size.

The early stages of syphilis include primary, secondary, and early latent syphilis. These are associated with high spirochete loads, and partner transmission rates approximate 30 to 60 percent (Garnett, 1997; Singh, 1999). In late-stage disease, transmission rates decline because of smaller inoculum sizes.

Maternal syphilis can cause fetal infection by several routes. Spirochetes readily cross the placenta to cause congenital infection. Although transplacental transmission is the most common route, neonatal infection may follow after contact with spirochetes through lesions at delivery or across the placental membranes. Fetal infection develops in >50 percent of untreated early syphilis cases and in 10 percent of late latent disease (Fiumara, 1975; Hollier, 2001).

Clinical Manifestations

Maternal Syphilis

This is staged according to clinical features and disease duration.

1. *Primary syphilis* is diagnosed by its characteristic chancre, which develops at the inoculation site. This solitary, painless lesion typically has a raised, firm border and a red, smooth ulcerated base without significant pus (Fig. 65-1). Nonsuppurative lymphadenopathy may develop. A chancre will usually resolve spontaneously in 2 to 8 weeks, even if untreated. Multiple lesions, if found, are predominantly in HIV-1 co-infected women.

2. *Secondary syphilis* stems from dissemination of spirochetes to affect multiple organ systems. Manifestations develop 4 to 10 weeks after the chancre appears and include dermatological abnormalities in up to 90 percent of women. A diffuse macular rash, plantar and palmar targetlike lesions, patchy alopecia, and mucous patches may be seen (Fig. 65-2). *Condylomata lata* are flesh-colored papules and nodules found on the perineum and perianal area (Fig. 65-3). These papules are teeming with spirochetes and are highly infectious. Most women with secondary syphilis also express constitutional symptoms such as fever, malaise, headache, and myalgias. Hepatitis, nephropathy, ocular changes, anterior uveitis, and periostitis can also develop.

3. *Latent syphilis* develops when primary or secondary syphilis is not treated but clinical manifestations still resolve. It is identified instead by serological testing. *Early latent syphilis* is subclinical disease acquired within the preceding 12 months. Disease diagnosed beyond 12 months is either *late latent syphilis* or *latent syphilis of unknown duration.*

4. *Tertiary syphilis* is a slowly progressive disease affecting any organ system but is rarely seen in reproductive-aged women.

FIGURE 65-1
Primary syphilis. Photograph of a chancre with a raised, firm border and smooth, red base.

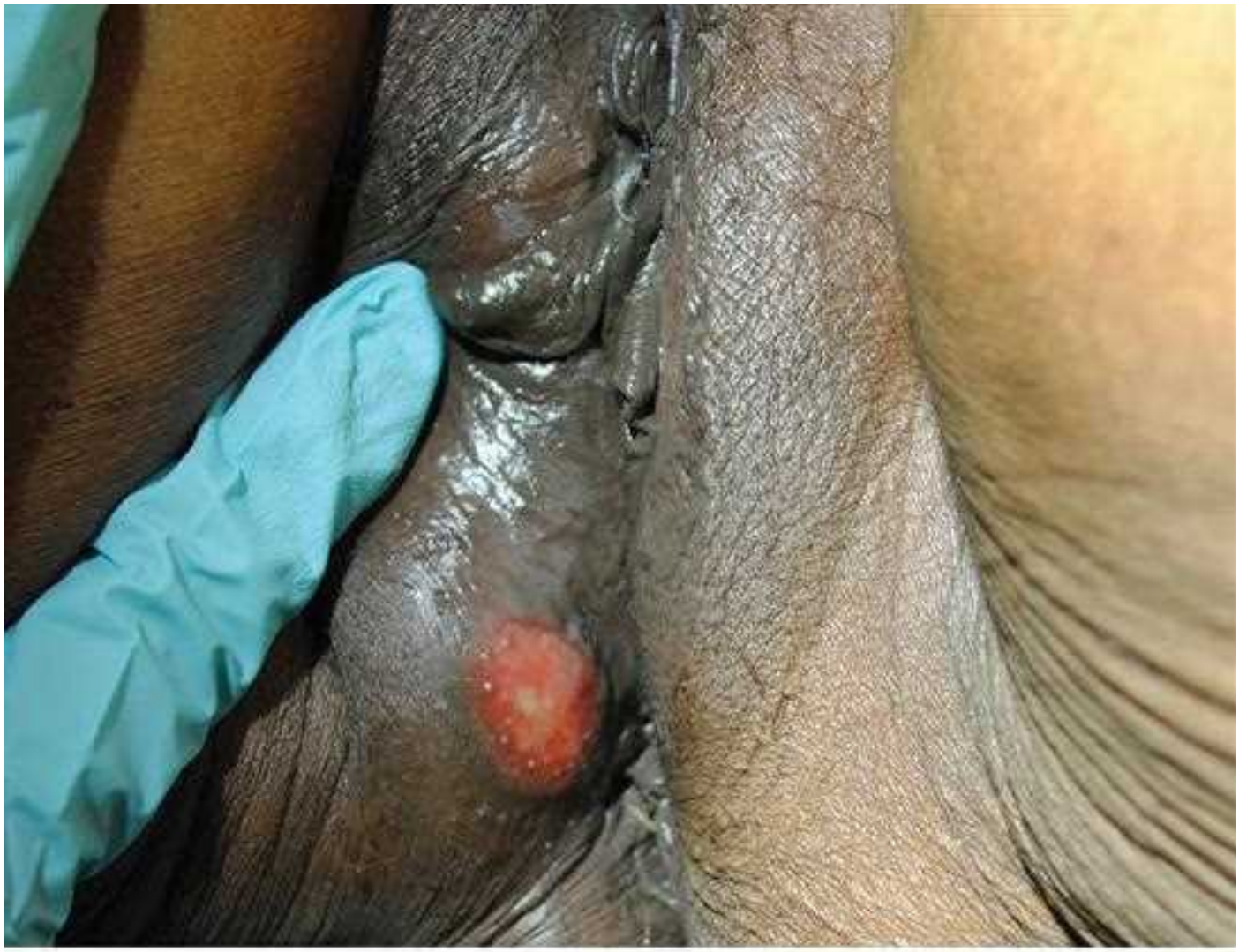


FIGURE 65-2
Secondary syphilis. **A.** Target lesions on the palms. **B.** Mucous patches around the nose and mouth. (Used with permission from Dr. Devin Macias.)

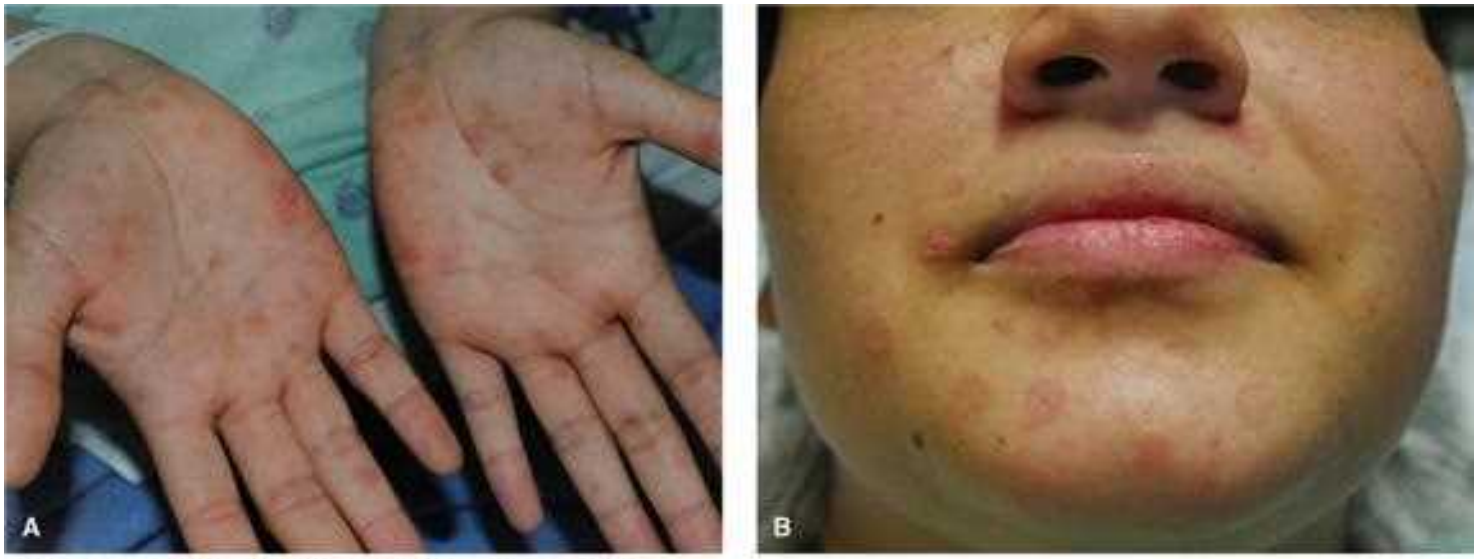
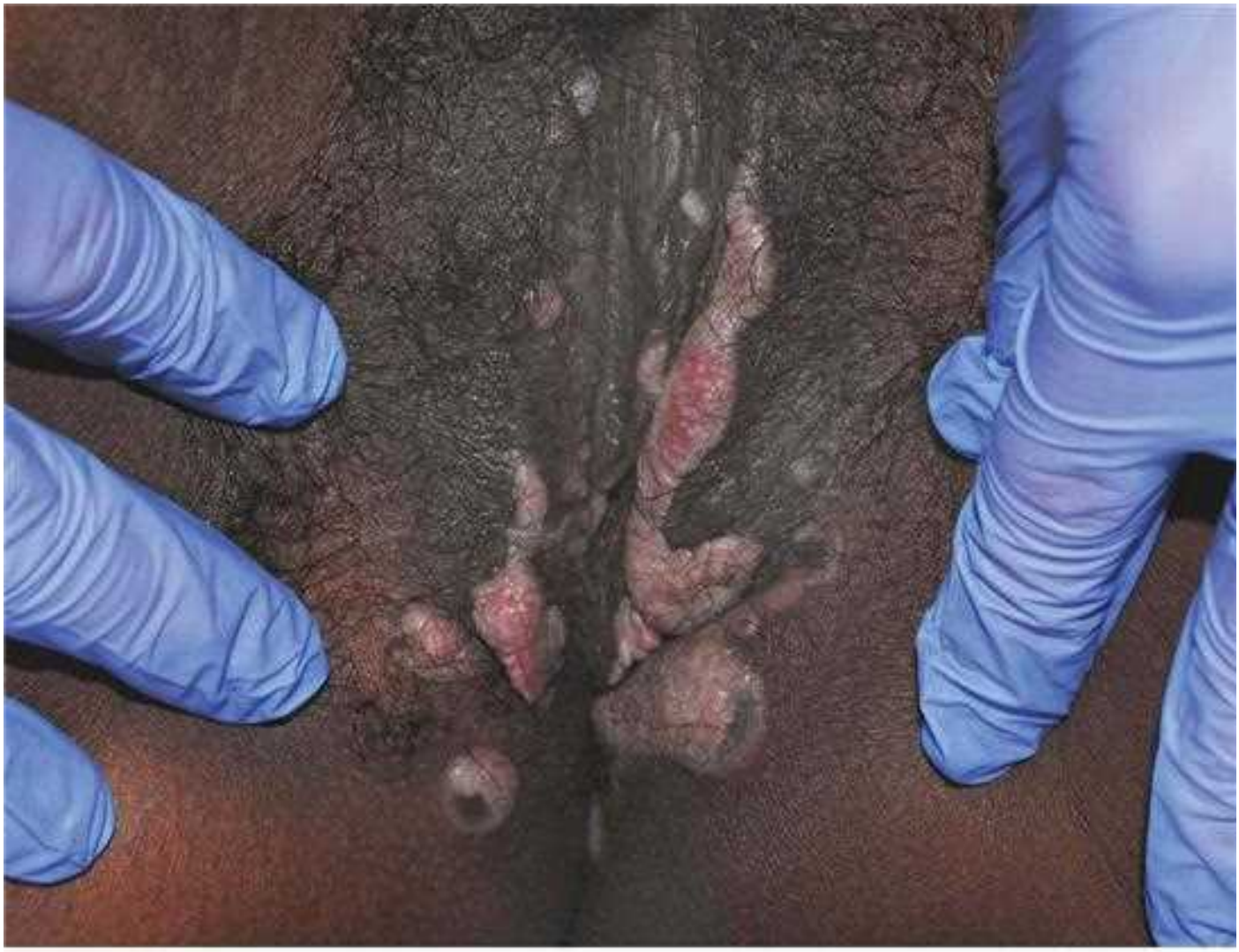


FIGURE 65-3

Condyloma lata. (Used with permission from Dr. Jonathan Willms. Reproduced with permission from Horsager R, Roberts S, Roger V, et al (eds): Williams Obstetrics 24th Edition Study Guide, New York, McGraw Hill Education, 2014.)

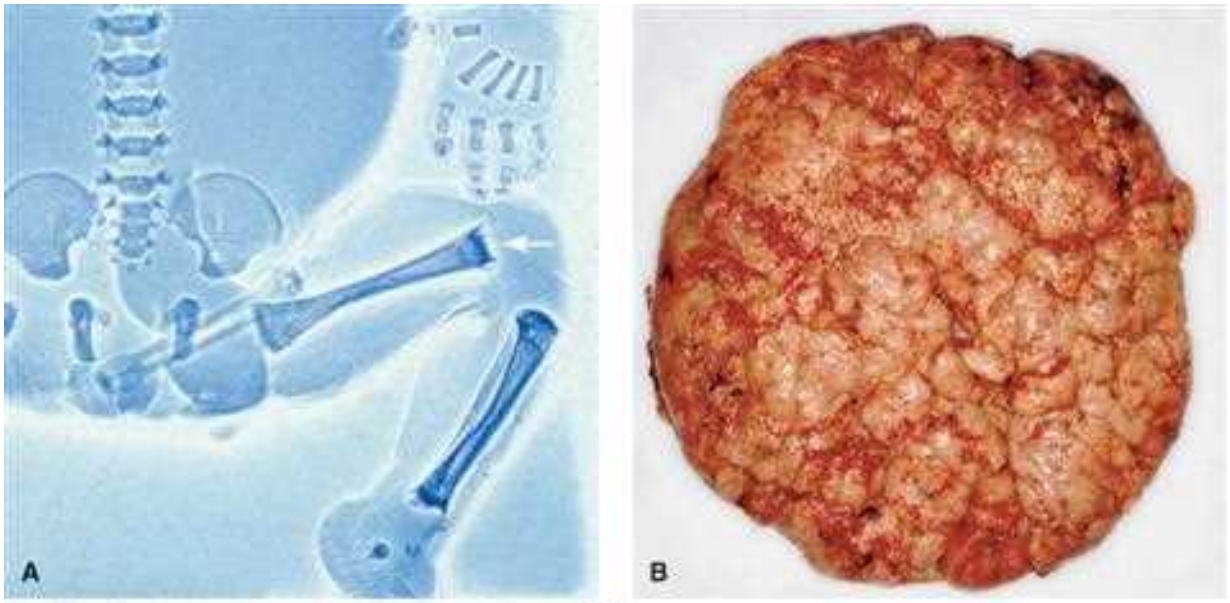


Congenital Syphilis

Without screening and treatment, approximately 70 percent of infected women will have an adverse pregnancy outcome (Hawkes, 2011). Maternal infection can lead to preterm labor, fetal death, fetal-growth restriction, or fetal infection (Gomez, 2013). Because of immune incompetence prior to midpregnancy, the fetus generally does not manifest the immunological inflammatory response characteristic of clinical disease before this time (Silverstein, 1962). Once fetal syphilis develops, however, it manifests as a continuum. Fetal hepatic abnormalities are followed by anemia and thrombocytopenia, then ascites and hydrops (Hollier, 2001). Stillbirth remains a major complication (Lawn, 2016; Su, 2016). The newborn may have jaundice with petechiae or purpuric skin lesions, lymphadenopathy, rhinitis, pneumonia, myocarditis, nephrosis, or long-bone involvement (Fig. 65-4).

FIGURE 65-4

Congenital syphilis. **A.** Fetogram of a stillborn infant infected with syphilis showing the "moth-eaten" appearance of the femurs (*arrow*). **B.** Enlarged hydropic placenta of a syphilis-infected neonate.



With syphilitic infection, the placenta becomes large and pale (see Fig. 65-4). Microscopically, villi lose their characteristic arborization and become thicker and clubbed. Sheffield and colleagues (2002c) described these villi in more than 60 percent of syphilitic placentas. Blood vessels markedly diminish in number, and in advanced cases, they almost entirely disappear as a result of endarteritis and stromal cell proliferation. Likely related, Lucas and coworkers (1991) demonstrated increased vascular resistance in uterine and umbilical arteries of infected pregnancies. The cord may also show evidence of infection. In a study of 25 untreated women, Schwartz and associates (1995) reported that necrotizing funisitis was present in a third.

Diagnosis

The United States Preventative Services Task Force recommends that clinicians screen all pregnant women for syphilis to prevent congenital infection (Wolff, 2009). Testing is ideally performed at the first prenatal visit. In populations with a high prevalence of syphilis, serological testing is repeated in the third trimester and again at delivery (Workowski, 2015).

Treponema pallidum cannot be cultured from clinical specimens. However, direct diagnosis of early-stage disease from lesion exudate, tissue, or body fluid can be completed by dark-field microscopic examination, by polymerase chain reaction (PCR), or by direct fluorescent antibody tests for *T pallidum* (DFA-TP) (Tsang, 2015). These methods are not widely available and are less sensitive for blood specimens (Grange, 2012; Henao-Martínez, 2014). Thus, in practice, diagnoses are mainly derived from clinical findings coupled with serological blood testing.

Serological testing is used for diagnostic and for screening purposes. There are two types. If the first of these is positive, then the second type is also performed. This combination identifies infection and clarifies disease stage. Traditionally, the first type is *nontreponemal testing,* and either the Venereal Disease Research Laboratory (VDRL) or the rapid plasma reagin (RPR) is selected. Both tests measure patient immunoglobulin M and G (IgM and IgG) antibodies formed against cardiolipin that is released from damaged host cells and possibly also from treponemes. Notably, these same antibodies can also be produced in response to other acute events that include recent vaccination, febrile illness, and pregnancy itself or in response to chronic conditions such as intravenous drug abuse, systemic lupus erythematosus, aging, leprosy, or cancer. As such, these all serve as potential sources of false-positive results (Larsen, 1995). Conversely, seroconversion occurs at around 3 weeks, but can take up to 6 weeks (Peeling, 2004). Thus, women with very early primary syphilis can have initially false-negative serological test results.

With positive nontreponemal test results, findings are quantified and expressed as titers. Because titers reflect disease activity, they increase during early syphilis and often exceed levels of 1:32 in secondary syphilis. Following treatment of primary and secondary syphilis, serological testing at 3 to 6 months usually confirms a fourfold drop in VDRL or RPR titers (Rac, 2014a). Because VDRL titers do not correspond directly to RPR titers, consistent use of the same test for surveillance is recommended. Those with treatment failure or reinfection may lack this expected decline. Importantly, some successfully treated

patients may still exhibit persistently low-level positive titers, which are referred to as “serofast.” This state is more likely in older individuals, those with lower initial nontreponemal antibody titers, and those with later stages of syphilis (Seña, 2015).

The second type of serological testing is *treponemal-specific.* It seeks patient antibodies formed specifically against *T pallidum.* The antibodies detected by treponemal assays appear up to a few weeks earlier than those detected by nontreponemal tests (Levett, 2015). Tests includes the fluorescent treponemal-antibody absorption tests (FTA-ABS), the *T pallidum* passive particle agglutination (TP-PA) test, and various immunoassays (Association of Public Health Laboratories, 2015). *Of note, these treponemal-specific tests generally remain positive throughout life.*

Each of the serological tests has limitations including false-positive and -negative results. Traditionally, nontreponemal tests have been used for screening in the United States, and results are then confirmed by a specific treponemal test. Within the past several years, some laboratories have implemented a reverse screening algorithm, namely, screening first with a treponemal-specific test (Binnicker, 2012; Centers for Disease Control and Prevention, 2011). Both approaches are effective if there is a program for appropriate screening, follow-up, and treatment.

In contrast to these tests, rapid “point-of-care” (POC) syphilis screening of blood or serum samples is being developed (Singh, 2015; Tucker, 2010). These may be best used for women with limited prenatal care. Most tests are treponemal-specific, and positive POC results can then be confirmed by a laboratory nontreponemal test. In hard-to-reach populations, some countries immediately treat women with positive POC results. This practice, however, risks overtreating previously cured women who still have residual persistent treponemal antibodies. This limitation may be overcome by newer POC dual tests, which simultaneously assess nontreponemal and treponemal antibodies (Causer, 2015).

Following maternal diagnosis, sonographic evaluation is performed for fetuses >20 weeks’ gestation to search for signs of congenital syphilis. Rac and associates (2014b) noted that 31 percent of infected women diagnosed at ≥18 weeks’ gestation had abnormal fetal sonographic findings. Hepatomegaly, placental thickening, hydramnios, ascites, hydrops fetalis, and elevated middle cerebral artery Doppler velocimetry measurements are indicative of fetal infection. Before 20 weeks, treatment is highly successful, and sonographic findings are rare (Nathan, 1997).

For fetuses of viable age with sonographic findings, antepartum fetal heart rate monitoring prior to treatment is recommended. Spontaneous late decelerations or a nonreactive tracing likely reflects an extremely ill fetus that may poorly tolerate a Jarisch-Herxheimer reaction, described next. In this extreme case, consultation with a neonatologist regarding a plan of delaying treatment, pursuing delivery, and then treating in the nursery is a consideration (Wendel, 2002).

Treatment

Syphilis therapy during pregnancy is given to eradicate maternal infection and to prevent or treat congenital syphilis. Parenteral penicillin G remains the preferred treatment for all stages of syphilis during pregnancy (Table 65-1). During pregnancy, authorities recommend that a second dose of benzathine penicillin G be given 1 week after the initial dose. Such treatment is also given for women with concomitant HIV infection (Workowski, 2015).

TABLE 65-1

Recommended Treatment for Pregnant Women with Syphilis

Category	Treatment
Early syphilis[a]	Benzathine penicillin G, 2.4 million units as a single injection—some recommend a second dose 1 week later
More than 1-year duration[b]	Benzathine penicillin G, 2.4 million units intramuscularly weekly for three doses

[a]Primary, secondary, and early latent syphilis of less than 1-year duration.

[b]Latent syphilis of unknown or more than 1-year duration; tertiary syphilis. Missed doses are not acceptable for pregnant women, and those who miss any dose of therapy must repeat the full course of therapy.

Data from Workowski, 2015.

Benzathine penicillin G is highly effective for early maternal infection. In a study of 340 pregnant women so treated, Alexander and associates (1999) reported six cases—1.8 percent—of congenital syphilis. Four of these six neonates were from a group of 75 women with secondary syphilis. The other two were identified in those delivered from a group of 102 women with early latent syphilis. Congenital syphilis was generally confined to neonates of women treated after 26 weeks and is likely related to the duration and severity of fetal infection. Sheffield and coworkers (2002b) reported that high maternal serological titers, preterm delivery, and delivery shortly after antepartum therapy are all risks for failure of maternal treatment to prevent neonatal infection.

There are no proven alternatives to penicillin therapy during pregnancy. Erythromycin and azithromycin may be curative for the mother, but because of limited transplacental passage, these drugs do not prevent all congenital disease (Berman, 2004; Wendel, 1988; Zhou, 2007). Moreover, in several countries, macrolide-resistant strains of *T pallidum* are now prevalent (Stamm, 2015). Cephalosporins may prove useful, but data are limited (Liang, 2016).

Tetracyclines, including doxycycline, are effective but generally not recommended during pregnancy, because of the risk for fetal deciduous-teeth discoloration.

All women with syphilis are offered counseling and testing for HIV and other STDs. Following syphilis treatment, serological testing to detect treatment failures is done at 3 to 6 months and usually confirms a fourfold drop in VDRL or RPR titers. During pregnancy, serological titers can be checked monthly in women at high risk for reinfection (Workowski, 2015).

In some instances, a woman may present without symptoms but describes recent sexual contact with a person who has been diagnosed with syphilis. She should be evaluated clinically and serologically. If her partner is diagnosed and their sexual contact occurred within the preceding 90 days, the gravida is treated presumptively for early syphilis, even if serological test results are negative. This accounts for early infection but before seroconversion. If contact was earlier than 90 days ago, treatment is based on serological results (Workwoski, 2015).

Penicillin Reactions

Women with a history of penicillin allergy should have either an oral stepwise penicillin-dose challenge or skin testing performed to confirm the risk of immunoglobulin E (IgE)-mediated anaphylaxis. If confirmed, penicillin desensitization, shown in Table 65-2, is recommended and then followed by benzathine penicillin G treatment (Wendel, 1985).

TABLE 65-2

Penicillin Allergy—Oral Desensitization Protocol for Patients with a Positive Skin Test

Penicillin V Suspension Dose[a]	Amount[b] (units/mL)	mL	Units	Cumulative Dose (units)
1	1000	0.1	100	100
2	1000	0.2	200	300
3	1000	0.4	400	700
4	1000	0.8	800	1500
5	1000	1.6	1600	3100
6	1000	3.2	3200	6300
7	1000	6.4	6400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

[a]Interval between doses: 15 minutes. Elapsed time: 3 hours and 45 minutes. Cumulative dose: 1.3 million units. Observation period: 30 minutes before parenteral administration of penicillin.

[b]The specific amount of drug was diluted in approximately 30 mL of water and administered orally.

From Wendel, 1985, with permission.

Distinct from allergy, a *Jarisch-Herxheimer reaction* develops following penicillin treatment in most women with primary syphilis and approximately half with secondary infection. Uterine contractions, mild maternal temperature elevation, decreased fetal movement, and fetal heart rate decelerations are

findings. Reaction treatment is supportive with antipyretics as needed, hydration, and oxygen supplementation (Klein, 1990). In a study of 50 gravidas who received benzathine penicillin for syphilis, Myles and associates (1998) reported a 40-percent incidence of Jarisch-Herxheimer reactions. Of the 31 women monitored electronically, 42 percent developed regular uterine contractions, and 39 percent developed variable decelerations. All contractions resolved within 24 hours of therapy. Accordingly, for fetuses of viable age, some recommend administering the first dose of antibiotic in labor and delivery and with continuous fetal monitoring for at least 24 hours (Rac, 2017). Others recommend this only if sonographic signs of fetal syphilis, described earlier, are found (Duff, 2014; Wendel, 2002). If this second plan is elected, patients are counseled on reaction signs and encouraged to seek evaluation if they develop.

GONORRHEA

Of notifiable STDs, infections caused by *Neisseria gonorrhoeae* are the second most common. The incidence of gonorrhea in the United States has continued to rise since 2009, and in 2015, the rate was 124 cases per 100,000 persons (Centers for Disease Control and Prevention, 2016c). The highest rates in women of any ethnicity were in those aged 15 to 24 years. In pregnant women, its prevalence approximates 0.6 percent (Blatt, 2012). In most pregnant women, infection is limited to the lower genital tract—the cervix, urethra, and periurethral and vestibular glands. Acute salpingitis is rare in pregnancy. But, pregnant women account for a disproportionate number of disseminated gonococcal infections (Bleich, 2012).

Gonococcal infection can have deleterious effects in any trimester. Untreated gonococcal cervicitis is associated with septic abortion as well as infection after voluntary abortion (Burkman, 1976). Preterm delivery, prematurely ruptured membranes, chorioamnionitis, and postpartum infection are more frequent in women with gonococcal infection (Alger, 1988; Johnson, 2011).

Vertical transmission of gonorrhea is predominantly due to fetal contact with vaginal infection during birth. The predominant sequela is gonococcal ophthalmia neonatorum, which can lead to corneal scarring, ocular perforation, and blindness. Transmission rates are high and approximate 40 percent (Laga, 1986). Accordingly, as discussed in Chapter 32 (Preventive Care), ocular prophylaxis is provided to newborns (Mabry-Hernandez, 2010).

Screening and Treatment

Pregnant women who live in high-prevalence areas or who are at risk for gonorrhea should undergo first-trimester screening. Risk factors include age ≤25 years; prior gonococcal infection; other STDs; prostitution; new or multiple sexual partners; drug abuse; black, Hispanic, or American Indian or Alaska Native ethnicity; and inconsistent condom use (American Academy of Pediatrics, 2017). For women who test positive, screening for syphilis, chlamydial infection, and HIV should precede treatment, if possible. Gonococcal infection is a marker for concomitant chlamydial infection. Thus, if chlamydial testing is unavailable, presumptive chlamydial therapy is given to women treated for gonorrhea.

Screening for gonorrhea in women is by culture or nucleic acid amplification tests (NAATs). NAATs have replaced culture in most laboratories, and kits are available for specific collection from the vagina, endocervix, or urine. Of these, vaginal or cervical samples are preferred, as urine collection may detect up to 10 percent fewer infections (Papp, 2014). If used, the initial urine stream, not midstream, is collected. NAATs are also recommended for diagnosis of rectal or pharyngeal disease, but participating laboratories must be CLIA (Clinical Laboratory Improvement Amendments) compliant with required test modifications. Culture is also available for these anatomical sites. Rapid POC tests for gonorrhea, although available, do not yet reach the sensitivity or specificity of culture or NAAT and have not been rigorously studied in pregnant women (Herbst de Cortina, 2016).

Gonorrhea treatment has evolved during the past decade due to the ability of *N gonorrhoeae* to rapidly develop antimicrobial resistance. The current treatment for uncomplicated gonococcal infection during pregnancy is 250 mg of ceftriaxone intramuscularly plus 1 g of azithromycin orally (Workowski, 2015). The latter provides another drug with a different mechanism of action against *N gonorrhoeae* and treats chlamydial co-infections. Patients are instructed to abstain from sexual intercourse for 7 days after they and their sexual partners have completed treatment. As an alternative regimen, a single, 400-mg oral dose of cefixime plus 1 g of azithromycin should be reserved for situations that preclude ceftriaxone treatment. With cephalosporin allergy, a 240-mg intramuscular dose of gentamicin can be coupled with a 2-g oral azithromycin dose. Repeat testing is recommended in the third trimester for any woman treated for gonorrhea in the first trimester and for any uninfected woman who is at high risk for gonococcal infection (American Academy of Pediatrics, 2017).

Treatment is recommended for sexual contacts. Expedited therapy, discussed in Herpes Simplex Virus, is a less-desirable option due to the now-preferred injectable regimen.

Disseminated Gonococcal Infections

Gonococcal bacteremia may cause disseminated infections that manifest as petechial or pustular skin lesions, arthralgias, or septic arthritis. For treatment of septic arthritis, the CDC recommends ceftriaxone, 1 g intramuscularly or intravenously (IV) every 24 hours plus a single 1-g oral dose of azithromycin (Workowski, 2015). Treatment is continued for 24 to 48 hours after clinical improvement, and therapy is then changed to an oral agent to complete 1 week of therapy. Prompt recognition and antimicrobial treatment will usually yield favorable outcomes in pregnancy (Bleich, 2012). Meningitis and endocarditis rarely complicate pregnancy, but they may be fatal (Bataskov, 1991; Burgis, 2006). For gonococcal *endocarditis*, ceftriaxone 1 to 2 g IV every 12 hours should be continued for at least 4 weeks, and for *meningitis*, 10 to 14 days. A single 1-g oral dose of azithromycin is also provided for chlamydial co-infection (Workowski, 2015).

CHLAMYDIAL INFECTIONS

Chlamydia trachomatis is an obligate intracellular bacterium that has several serotypes, including those that cause lymphogranuloma venereum. The most commonly encountered strains are those that attach only to columnar or transitional cell epithelium and cause cervical infection. It is the most common reportable STD in the United States, and the overall chlamydial infection rate among women was 646 cases per 100,000 females in 2015 (Centers for Disease Control and Prevention, 2016c).

Most pregnant women have asymptomatic infection, but a third have urethral syndrome, urethritis, or Bartholin gland infection (Peipert, 2003). Mucopurulent cervicitis may be due to chlamydial or gonococcal infection or both. Other chlamydial infections not usually seen in pregnancy are endometritis, salpingitis, reactive arthritis, and Reiter syndrome.

The role of chlamydial infection in pregnancy complications remains controversial. A few studies have reported a direct association between *C trachomatis* and miscarriage, whereas most show no correlation (Baud, 2011; Coste, 1991; Paukku, 1999). It is disputed whether untreated cervical infection increases the risk of preterm delivery, preterm ruptured membranes, low birthweight, or perinatal mortality (Andrews, 2000, 2006; Blas, 2007; Johnson, 2011; Moodley, 2017; Silva, 2011). Chlamydial infection has not been associated with a greater risk of chorioamnionitis or with peripartum pelvic infection (Berman, 1987; Gibbs, 1987). However, delayed postpartum uterine infection has been described by Hoyme and associates (1986). The syndrome, which develops 2 to 3 weeks postpartum, is distinct from early postpartum metritis. It is characterized by vaginal bleeding or discharge, low-grade fever, and uterine tenderness.

Infection poses a higher risk to the newborn than to the mother. Vertical transmission leads to infection in 8 to 44 percent of neonates delivered vaginally from affected women (Rosenman, 2003). Of neonatal infections, conjunctivitis is the most common (Chap. 32, Preventive Care). Perinatal transmission to newborns can also cause pneumonia.

Screening and Treatment

Currently, the U.S. Preventive Services Task Force (LeFevre, 2014) as well as the American Academy of Pediatrics and American College of Obstetricians and Gynecologists (2017) recommend chlamydia screening for all women at the first prenatal visit. The College further suggests testing in the third trimester for those treated in the first trimester; all women aged ≤25 years; and those aged ≥25 years with behavioral factors, which mirror those for women at risk for gonorrhea. In one review of repeat chlamydial infections among women, the reinfection rate was 14 percent, and most recurred within the first 8 to 10 months (Hosenfeld, 2009).

Diagnosis is made predominantly by culture or NAAT. Cultures are more expensive and less accurate than newer NAATs (Greer, 2008). Of samples for NAAT, vaginal or cervical samples are preferred, as urine collection may detect up to 10 percent fewer infections (Papp, 2014; Wiesenfeld, 2017). However, Roberts and associates (2011) evaluated NAAT of urine specimens compared with cervical secretions in more than 2000 pregnant women and found them to be equivalent. As with gonorrhea, the first portion of the urine stream is collected.

Currently recommended treatment regimens for chlamydial infections are shown in Table 65-3. Azithromycin is first-line treatment and is safe and effective in pregnancy. The fluoroquinolones and doxycycline are usually avoided in pregnancy, and erythromycin estolate is contraindicated because of drug-related hepatotoxicity. Chlamydial testing is repeated 3 to 4 weeks after therapy completion and again 3 months after treatment. In high-risk individuals, third-trimester rescreening is recommended (Workowski, 2015).

TABLE 65-3

Oral Treatment of *Chlamydia trachomatis* Infections During Pregnancy

Regimen	Drug and Dosage
Preferred	Azithromycin, 1 g as a single dose
Alternative	Amoxicillin, 500 mg three times daily for 7 d
	or
	Erythromycin base, 500 mg four times daily for 7 d
	or
	Erythromycin ethylsuccinate, 800 mg four times daily for 7 d
	or
	Erythromycin base, 250 mg four times daily for 14 d
	or
	Erythromycin ethylsuccinate, 400 mg four times daily for 14 d

Data from Workowski, 2015.

Expedited Partner Therapy

To prevent STD transmission, guidelines for expedited partner therapy (EPT) have been created by the Centers for Disease Control and Prevention (2006a) and are endorsed by the American College of Obstetricians and Gynecologists (2015). With EPT, a prescription is provided to the diagnosed patient for their partner. It is delivered by the patient to their partner without medical assessment of the partner or professional counseling. EPT ideally does not replace traditional strategies, such as standard patient referral with screening for other STDs.

EPT is acceptable for treatment of sexual contacts with chlamydial infection. In light of new guidelines that recommend injectable ceftriaxone, EPT for gonorrhea is less desirable unless the partner will otherwise not seek treatment (Centers for Disease Control and Prevention, 2016a). Fewer data are available to assess this strategy for trichomoniasis (Kissinger, 2006; Schwebke, 2010). EPT is not recommended for syphilis (Workowski, 2015).

Although sanctioned by the CDC, EPT is not legal in several states. Moreover, the risk of litigation in the event of adverse outcomes may be elevated when a practice has uncertain legal status or is outside formally accepted community practice standards (Centers for Disease Control and Prevention, 2006a). The legal status of EPT in each of the 50 states can be found at: http://www.cdc.gov/std/ept/legal/default.htm.

Lymphogranuloma Venereum

L_1, L_2, and L_3 serovars of *C trachomatis* cause *lymphogranuloma venereum (LGV).* The primary genital infection is transient, is seldom recognized, and is not linked with vertical transmission to the fetus. It can be confused with chancroid. Classically, matted inguinal adenitis may develop on either side of the inguinal ligament to give rise to the “groove sign.” At times, these nodes may suppurate. Ultimately, the lymphatics of the lower genital tract and perirectal tissues may be involved. Here, sclerosis and fibrosis can cause vulvar elephantiasis and severe rectal stricture. Fistula formation involving the rectum, perineum, and vulva may also evolve.

For treatment during pregnancy, erythromycin base, 500 mg orally four times daily, is given for 21 days (Workowski, 2015). Some authorities instead use szithromycin, 1 g orally weekly for 21 days, although data regarding efficacy are scarce.

HERPES SIMPLEX VIRUS

This virus poses a disproportionately higher risk to the newborn than to the mother. Thus, strategies in pregnancy aim to curb rates of vertical transmission.

Adult Disease

Two types of herpes simplex viruses are distinguished based on immunological differences. Yet, the two viruses have significant DNA sequence homology, and thereby, prior infection with one type attenuates a primary infection with the other. Type 2 HSV is recovered almost exclusively from the genital tract and is usually transmitted by sexual contact. Type 1 is responsible for most nongenital infections and typically is acquired in childhood. However, more than half of new cases of genital herpes in adolescents and young adults are now caused by HSV-1 infection (Bernstein, 2013). This rise in the prevalence of HSV-1 genital disease is thought to stem from an increase in oral-genital sexual practices. Another explanation is that HSV-1 acquisition has declined in childhood as a result of improved living conditions and hygiene (Bradley, 2014; Xu, 2007). Without prior exposure, this renders young people without HSV-1 antibodies susceptible to *genital* acquisition of HSV-1 or -2.

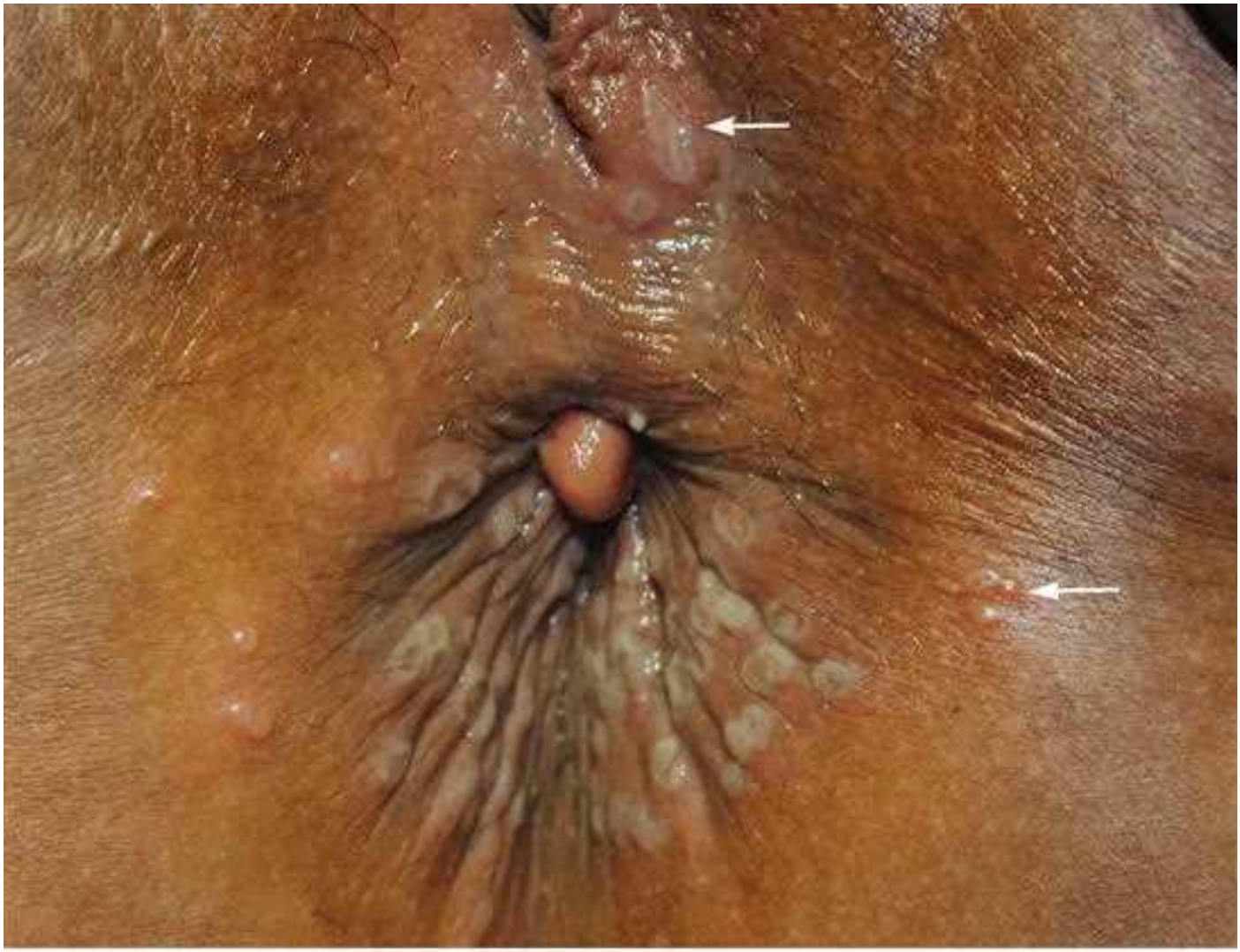
Genital herpes simplex virus affects an estimated 50 million adolescents and adults (Workowski, 2015). Most women are unaware of their infection, but HSV-2 seroprevalence among non-Hispanic white females in the United States was 15.3 from 2007 to 2010 and among black females, it was 53 percent (Fanfair, 2014; Schulte, 2014). In one study of nearly 16,000 pregnant women from 2000 to 2010, the overall seroprevalence of HSV-2 was 16 percent, and for HSV-1, it was 66 percent (Delaney, 2014). Seronegative pregnant women have a 4 to 5 percent risk to acquire HSV-1 or -2 during pregnancy (Brown, 1997; Kulhanjian, 1992). For those who are HSV-1 seropositive, acquisition risk for HSV-2 approximates 2 percent (Brown, 1997).

Clinical Manifestations

Once transmitted by contact, HSV-1 or -2 replicates at the entry site. Following mucocutaneous infection, the virus moves retrograde along sensory nerves. It then remains latent in cranial nerves or dorsal spinal ganglia, but recurrences are common. HSV infections may be categorized into three groups.

First episode primary infection describes the case in which HSV-1 or 2 is isolated from a lesion in the absence of HSV-1 or -2 serological antibodies. The typical incubation period of 6 to 8 days (range 1 to 26 days) may be followed by a papular eruption with itching or tingling, which then becomes painful and vesicular. Multiple vulvar and perineal lesions may or may not coalesce, and then ulcerate (Fig. 65-5). Associated inguinal adenopathy can be severe. Many women do not present with typical lesions. Instead, a pruritic or painful abraded area or knife-cut may be found. Cervical involvement is common, although it may be inapparent clinically. Transient systemic influenza-like symptoms are frequent and are presumably caused by viremia. Some cases are severe enough to require hospitalization. Hepatitis, encephalitis, or pneumonia infrequently develop, and disseminated disease is rare. After 2 to 4 weeks, all signs and symptoms of infection disappear. Instead of these classic symptoms, the percentage of asymptomatic primary HSV-2 genital infections may be as high as 90 percent (Fanfair, 2013).

FIGURE 65-5
First-episode primary genital herpes simplex virus infection. Vesicles and knife-cut lesions are indicated by arrows. Small ulcers rim the anus. Similar lesions can typically be seen on the vulva.



First episode nonprimary infection is diagnosed when one HSV type is isolated from a lesion in a woman who has only the other serological HSV-type antibody present. In general, compared with primary infection, nonprimary infections are characterized by fewer lesions, less pain, fewer systemic manifestations, and briefer duration of lesions and viral shedding. This is likely because of some immunity from cross-reacting antibodies, for example, from childhood-acquired HSV-1 infection.

Recurrent disease is characterized by isolation of HSV-1 or -2 from the genital tract in women with the same serotype antibodies. During the latency period, in which viral particles reside in nerve ganglia, reactivation is common and mediated through poorly understood stimuli. The resulting lesions generally are fewer in number, are less tender, and shed virus for a shorter period than those of primary infection. Typically, they recur at the same sites. Genital disease recurrences are more frequently caused by HSV-2 compared with HSV-1. Recurrences are most frequent in the first year after initial infection, and rates slowly decline subsequently (Benedetti, 1999). Gravidas with a known prior history of genital HSV often experience recurrences (Sheffield, 2006).

Asymptomatic viral shedding is defined by the absence of clinical findings. Most infected women shed virus intermittently over time, and most HSV transmission to a partner occurs during these periods of asymptomatic viral shedding.

Vertical Transmission

The virus can be passed to the fetus/neonate by three routes: (1) peripartum in 85 percent, (2) postnatal in 10 percent, or (3) intrauterine in 5 percent (James, 2015). As discussed in Chapter 18 (First-Trimester Spontaneous Abortion), evidence does not suggest an obvious link between HSV infection and miscarriage (Zhou, 2015).

Peripartum transmission is by far the more frequent route of infection, and the fetus is exposed to virus shed from the cervix or lower genital tract. HSV-1 or -2 invades the uterus following membrane rupture or is transmitted by contact at delivery. The newborn is mainly infected, but rare cases of maternal endometritis have been described (Hollier, 1997; McGill, 2012). Neonatal manifestations vary. First, infection may be localized to the skin, eye, or mouth—SEM disease—in approximately 40 percent of cases. Second, central nervous system disease with encephalitis is seen in 30 percent. Last, disseminated disease with involvement of multiple major organs is found in 32 percent. Localized infection is usually associated with a good outcome. Conversely, even with

acyclovir treatment, disseminated infection has a mortality rate of nearly 30 percent (Corey, 2009; Kimberlin, 2011). Of disseminated or cerebral infection survivors, serious developmental and central nervous system morbidity is seen in 20 to 50 percent.

The neonatal infection rate is 0.5 to 1 per 10,000 births in the United States (Flagg, 2011; Mahnert, 2007). Most infected newborns are born to mothers with no reported history of HSV infection (Gardella, 2010). The risk of neonatal infection correlates with the presence of HSV in the genital tract, the HSV type, invasive obstetrical procedures, and stage of maternal infection (Brown, 2005, 2007). For example, neonates born to women who acquire genital HSV near the time of delivery have a 30- to 50-percent risk of infection. This is attributed to higher viral loads and the lack of transplacental protective antibodies (Brown, 1997, 2000). Women with recurrent HSV have less than a 1-percent risk of neonatal infection (Pasternak, 2010; Prober, 1987).

Postpartum transmission is uncommon and passed to the newborn by contact with an infected mother, family member, or health-care worker. The clinical presentation mirrors that with peripartum transmission.

In utero transmission of HSV-1 or HSV-2 is rare and is part of the TORCH (toxoplasmosis, other, rubella, cytomegalovirus, herpes virus) collection of infections. Intrauterine HSV infection classically leads to disease involving the skin (blisters, scarring), the central nervous system (hydranencephaly, microcephaly, intracranial calcification), or the eyes (chorioretinitis, microphthalmia) (Hutto, 1987). Bone and viscera can be involved (Marquez, 2011). If seen sonographically, findings should prompt viral serological testing as described next. PCR analysis of an amniocentesis sample is another potential tool (Diguet, 2006).

Diagnosis

Several organizations recommend against routine serological HSV screening in asymptomatic gravidas (American College of Obstetricians and Gynecologists, 2016b; Workowski, 2015; U.S. Preventive Services Task Force, 2016). However, for those with a clinically suspicious lesion, a diagnosis should be confirmed by laboratory testing. Available HSV tests are either virological or type-specific serological tests.

Direct virological tests are can be performed on a specimen from the mucocutaneous lesion. PCR or culture of the sample is a testing option. Of the two, PCR assays are more sensitive, the results generally are available in 1 to 2 days, and specimen handling is easier. In contrast, for viral culture, the sensitivity of HSV isolation is relatively low as vesicular lesions ulcerate and then crust. Also, results sometimes are not available for 7 to 14 days (Strick, 2006). Regardless of the test performed, HSV viral types should be differentiated (LeGoff, 2014). Importantly, a negative culture or PCR result does not exclude infection. In contrast, false-positive results are rare.

Serological assays are available to detect antibodies produced against specific HSV glycoproteins, G1 and G2. These proteins evoke type-specific antibody responses to HSV-1 and HSV-2 infection, respectively, and they reliably differentiate the two. IgG antibodies develop 1 to 2 weeks after a primary infection and then persist. This permits confirmation of clinical infection and identification of asymptomatic carriers. Providers should request type-specific glycoprotein G-based assays when serology is being performed. Sensitivity approaches 90 to 100 percent, and specificity is 99 to 100 percent (Wald, 2002). IgM antibody detection is not a useful test.

Management

In nonpregnant patients, antiviral therapy with acyclovir, valacyclovir, or famciclovir is used to treat first-episode genital herpes. Oral or parenteral preparations attenuate clinical infection and viral shedding duration. Suppressive therapy is also an option to limit recurrent infections and to reduce heterosexual transmission (Corey, 2004).

In pregnant women, acyclovir is safe (Briggs, 2015). Through 1999, the manufacturers of acyclovir and valacyclovir maintained a registry of outcomes following exposure to these drugs during pregnancy. More than 700 neonates exposed during the first trimester were evaluated, and there were no adverse effects attributable to acyclovir (Stone, 2004). At this time, data are insufficient regarding famciclovir exposure, although a pregnancy registry is being maintained (1–888–669–6682).

For a primary outbreak during pregnancy, women may be given antiviral therapy to attenuate and decrease the duration of symptoms and viral shedding (Table 65-4). Women with HIV co-infection may require a longer duration of treatment. Those with severe or disseminated HSV are given IV acyclovir, 5 to 10 mg/kg every 8 hours for 2 to 7 days until clinically improved. This is followed by oral antiviral drugs to complete at least 10 days of total therapy (Workowski, 2015). For intense discomfort, oral analgesics and topical anesthetics may provide some relief, and comorbid urinary retention is treated with an indwelling bladder catheter.

TABLE 65-4

Oral Antiviral Medications for Herpesvirus Infection in Pregnancy[a]

Indication	Pregnancy Recommendation
Primary or first episode infection	Acyclovir, 400 mg three times daily for 7–10 d ***or*** Valacyclovir, 1 g twice daily for 7–10 days
Symptomatic recurrent infection (episodic therapy)	Acyclovir, 400 mg three times daily for 5 days ***or*** Acyclovir, 800 mg twice daily for 5 days ***or*** Acyclovir, 800 mg three times daily for 2 d ***or*** Valacyclovir, 500 mg twice daily for 3 days ***or*** Valacyclovir, 1 g once daily for 5 days
Daily suppression	Acyclovir, 400 mg three times daily from 36 weeks until delivery ***or*** Valacyclovir, 500 mg twice daily from 36 weeks until delivery

[a]Famciclovir not preferred during pregnancy due to fewer safety data.

Data from Workowski, 2015.

For recurrent HSV infections during pregnancy, antiviral treatment is provided mainly for symptom relief (see Table 65-4). Although uncommon, acyclovir resistance has been reported, predominantly with HSV-2 and in immunocompromised patients (Andrei, 2013).

During pregnancy, amniocentesis, percutaneous cord blood sampling, or transabdominal chorionic villus sampling may be performed even with active genital lesions. With active lesions, however, internal electronic monitoring during labor is not recommended. Transcervical procedures may best be delayed until lesions have resolved (American College of Obstetricians and Gynecologists, 2016b).

Peripartum Shedding Prophylaxis

To diminish vertical transmission risks, cesarean delivery is indicated for women with active genital lesions or prodromal symptoms (American College of Obstetricians and Gynecologists, 2016b). Several studies have shown that acyclovir or valacyclovir suppression initiated at 36 weeks' gestation for gravidas with recurrences during pregnancy lowers the number of HSV outbreaks at term. The goal is to decrease the need for cesarean delivery (Hollier, 2008). This suppressive therapy will also decrease viral shedding (Scott, 2002; Sheffield, 2006; Watts, 2003). One systematic review evaluated acyclovir prophylaxis given from 36 weeks to delivery to women with HSV recurrence during pregnancy. Sheffield and colleagues (2003) found that suppressive therapy was associated with significantly lower rates of clinical HSV recurrence, cesarean deliveries for HSV recurrences, total HSV detection, and asymptomatic shedding. Subsequent studies using valacyclovir suppression have shown similar results (Andrews, 2006; Sheffield, 2006). Because of these studies, the American College of Obstetricians and Gynecologists (2016b) recommends viral therapy at or beyond 36 weeks for women who had primary genital herpes infection or active recurrent genital herpes during pregnancy. It is unclear whether suppression is needed for women with outbreaks before but not during pregnancy. Notably, despite maternal antiviral suppression, several cases of atypical neonatal herpes infection have been reported (Pinninti, 2012).

On presentation for delivery, a woman with a history of HSV should be questioned regarding prodromal symptoms such as vulvar burning or itching. A careful examination of the vulva, vagina, and cervix is performed, and women without genital lesions may proceed with labor and delivery. Use of a fetal scalp electrode can raise the transmission risk. But, electrode placement is reasonable if needed in the absence of active lesions (American College of Obstetricians and Gynecologists, 2016b).

Suspicious lesions should be cultured or PCR tested. Cesarean delivery is indicated for women with genital lesions or prodromal symptoms. It is not recommended for women with a history of HSV infection but no active genital disease at the time of delivery. Moreover, an active lesion in a nongenital area is not an indication for cesarean delivery. Instead, an occlusive dressing is placed, and vaginal delivery is allowed.

With preterm ruptured membranes, no evidence suggests that external lesions cause ascending fetal infection. Major and associates (2003) described expectant management of preterm premature membrane rupture in 29 women at gestational ages <31 weeks. There were no cases of neonatal HSV, and the maximum infection risk was calculated to be 10 percent. Antiviral treatment is recommended. For women with a clinical recurrence at delivery, there is not

an absolute duration of membrane rupture beyond which the fetus would not benefit from cesarean delivery (American College of Obstetricians and Gynecologists, 2016d).

Women with active HSV may breastfeed if there are no active breast lesions. Strict hand washing is essential. Valacyclovir and acyclovir may be used for symptomatic maternal lesions during breastfeeding, as drug concentrations in breast milk are low. One study found the acyclovir concentration to be only 2 percent of that used for therapeutic dosing of the neonate (Sheffield, 2002a).

CHANCROID

Haemophilus ducreyi can cause painful, nonindurated genital ulcers termed soft chancres. At times, these are accompanied by painful suppurative inguinal lymphadenopathy. Although common in some developing countries, only 11 cases were reported in the United States in 2015 (Centers for Disease Control and Prevention, 2016c). Appropriate media are not widely accessible, and no Food and Drug Administration (FDA)-cleared PCR test is yet available. Instead, painful genital ulcer(s) and negative screening for syphilis or HSV leads to a presumptive diagnosis. Treatment in pregnancy is azithromycin, 1 g orally as a single dose; erythromycin base, 500 mg orally three times daily for 7 days; or ceftriaxone, 250 mg in a single intramuscular dose (Workowski, 2015).

HUMAN PAPILLOMAVIRUS

This is a common STD, and more than 40 types infect the genital tract. In the United States from 2005 to 2006, the overall HPV prevalence was 40 percent in females aged 14 to 59 years (Liu, 2016). Prevalence is highest in younger women, and some of this seroprevalence now reflects HPV vaccination in this age group (Brouwer, 2015). Most reproductive-aged women become infected within a few years of becoming sexually active, and most infections are asymptomatic and transient. High-risk types are those with the most oncogenic potential. Of these, HPV types 16 and 18 are often associated with dysplasia (Chap. 63, Epithelial Neoplasia). Mucocutaneous external genital warts termed condyloma acuminata are usually caused by types 6 and 11.

For unknown reasons, genital warts frequently increase in number and size during pregnancy. These lesions may sometimes grow to fill the vagina or cover the perineum, thus making vaginal delivery or episiotomy difficult. Maternal HPV infection does not appear to be related to preterm labor (Subramaniam, 2016).

Condyloma Acuminata Treatment

Genital wart eradication during pregnancy is usually not necessary unless they are symptomatic. Therapy is directed toward debulking symptomatic warts yet minimizing treatment toxicity to the mother and fetus. Several agents are available, but no definitive evidence supports superiority of one over another (Workowski, 2015). Response to treatment during pregnancy may be incomplete, but lesions frequently improve or regress rapidly following delivery.

Trichloroacetic or bichloracetic acid, 80- to 90-percent solution, applied topically weekly, is an effective regimen for external warts. Some prefer *cryotherapy, laser ablation*, or *surgical excision*. Agents not recommended in pregnancy because of concerns for maternal and fetal safety include podophyllin resin, podofilox solution or gel, imiquimod cream, and sinecatechins.

There are three vaccines available for long-term prevention. Gardasil (HPV4) is a quadrivalent vaccine against HPV types 6, 11, 16, and 18. This is being replaced by Gardasil 9 (HPV9), a nonavalent vaccine that protects against all the types in HPV4 plus types 31, 33, 45, 52, and 58. Cervarix (HPV2) is a bivalent vaccine against HPVs 16 and 18. One of these vaccines is selected and given as a three-dose series on a schedule of 0, 1–2, and 6 months for those aged 15 to 26 years. A two-dose regimen, given at 0 and again at 6 to 12 months, is now recommended for girls aged 9 to 14 years (Meites, 2016). Vaccines are licensed for females aged 9 to 26 years, and the target age is 11 to 12 years. The vaccines are not recommended for pregnant women, however, inadvertent exposures do occur. No adverse pregnancy outcomes are associated with the vaccines (Moreira, 2016; Panagiotou, 2015; Vichnin, 2015). If a woman is found to be pregnant after starting the vaccination series, the remaining doses are delayed and given after delivery (American College of Obstetricians and Gynecologists, 2017a). Women who are breastfeeding may receive the vaccine.

Neonatal Infection

Vertical transmission rates of HPV to the newborn are minimal. Juvenile-onset recurrent respiratory papillomatosis (JoRRP) is a rare, benign neoplasm of the larynx. It can cause hoarseness and respiratory distress in children and is most often caused by HPV 6 or 11. Risks for infection are maternal genital HPV infection and longer labors (Niyibizi, 2014). Many newborns are likely exposed to HPV, but few develop JoRRP (Silverberg, 2003; Smith, 2004; Tenti, 1999). For example, the national incidence of JoRRP in 2006 in the United States ranged from 0.5 to 1 per 100,000 children (Marsico, 2014).

The benefit of cesarean delivery to decrease transmission risk is unknown, and thus it is currently not recommended solely to prevent HPV transmission (Workowski, 2015). HPV vaccination may ultimately decrease JoRRP rates in the future (Matys, 2012).

VAGINITIS

Pregnant women frequently develop increased vaginal discharge. This may be a physiological discharge, described in Chapter 4 (Cervix), but should be differentiated from symptomatic vaginitis, which is also common in pregnancy. Fortunately, vaginitis is prevented in part by normal vaginal flora. To better

understand this, studies of the composition and function of the normal vaginal microflora are currently underway with the Vaginal Human Microbiome Project (Huang, 2014).

Bacterial Vaginosis

Diagnosis

Not an infection in the ordinary sense, bacterial vaginosis (BV) is a maldistribution of normal vaginal flora. With BV, numbers of lactobacilli are decreased, and anaerobic bacteria species are overrepresented. These anaerobes include *Gardnerella, Prevotella, Mobiluncus,* and *Bacteroides* species; *Atopobium vaginae*; and BV-associated bacteria, provisionally named BVAB1, BVAB2, and BVAB3. These last three are newly recognized bacteria found in women with BV (Fredricks, 2005).

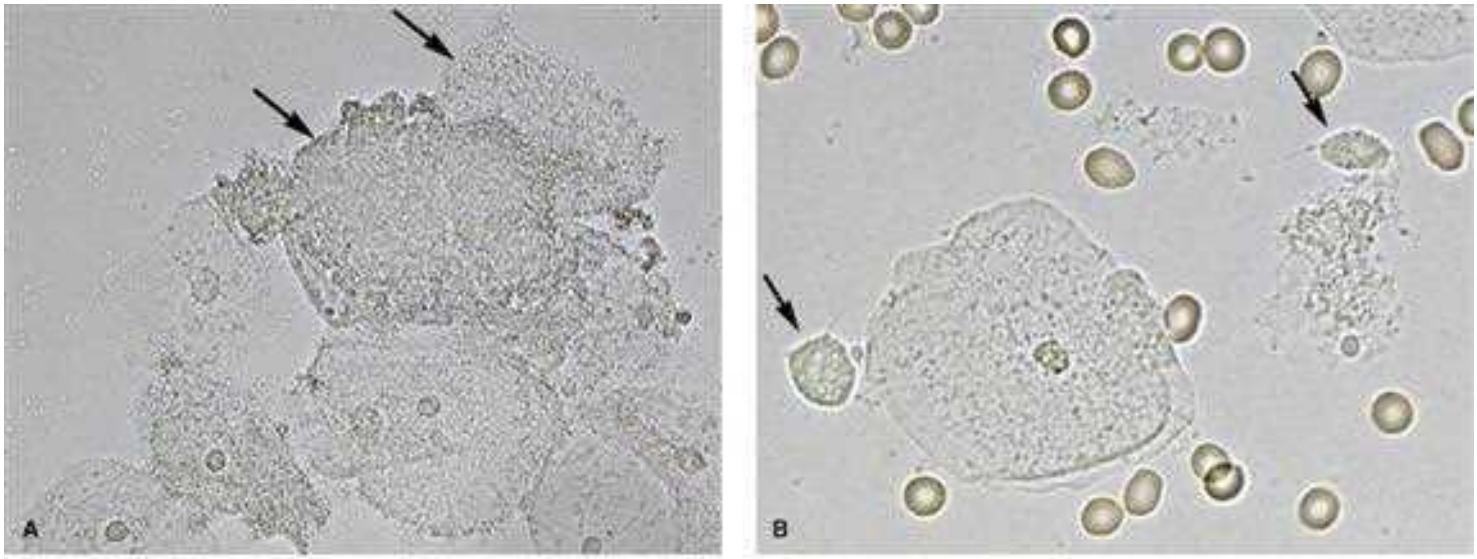
Molecular ribosomal RNA gene sequencing techniques have greatly aided this understanding of the vaginal flora, also called the *vaginal microbiota*. Five types of vaginal microbiota exist, referred to as *community state types (CSTs)*. And, a woman can be categorized to one of these five CSTs based on her vaginal microbiota composition (Ravel, 2011). Researchers have begun to quantify the risk of BV by these CST groups. Specifically, CSTs I, II, III, and V are rich in lactobacilli. In contrast, CST IV is a heterogeneous microbiota of strict anaerobes and is associated with BV. CSTs vary racially, and CST IV is also the most common in asymptomatic, healthy black women (Fettweis, 2014). Pregnancy-related changes in vaginal microbiota are also being defined and may hold keys to adverse BV-related pregnancy outcomes, discussed subsequently (Romero, 2014).

Of childbearing-aged women in the United States, nearly 30 percent have BV. In black women, the prevalence approximates 50 percent (Allsworth, 2007). Most women are asymptomatic, but a foul, thin vaginal discharge is a typical complaint. Associated risk factors are douching, multiple partners, smoking, and altered host immunity (Desseauve, 2012; Koumans, 2007; Murphy, 2016).

For clinical diagnosis of BV, three of the four following criteria are present: (1) vaginal pH >4.5; (2) a thin, milky, noninflammatory vaginal discharge; (3) >20 percent clue cells seen microscopically; and (4) a fishy odor after addition of 10-percent potassium hydroxide to vaginal secretion samples (Amsel, 1983). The last is described as a positive “whiff test.” Likewise, alkalinity of seminal fluid and blood are responsible for foul-odor complaints after intercourse and with menses in affected women. Clue cells are vaginal epithelial cells containing many attached bacteria, which create a poorly defined stippled cellular border (Fig. 65-6). The higher vaginal pH stems from diminished acid production by lactobacilli. Similarly, *Trichomonas vaginalis* infection is also associated with anaerobic overgrowth and resultant elaborated amines. Thus, women diagnosed with BV should have no microscopic evidence of trichomoniasis (see Fig. 65-6).

FIGURE 65-6

A. Bacterial vaginosis. Microscopy reveals several squamous cells heavily studded with bacteria. Clue cells are covered to the extent that cell borders are blurred and nuclei are not visible (*arrows*). **B.** Trichomonads (*arrows*). (Reproduced with permission from McCord E, Rahn DD, Hoffman BL: Gynecologic infection. In Hoffman BL, Schorge JO, Bradshaw KD, et al (eds): Williams Gynecology, 3rd ed. New York, McGraw Hill Education, 2016. Photo contributors: Lauri Campagna and Mercedes Pineda, WHNP.)



The Nugent score, used primarily in research studies rather than clinical practice, is a system employed for diagnosing BV (Nugent, 1991). During microscopic examination of a gram-stained vaginal discharge smear, scores are calculated by assessing bacteria staining and morphology.

Treatment

Several adverse pregnancy-related health outcomes associated with BV are preterm birth, premature rupture of the membranes, and postpartum endometritis (Hillier, 1995; Leitich, 2003; Watts, 1990). It also increases susceptibility to STDs, including HIV (Atashili, 2008; Brotman, 2010). For women at low risk for preterm birth, however, treatment of BV does not reduce preterm birth rates (Brocklehurst, 2013; Carey, 2000). For high-risk women, evidence is conflicting. Currently, the American College of Obstetricians and Gynecologists (2016c), CDC, and U.S. Preventive Services Task Force do not recommend routine BV screening of asymptomatic gravidas—at either high or low risk for preterm delivery—to prevent preterm birth (Nygren, 2008; Workowski, 2015).

Treatment is reserved for symptomatic women. Preferred drugs are metronidazole, 500 mg twice daily orally for 7 days; metronidazole 0.75-percent gel, one applicator intravaginally, daily for 5 days; or clindamycin 2-percent cream, one applicator intravaginally nightly for 7 days. Alternatives are clindamycin, 300 mg orally twice daily for 7 days, or 100-mg clindamycin ovules placed intravaginally nightly for 3 days (Workowski, 2015). It is still debated whether BV is a sexually transmitted infection. But, treatment of a male partner does not appear to lower recurrence rates (Amaya-Guio, 2016).

Trichomoniasis

Diagnosis

Vaginitis caused by *Trichomonas vaginalis* is common, and its prevalence in the United States approximates 3 percent in nonpregnant and pregnant women (Allsworth, 2009; Satterwhite, 2013). The prevalence is higher in those older than 30 years compared with younger women. Risks include black race, douching, and greater number of lifetime sexual partners (Sutton, 2007). Among women, frequent sites of infection include the urethra, endocervix, and vagina. Symptomatic vaginitis is characterized by yellow purulent discharge, pruritus, vulvovaginal erythema, and colpitis macularis, which is often termed a "strawberry cervix" and reflects a patchy, maculoerythematous ectocervix (Wølner-Hanssen, 1989).

Trichomonads are flagellated, pear-shaped, motile organisms that are somewhat larger than leukocytes. These parasites can readily be seen microscopically moving briskly in a sample mixed on a slide with saline. Prompt inspection of vaginal secretions is advantageous because trichomonads slow with cooling. At times, *T vaginalis* may be found incidentally on a Pap test slide. Both of these microscopic slide tests have low diagnostic sensitivity that approximates only 60 percent (Krieger, 1988; Wiese, 2000). And, Pap tests can yield false-positive results. Thus, Pap test trichomonad findings warrant wet-prep microscopy or other diagnostic confirmation (American College of Obstetricians and Gynecologists, 2017c). Of other tests, culture is expensive, lengthy, and sensitivities are 75 to 95 percent (Association of Public Health Laboratories, 2016; Huppert, 2007). Laboratory NAAT analysis of a vaginal, endocervical, or urine sample is available, is completed in minutes to hours, and offers superior sensitivity of 95 to 100 percent (Schwebke, 2011; Van Der Pol, 2014). Rapid POC testing is also available but may sacrifice sensitivity for speed. The OSOM Trichomonas Rapid Test provides results in 10 minutes, is suitable for office use, and has sensitivities of 88 to 98 percent (Herbst de Cortina, 2016).

Treatment

Metronidazole, administered orally in a single 2-g dose, is effective in eradicating *T vaginalis.* For those with HIV infection, treatment instead with metronidazole 500 mg orally twice daily for 7 days improves efficacy. Because of the high rate of reinfection among women treated for trichomoniasis, retesting for *T vaginalis* is recommended for all sexually active women within 3 months following initial treatment (Workowski, 2015).

Metronidazole, an FDA category B drug, is not teratogenic or fetotoxic, but has displayed some tumorigenicity in animal studies (Briggs, 2015; Czeizel, 1998). For this reason, the manufacturer recommends against its use during the first trimester (Pfizer, 2016). Fewer data are available for tinidazole, which is a category C drug, and thus metronidazole is preferred. Metronidazole and tinidazole have similar chemical structures, and those allergic to metronidazole may also react to tinidazole. For allergic patients, metronidazole desensitization is effective, and one scheme is outlined in the study by Helms and coworkers (2008). With postpartum breastfeeding, feeds are delayed for 24 hours following the last oral metronidazole dose per manufacturer prescribing information. For tinidazole, the delay is 72 hours.

Perinatal transmission of trichomoniasis by direct contact in the birth canal is rare but may lead to neonatal respiratory or genital infection (Bruins, 2013; Trintis, 2010). Some studies have linked trichomonal infection with preterm birth. A few other studies implicate this infection with preterm premature rupture of membranes and small-for-gestational age newborns (Silver, 2014). However, treatment did not lower preterm birth rates in a randomized study by Klebanoff and colleagues (2001). Also, in this study, but not one by Mann and coworkers (2009), treatment for trichomoniasis was associated instead with a higher preterm birth rate.

In sum, treatment for symptomatic women is reasonable and outlined above. For most asymptomatic women during pregnancy, screening is not recommended. However, for pregnant women with HIV infection, screening at the first prenatal visit and prompt treatment are encouraged. This is because *T vaginalis* infection in pregnant women with HIV may be a risk factor for vertical HIV transmission (Gumbo, 2010; Workowski, 2015).

Candidiasis

Candida albicans or other candidal species can be identified by culture from the vagina during pregnancy in approximately 20 percent of women. A link between candidiasis and preterm birth is not robust (Cotch, 1998; Kiss, 2004; Roberts, 2015). Thus, asymptomatic colonization requires no treatment. The organism, however, can create an extremely profuse, irritating discharge.

For symptoms, effective treatment is a 100-mg miconazole vaginal suppository or a 2-percent butoconazole, 1-percent clotrimazole, 2-percent miconazole, or 0.4-percent terconazole cream, any of which is used daily for 7 days. A shorter, 3-day regimen is daily 2-percent clotrimazole, 4-percent miconazole, or 0.8-

percent tioconazole cream, or daily 200-mg miconazole or 80-mg terconazole suppository (Workowski, 2015). In some women, infection is likely to recur and require repeated treatment during pregnancy. In these cases, symptomatic infection usually subsides after pregnancy (Sobel, 2007). For treatment, the American College of Obstetricians and Gynecologists (2017c) and the CDC recommend topical rather than oral azoles for symptoms. As discussed further in Chapter 12 (Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blocking Drugs), oral fluconazole is generally not considered teratogenic, but in 2016, the FDA released a safety alert regarding a possible link with miscarriage (Mølgaard-Nielsen, 2016).

HUMAN IMMUNODEFICIENCY VIRUS

Etiopathogenesis and Epidemiology

Causative agents of acquired immunodeficiency syndrome (AIDS) are RNA retroviruses termed *human immunodeficiency viruses*, *HIV-1* and *HIV-2*. Most cases worldwide are caused by HIV-1 infection. Sexual intercourse is the major mode of transmission. The virus also is passed by blood, and infected mothers may infect their fetuses during labor and delivery or by breast milk. The primary determinant of transmission is the plasma HIV-1 viral load.

For sexual transmission, the viral HIV envelope binds to mucosal dendritic cells. These cells then present the viral particle to specific T lymphocytes. These lymphocytes are defined phenotypically by their *cluster of differentiation 4 (CD4)* glycoprotein surface antigens. The CD4 site serves as a receptor for the virus. Once infected, CD4 T lymphocytes may die, and the common denominator of clinical illness with AIDS is profound immunodeficiency that gives rise to various opportunistic infections and neoplasms.

In the United States, the CDC (2016c) estimated that more than 1.2 million individuals were infected in 2013, and new cases numbered more than 39,000. Approximately 8500 women with HIV give birth annually in the United States. However, the estimated number of perinatally acquired HIV cases has decreased dramatically, and the perinatal transmission rate in 2013 was 1.8 percent (Centers for Disease Control and Prevention, 2016b, 2017). This is predominantly due to the implementation of prenatal HIV testing and antiretroviral therapy (ART) for the woman and then her neonate.

Clinical Manifestations

The incubation period from exposure to clinical disease averages 3 to 6 weeks. Acute HIV infection is similar to many other viral syndromes and usually lasts less than 10 days. Common symptoms, if any, include fever, fatigue, rash, headache, lymphadenopathy, pharyngitis, myalgias, nausea, and diarrhea. After symptoms abate, the level of viremia usually decreases to a set point, and patients with the highest viral burden at this time progress more rapidly to AIDS and death (Fauci, 2007). According to the CDC, AIDS is defined by a CD4 T-cell count <200 cells/μL, by CD4 T-cells comprising <14 percent of all lymphocytes, or one of several AIDS-defining illnesses (Schneider, 2008; Selik, 2014). Route of infection, the pathogenicity of the infecting viral strain, the initial viral inoculum, and the immunological status of the host all affect the rapidity of progression.

Prenatal HIV Screening

The CDC (2006b) and the American College of Obstetricians and Gynecologists (2016e) recommend prenatal HIV screening using an *opt-out approach*. This means that a woman is notified that HIV testing is included in a comprehensive set of antenatal tests, but that testing may be declined. Women are given information regarding HIV but are not required to sign a specific consent. Through the use of such opt-out strategies, HIV testing rates have increased. Specific state laws concerning screening vary and can be found at: www.cdc.gov/hiv/policies/law/states/testing.html.

Repeat testing during the third trimester, preferably before 36 weeks' gestation, is *considered* for all pregnant women. Retesting is *recommended* for those at risk for acquiring HIV or for women in high-risk areas, namely, those with rates of HIV infection of 1 per 1000 pregnant women screened (Workowski, 2015). At-risk factors include injection drug use, prostitution, a suspected or known HIV-infected sexual partner, multiple sexual partners, or a diagnosis of another STD (American College of Obstetricians and Gynecologists, 2016e).

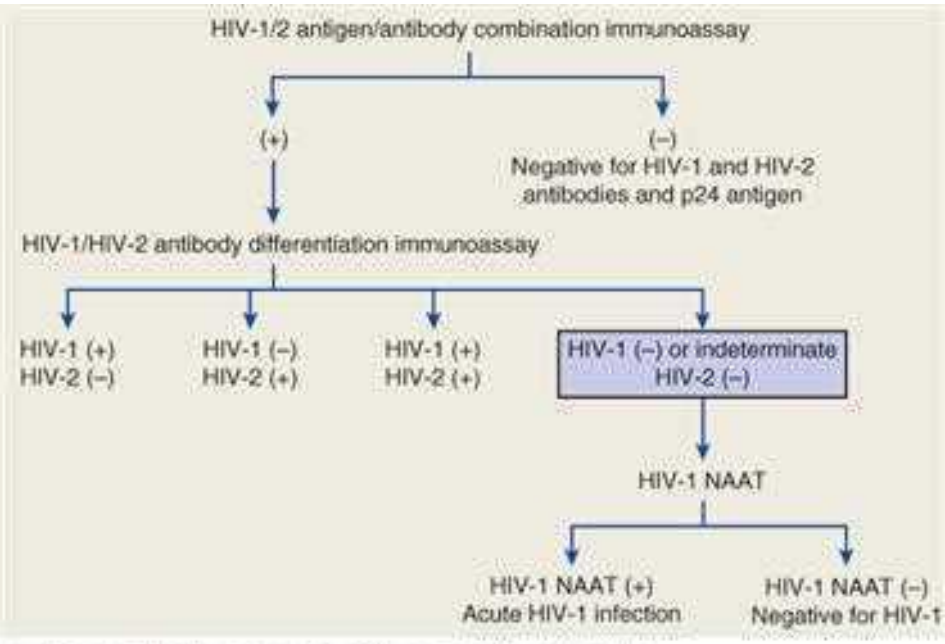
The initial laboratory screening test for HIV is an antigen/antibody combination immunoassay that detects antibodies against HIV-1 and HIV-2 and detects HIV-1 p24 antigen (Centers for Disease Control and Prevention, 2014). Antibody can be detected in most patients within 1 month of infection, and thus, antibody serotesting may not exclude early infection. Instead, for acute primary HIV infection, identification of viral p24 core antigen or viral RNA is possible. No further testing is required for specimens that are negative on the initial immunoassay unless a known exposure to HIV has occurred.

As shown in Figure 65-7, specimens with a "reactive" (that is, a positive) antigen/antibody combination immunoassay result should be tested with an antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies. The HIV-1/HIV-2 antibody differentiation immunoassay is resulted as positive or negative for HIV-1 antibodies, for HIV-2 antibodies, or for HIV antibodies, undifferentiated. If these two serial immunoassays are discordant, an HIV-1 NAAT—qualitative or quantitative HIV RNA test—is performed (Centers for Disease Control and Prevention, 2014).

FIGURE 65-7

Algorithm for HIV testing. In the pathway colored light-blue, for specimens that are reactive on the initial antigen/antibody combination immunoassay and nonreactive or indeterminate on the HIV-1/HIV-2 antibody differentiation immunoassay, a nucleic acid amplification test (NAAT) is implemented. A positive HIV-1 NAAT result and nonreactive HIV-1/HIV-2 antibody differentiation immunoassay result indicate laboratory evidence for acute HIV-1 infection. A positive HIV-1 NAAT result and indeterminate HIV-1/HIV-2 antibody differentiation immunoassay result indicate the presence of HIV-1 infection confirmed by HIV-1

NAAT. A negative HIV-1 NAAT result and nonreactive or indeterminate HIV-1/HIV-2 antibody differentiation immunoassay result indicate a false-positive result on the initial antigen/antibody combination immunoassay. (Reproduced with permission from Centers for Disease Control and Prevention, 2014.)



Women with undocumented HIV status at delivery should have a fourth-generation HIV antigen/antibody combination screening test performed on a blood sample. A negative screening test result does not need confirmation. However, in cases of recent HIV exposure, consideration is given to peripartum interventions to reduce perinatal transmission despite negative HIV testing. Repeat interval testing is recommended to exclude very early infection not identified with the initial screen. With a positive fourth-generation HIV testing result, peripartum and neonatal interventions to reduce perinatal transmission are initiated. This includes avoidance of breastfeeding, although breast milk may be stored until confirmatory test results are available. Interventions can be discontinued if confirmatory testing is negative. To confirm a positive result from any initial HIV test, the laboratory testing algorithm in Figure 65-7 should be used and begins with the antigen/antibody combination immunoassay.

Vertical Transmission

Viral burden and neonatal infection rates are directly related. In one cohort, neonatal infection was 1 percent with <400 copies/mL, and it was 23 percent when maternal viral RNA levels were >30,000 copies/mL (Cooper, 2002). Among 2615 infants born to mothers taking ART before conception and during pregnancy, there were no cases of vertical transmission with maternal viral loads <50 copies/mL at delivery (Mandelbrot, 2015). Transmission of HIV infection, however, has been observed at all HIV RNA levels, including those that were nondetectable by current assays. Transplacental HIV transmission can occur early, and the virus has even been identified in specimens from elective abortion (Lewis, 1990). Kourtis and colleagues (2001) estimated that 20 percent of vertical transmission occurs before 36 weeks' gestation, 50 percent in the days before delivery, and 30 percent intrapartum. Transmission rates for breastfeeding may be as high as 30 to 40 percent and are associated with increasing HIV viral burden (Kourtis, 2006, 2007; Slyker, 2012). In nonpregnant individuals, concomitant STDs and horizontal HIV transmission are linked. Evidence also supports that vertical transmission rates may be increased by comorbid STDs (Schulte, 2001; Watts, 2012).

Antepartum Care

Pregnant women with HIV infection need special attention and are seen in consultation by physicians with special interest in this field. An additional resource is the National Perinatal HIV Hotline (1–888–448–8765), which is a federally funded service that provides free antepartum, intrapartum, or postpartum consultation to providers. At Parkland Hospital, an HIV-infected pregnant woman is initially assessed with the following:

Standard prenatal laboratory surveys that include serum creatinine, complete blood count, and bacteriuria screening

Plasma HIV RNA quantification—"viral load"—CD4 T-cell count, and antiretroviral resistance testing

Serum hepatic aminotransferase levels

HSV-1 and 2, cytomegalovirus, toxoplasmosis, and hepatitis B and C serological screening

Baseline chest radiograph

Tuberculosis testing with purified protein derivative (PPD) skin testing, or interferon-gamma release assay

Evaluation of need for pneumococcal, hepatitis A, hepatitis B, Tdap, and influenza vaccines

Sonographic evaluation to establish gestational age.

During pregnancy, the risk of HIV transmission does not appear to be increased with amniocentesis or other invasive diagnostic procedures in women receiving effective ART resulting in viral suppression (Floridia, 2017). For women not receiving ART, the risk rises approximately twofold (Mandelbrot, 1996). If amniocentesis is performed, efforts are taken to avoid passing through the placenta (Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2016).

Antiretroviral Therapy

In overview, the ideal strategy to suppress viral load and minimize vertical HIV transmission includes: (1) preconceptional ART, (2) antepartum ART, (3) intrapartum continuation of the antepartum oral ART regimen plus IV zidovudine, and (4) newborn ART prophylaxis. ART is recommended for all HIV-infected pregnant women, and it should be initiated as early in pregnancy as possible. Treatment reduces the risk of perinatal transmission regardless of CD4 T-cell count or HIV RNA level. Adherence is essential because the risk of viral drug resistance is lessened. As for nonpregnant adults, pregnant women are treated with at least three antiviral agents.

The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (2016) has issued guidelines for four different scenarios during pregnancy (Table 65-5).

TABLE 65-5

Recommendations for HIV Antiviral Drug Use During Pregnancy

Clinical Scenario	Recommendations
Taking ART and becomes pregnant	Continue current medication if viral suppression adequate and patient tolerating
ART naïve	Initiate ART: combine two NRTIs with either a ritonavir-boosted PI or an integrase inhibitor – Preferred NRTI dual combinations: abacavir/lamivudine, tenofovir disoproxil fumarate (TDF)/emtricitabine, or TDF/lamivudine. If abacavir is used, HLA-B*5701 testing is completed to identified potential hypersensitivity reaction – Preferred PI: atazanavir/ritonavir or darunavir/ritonavir – Preferred integrase inhibitor: raltegravir
Prior ART use but not currently	Initiate ART with regimen based on prior therapy history and resistance testing
No ART use and presents in labor	IV ZDV (see Intrapartum Care)
Antepartum care	See antepartum screening test list (Delivery Planning)
	ART should be initiated as early as possible
	For those with HIV RNA levels >500–1000 copies/mL, order HIV antiretroviral drug-resistance testing but do not delay ART initiation awaiting results
	Repeat HIV RNA levels 2–4 weeks after initiating (or changing) ART drugs; monthly until RNA levels are undetectable; then at least every 3 mo; and finally at 34–36 weeks' gestation for delivery planning
	CD4+ count should be monitored at the initial visit and every 3–6 mo
Intrapartum care	If HIV RNA level >1000 copies/mL or is unknown before labor or ROM, plan cesarean delivery at 38 weeks' gestation
	If HIV RNA levels >1000 or is unknown but labor or ROM has ensued, benefits of cesarean delivery are unclear and labor plans are individualized
	If HIV RNA level ≤1000 copies/mL, vaginal delivery is permitted; cesarean delivery not routinely recommended
	Start IV ZDV if HIV RNA level >1000 copies/mL near delivery or is unknown. Dosing is 2 mg/kg IV load over 1 hr, then 1 mg/kg/hr until delivery. IV ZDV should begin 3 hr before scheduled cesarean delivery
	Those taking oral antepartum ART should take this during labor with sips of water

ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; ROM = rupture of membranes; ZDV = zidovudine.

Adapted from the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, 2016. Department of Health and Human Services.

The following paragraphs summarize these recommendations. First, women already taking ART at pregnancy onset are encouraged to continue the regimen if viral suppression is adequate. Didanosine, stavudine, and full-dose ritonavir, which differs from ritonavir-boosted agents, are exceptions due to pregnancy toxicity but not teratogenicity.

Second, women who have never received antiretroviral therapy—*antiretroviral naïve*—are given ART regardless of trimester. In general, the starting regimen comprises two nucleoside reverse transcriptase inhibitors plus either a ritonavir-boosted protease inhibitor or an integrase inhibitor.

Third, women who have previously received antiretroviral therapy but are currently not taking medications should undergo HIV resistance testing because prior ART use raises their risk of drug resistance. Typically, ART is initiated prior to receiving results of these drug-resistance tests. In this case, initial ART

selection should factor results of prior resistance testing, if available; prior ART regimen; and current ART pregnancy guidelines, that is, those for ART-naïve women. Drug-resistance testing may then modify the initial regimen.

For these three categories of women taking antepartum ART, therapy surveillance is outlined in Table 65-5. Most patients with adequate viral response have at least a 1-log viral load decline within 1 to 4 weeks after starting therapy. For those who fail to achieve this decline, options include review of drug resistance study results, confirmation of regimen compliance, and ART modification.

During labor and delivery, oral medications can be taken with sips of water. Additionally, IV zidovudine is given to women with an HIV RNA viral load >1000 copies/mL or who have an unknown viral load near delivery. At Parkland Hospital, we administer intrapartum IV zidovudine to all HIV-positive women, regardless of viral load. A 2 mg/kg load is infused over 1 hour followed by zidovudine 1 mg/kg/hr until delivery. In this instance, for gravidas already taking antepartum oral zidovudine, their oral dose can be held, and IV drug is instead administered. HIV-infected women undergoing a scheduled cesarean delivery are given IV zidovudine as a loading dose followed by 2 more hours of continuous maintenance therapy—a total of 3 hours of infused zidovudine.

The fourth group includes women who present in labor and who are taking no medications. These women are given IV zidovudine intrapartum as just described.

Delivery Planning

During labor, artificial membrane rupture, fetal scalp electrode placement, episiotomy, and operative vaginal delivery are reserved for clear obstetrical indications (Mandelbrot, 1996; Peters, 2016). Labor augmentation is used when needed to shorten the interval to delivery to further lower the transmission risk. Delayed cord clamping in preterm neonates is acceptable. Neuraxial analgesia is suitable. Postpartum hemorrhage is best managed with oxytocin and prostaglandin analogues. *Methylergonovine (Methergine) and other ergot alkaloids adversely interact with reverse transcriptase and protease inhibitors to cause severe vasoconstriction.*

In some cases, cesarean delivery lowers HIV prenatal transmission (European Mode of Delivery Collaboration, 1999; International Perinatal HIV Group, 1999). The American College of Obstetricians and Gynecologists (2017b) recommends that scheduled cesarean delivery be discussed and recommended for HIV-infected women with HIV-1 RNA loads >1000 copies/mL. Scheduled delivery is recommended at 38 weeks' gestation in these women to avert spontaneous labor.

For women with HIV RNA levels ≤1000 copies/mL, data are insufficient to predict similar benefits, and scheduled cesarean delivery is unlikely to confer additional risk reduction for women already taking ART and achieving viral suppression (Briand, 2013; Jamieson, 2007; Read, 2005). Vaginal delivery in this group may be elected. However, if cesarean delivery is instead chosen for a well-counseled woman in this group, it should be performed at 39 weeks. Similarly, cesarean delivery performed for obstetrical indications in this lower-viral-load group should be done at 39 weeks when possible.

Postpartum Care

Vertical transmission is increased by breastfeeding, and it generally is not recommended for HIV-positive women in the United States, where formula is readily available (Read, 2003). In nutritionally deprived countries, where infectious disease and malnutrition are primary causes of infant death, the World Health Organization (2016) recommends exclusive breastfeeding during the first 6 to 12 months.

The Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission (2016) strongly recommends that ART regimens not be discontinued postpartum but continued lifelong for the advantages of viral suppression. Ideally, all those planning pregnancy should be receiving ART and have a plasma viral load below detectable levels before conception. As one benefit, interpregnancy viral load suppression is associated with less vertical transmission in a subsequent pregnancy (French, 2014; Mandelbrot, 2015; Stewart, 2014; Townsend, 2014). Reassuringly, for those seeking subsequent pregnancy, when ART is available, repeated pregnancy in a healthy woman with HIV has no significant effect on disease progression (Calvert, 2015). Linkage to general HIV care postpartum is critical to maintain viral suppression (Swain, 2016).

For women who do not have HIV infection, but whose partner is seropositive, current guidance supports the use of highly active antiretroviral therapy with viral suppression in the infected partner (treatment as prevention), and consideration of antiretroviral preexposure prophylaxis (PreP) for the HIV-negative partner. The well-counseled couple can consider periovulatory condomless intercourse, or uterine insemination or in vitro fertilization after sperm washing for assisted conception (Brooks, 2017; Kawwass, 2017).

If, instead, pregnancy is undesired, effective contraception is discussed (Chap. 38, Introduction). Counseling also includes education for decreasing high-risk sexual behaviors to prevent transmission and to decrease other STD acquisition. Similarly, women with HIV have unique gynecological issues, such as genital neoplasia, which require special attention (American College of Obstetricians and Gynecologists, 2016a; Werner, 2016).

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APPENDIX I: Serum and Blood Constituents

HEMATOLOGY					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Erythropoietin[b] (U/L)	4–27	12–25	8–67	14–222	7, 10, 47
Ferritin[b] (ng/mL)	10–150d	6–130	2–230	0–116	7, 10, 39, 42, 45, 47, 62, 70
Folate, red blood cell (ng/mL)	150–450	137–589	94–828	109–663	45, 46, 72
Folate, serum (ng/mL)	5.4–18.0	2.6–15.0	0.8–24.0	1.4–20.7	7, 43, 45, 46, 53, 58, 72
Haptoglobin (mg/mL)	25–250	130 ± 43	115 ± 50	135 ± 65	26A
Hemoglobin[b] (g/dL)	12–15.8d	11.6–13.9	9.7–14.8	9.5–15.0	10, 45, 47, 58, 62
Hematocrit[b] (%)	35.4–44.4	31.0–41.0	30.0–39.0	28.0–40.0	6, 7, 10, 42, 45 58, 66
Iron, total binding capacity (TIBC)[b] (µg/dL)	251–406	278–403	Not reported	359–609	62
Iron, serum[b] (µg/dL)	41–141	72–143	44–178	30–193	10, 62
Mean corpuscular hemoglobin (MCH) (pg/cell)	27–32	30–32	30–33	29–32	42
Mean corpuscular volume (MCV) (×m^3)	79–93	81–96	82–97	81–99	6, 42, 45, 58
Platelet (×10^9/L)	165–415	174–391	155–409	146–429	4, 6, 16, 42, 45
Mean platelet volume (MPV) (μm^3)	6.4–11.0	7.7–10.3	7.8–10.2	8.2–10.4	42

HEMATOLOGY					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Red blood cell count (RBC) ($\times 10^6/mm^3$)	4.00–5.20[d]	3.42–4.55	2.81–4.49	2.71–4.43	6, 42, 45, 58
Red cell distribution width (RDW) (%)	<14.5	12.5–14.1	13.4–13.6	12.7–15.3	42
White blood cell count (WBC) ($\times 10^3/mm^3$)	3.5–9.1	5.7–13.6	5.6–14.8	5.9–16.9	6, 9, 42, 45, 58
Neutrophils ($\times 10^3/mm^3$)	1.4–4.6	3.6–10.1	3.8–12.3	3.9–13.1	4, 6, 9, 42
Lymphocytes ($\times 10^3/mm^3$)	0.7–4.6	1.1–3.6	0.9–3.9	1.0–3.6	4, 6, 9, 42
Monocytes ($\times 10^3/mm^3$)	0.1–0.7	0.1–1.1	0.1–1.1	0.1–1.4	6, 9, 42
Eosinophils ($\times 10^3/mm^3$)	0–0.6	0–0.6	0–0.6	0–0.6	6, 9
Basophils ($\times 10^3/mm^3$)	0–0.2	0–0.1	0–0.1	0–0.1	6, 9
Transferrin (mg/dL)	200–400[c]	254–344	220–441	288–530	39, 42
Transferrin, saturation without iron (%)	22–46[b]	Not reported	10–44	5–37	47
Transferrin, saturation with iron (%)	22–46[b]	Not reported	18–92	9–98	47

COAGULATION					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Antithrombin III, functional (%)	70–130	89–114	78–126	82–116	15, 16, 39A

COAGULATION					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
D-Dimer (µg/mL)	0.22–0.74	0.05–0.95	0.32–1.29	0.13–1.7	16, 25, 25C, 35, 39A, 41A, 51
Factor V (%)	50–150	75–95	72–96	60–88	40
Factor VII (%)	50–150	100–146	95–153	149–2110	16
Factor VIII (%)	50–150	90–210	97–312	143–353	16, 40
Factor IX (%)	50–150	103–172	154–217	164–235	16
Factor XI (%)	50–150	80–127	82–144	65–123	16
Factor XII (%)	50–150	78–124	90–151	129–194	16
Fibrinogen (mg/dL)	233–496	244–510	291–538	301–696	16, 25, 25C, 39A, 41A, 42, 51
Fibronectin (mg/L)	290 ± 85	377 ± 309	315 ± 295	334 ± 257	27A
Homocysteine (µmol/L)	4.4–10.8	3.34–11	2.0–26.9	3.2–21.4	43, 45, 46, 53, 72
International normalized ratio (INR)	0.9–1.04[g]	0.86–1.08	0.83–1.02	0.80–1.09	15, 41A
Partial thromboplastin time, activated (aPTT) (sec)	26.3–39.4	23.0–38.9	22.9–38.1	22.6–35.0	15, 16, 41A, 42
Prothrombin time (PT) (sec)	12.7–15.4	9.7–13.5	9.5–13.4	9.6–12.9	16, 41A, 42
Protein C, functional (%)	70–130	78–121	83–133	67–135	15, 24, 40
Protein S, total (%)	70–140	39–105	27–101	33–101	16, 24, 40

COAGULATION					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Protein S, free (%)	70–140	34–133	19–113	20–65	24, 40
Protein S, functional activity (%)	65–140	57–95	42–68	16–42	40
Thrombin time (TT) (sec)	17.7 ± 2.8	16.1 ± 1.5	15.4 ± 2.7	16.5 ± 2.4	27A
Thrombomodulin (ng/mL)	2.7 ± 3.1	4.3 ± 1.3	4.2 ± 1.2	3.6 ± 1.3	27A
Tissue plasminogen activator (ng/mL)	1.6–13[h]	1.8–6.0	2.36–6.6	3.34–9.20	15, 16, 25C
Tissue plasminogen activator inhibitor-1 (ng/mL)	4–43	16–33	36–55	67–92	16, 25C
von Willebrand disease von Willebrand factor antigen (%)	75–125	62–318	90–247	84–422	39A, 44A, 73
ADAMTS-13, von Willebrand cleaving protease (%)	40–170[i]	40–160	22–135	38–105	39A, 44A

BLOOD CHEMICAL CONSTITUTENTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Alanine aminotransferase (ALT) (U/L)	7–41	3–30	2–33	2–25	5, 39, 42, 70
Albumin (g/dL)	4.1–5.3d	3.1–5.1	2.6–4.5	2.3–4.2	3, 5, 26, 29, 39, 42, 72
Alkaline phosphatase (U/L)	33–96	17–88	25–126	38–229	3, 5, 39, 42, 70
Alpha-1 antitrypsin (mg/dL)	100–200	225–323	273–391	327–487	42

BLOOD CHEMICAL CONSTITUTENTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Alpha-fetoprotein (ng/mL)	—	—	~130–400	~130–590	39B
Ammonia (μM)	31 ± 3.2	—	—	27.3 ± 1.6	31A
Amylase (U/L)	20–96	24–83	16–73	15–81	32, 39, 42, 68
Anion gap (mmol/L)	7–16	13–17	12–16	12–16	42
Aspartate aminotransferase (AST) (U/L)	12–38	3–23	3–33	4–32	5, 39, 42, 70
Bicarbonate (mmol/L)	22–30	20–24	20–24	20–24	42
Bilirubin, total (mg/dL)	0.3–1.3	0.1–0.4	0.1–0.8	0.1–1.1	5, 39
Bilirubin, unconjugated (mg/dL)	0.2–0.9	0.1–0.5	0.1–0.4	0.1–0.5	5, 42
Bilirubin, conjugated (mg/dL)	0.1–0.4	0–0.1	0–0.1	0–0.1	5
Bile acids (μmol/L)	0.3–4.8[j]	0–4.9	0–9.1	0–11.3	5, 14
CA-125 (μg/mL)	7.2–27	2.2–268	12–25.1	16.8–43.8	3A, 30A, 67A
Calcium, ionized (mg/dL)	4.5–5.3	4.5–5.1	4.4–5.0	4.4–5.3	26, 42, 48, 56
Calcium, total (mg/dL)	8.7–10.2	8.8–10.6	8.2–9.0	8.2–9.7	3, 29, 39, 42, 48, 56, 63
Ceruloplasmin (mg/dL)	25–63	30–49	40–53	43–78	42, 44
Chloride (mEq/L)	102–109	101–105	97–109	97–109	20, 39, 42
Creatinine (mg/dL)	0.5–0.9d	0.4–0.7	0.4–0.8	0.4–0.9	39, 42, 45

BLOOD CHEMICAL CONSTITUTENTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Gamma-glutamyl transpeptidase (GGT) (U/L)	9–58	2–23	4–22	3–26	5, 42, 39, 70
Lactate dehydrogenase (U/L)	115–221	78–433	80–447	82–524	42, 29, 39, 70
Lipase (U/L)	3–43	21–76	26–100	41–112	32
Magnesium (mg/dL)	1.5–2.3	1.6–2.2	1.5–2.2	1.1–2.2	3, 26, 29, 39, 42, 48, 63
Osmolality (mOsm/kg H_2O)	275–295	275–280	276–289	278–280	17, 63
Phosphate (mg/dL)	2.5–4.3	3.1–4.6	2.5–4.6	2.8–4.6	3, 26, 33, 39, 42
Potassium (mEq/L)	3.5–5.0	3.6–5.0	3.3–5.0	3.3–5.1	20, 26, 29, 39, 42, 63, 66
Prealbumin (mg/dL)	17–34	15–27	20–27	14–23	42
Protein, total (g/dL)	6.7–8.6	6.2–7.6	5.7–6.9	5.6–6.7	26, 29, 42
Sodium (mEq/L)	136–146	133–148	129–148	130–148	17, 26, 29, 39, 42, 63, 66
Urea nitrogen (mg/dL)	7–20	7–12	3–13	3–11	20, 39, 42
Uric acid (mg/dL)	2.5–5.6d	2.0–4.2	2.4–4.9	3.1–6.3	17, 39, 42

METABOLIC AND ENDOCRINE TESTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Aldosterone (ng/dL)	2–9	6–104	9–104	15–101	21, 34, 69

METABOLIC AND ENDOCRINE TESTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Angiotensin-converting enzyme (ACE) (U/L)	9–67	1–38	1–36	1–39	20, 54
Cortisol (µg/dL)	0–25	7–19	10–42	12–50	42, 69
Hemoglobin A_{1C} (%)	4–6	4–6	4–6	4–7	48, 49, 59
Parathyroid hormone (pg/mL)	8–51	10–15	18–25	9–26	3
Parathyroid hormone-related protein (pmol/L)	<1.3e	0.7–0.9	1.8–2.2	2.5–2.8	3
Renin, plasma activity (ng/mL/hr)	0.3–9.0e	Not reported	7.5–54.0	5.9–58.8	20, 34
Thyroid stimulating hormone (TSH) (µIU/mL)	0.34–4.25	0.60–3.40	0.37–3.60	0.38–4.04	39, 42, 57
Thyroxine-binding globulin (mg/dL)	1.3–3.0	1.8–3.2	2.8–4.0	2.6–4.2	42
Thyroxine, free (fT_4) (ng/dL)	0.8–1.7	0.8–1.2	0.6–1.0	0.5–0.8	42, 57
Thyroxine, total (T_4) (µg/dL)	5.4–11.7	6.5–10.1	7.5–10.3	6.3–9.7	29, 42
Triiodothyronine, free (fT_3) (pg/mL)	2.4–4.2	4.1–4.4	4.0–4.2	Not reported	57
Triiodothyronine, total (T_3) (ng/dL)	77–135	97–149	117–169	123–162	42

VITAMINS AND MINERALS

VITAMINS AND MINERALS	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Copper (μg/dL)	70–140	112–199	165–221	130–240	2, 30, 42
Selenium (μg/L)	63–160	116–146	75–145	71–133	2, 42
Vitamin A (retinol) (μg/dL)	20–100	32–47	35–44	29–42	42
Vitamin B_{12} (pg/mL)	279–966	118–438	130–656	99–526	45, 72
Vitamin C (ascorbic acid) (mg/dL)	0.4–1.0	Not reported	Not reported	0.9–1.3	64
Vitamin D, 1,25-dihydroxy (pg/mL)	25–45	20–65	72–160	60–119	3, 48
Vitamin D, 24,25-dihydroxy (ng/mL)	0.5–5.0e	1.2–1.8	1.1–1.5	0.7–0.9	60
Vitamin D, 25-hydroxy (ng/mL)	14–80	18–27	10–22	10–18	3, 60
Vitamin E (α-tocopherol) (μg/mL)	5–18	7–13	10–16	13–23	42
Zinc (μg/dL)	75–120	57–88	51–80	50–77	2, 42, 58

AUTOIMMUNE AND INFLAMMATORY MEDIATORS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
C3 complement (mg/dL)	83–177	62–98	73–103	77–111	42

AUTOIMMUNE AND INFLAMMATORY MEDIATORS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
C4 complement (mg/dL)	16–47	18–36	18–34	22–32	42
C-reactive protein (CRP) (mg/L)	0.2–3.0	Not reported	0.4–20.3	0.4–8.1	28
Erythrocyte sedimentation rate (ESR) (mm/hr)	0–20d	4–57	7–47	13–70	71
IgA (mg/dL)	70–350	95–243	99–237	112–250	42
IgG (mg/dL)	700–1700	981–1267	813–1131	678–990	42
IgM (mg/dL)	50–300	78–232	74–218	85–269	42

SEX HORMONES					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Dehydroepiandrosterone sulfate (DHEAS) (µmol/L)	1.3–6.8[e]	2.0–16.5	0.9–7.8	0.8–6.5	52
Estradiol (pg/mL)	<20–443[d,f]	188–2497	1278–7192	6137–3460	13, 52
Progesterone (ng/mL)	<1–20[d]	8–48		99–342	13, 52
Prolactin (ng/mL)	0–20[d]	36–213	110–330	137–372	3, 13, 38, 49
Sex hormone binding globulin (nmol/L)	18–114[d]	39–131	214–717	216–724	1, 52

SEX HORMONES					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Testosterone (ng/dL)	6–86[d]	25.7–211.4	34.3–242.9	62.9–308.6	52
17-Hydroxyprogesterone (nmol/L)	0.6–10.6[d,e]	5.2–28.5	5.2–28.5	15.5–84	52

LIPIDS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Cholesterol, total (mg/dL)	<200	141–210	176–299	219–349	8, 18, 31, 42
HDL-cholesterol (mg/dL)	40–60	40–78	52–87	48–87	8, 18, 31, 42, 55
LDL-cholesterol (mg/dL)	<100	60–153	77–184	101–224	8, 18, 31, 42, 55
VLDL-cholesterol (mg/dL)	6–40e	10–18	13–23	21–36	31
Triglycerides (mg/dL)	<150	40–159	75–382	131–453	8, 18, 31, 39, 42, 55
Apolipoprotein A-I (mg/dL)	119–240	111–150	142–253	145–262	18, 39, 49
Apolipoprotein B (mg/dL)	52–163	58–81	66–188	85–238	18, 39, 49

CARDIAC

CARDIAC	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Atrial natriuretic peptide (ANP) (pg/mL)	Not reported	Not reported	28.1–70.1	Not reported	11
B-type natriuretic peptide (BNP) (pg/mL)	22 ± 10	22 ± 10	32 ± 15	31 ± 21	12A
Creatine kinase (U/L)	39–238[d]	27–83	25–75	13–101	41, 42
Creatine kinase-MB (U/L)	<6[k]	Not reported	Not reported	1.8–2.4	41
NT-pro-BNP (pg/mL)	50 ± 26	60 ± 45	60 ± 40	43 ± 34	12A
Troponin I (ng/mL)	0–0.08	Not reported	Not reported	0–0.064 (intrapartum)	36, 65

BLOOD GAS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Bicarbonate (HCO_3^-) (mEq/L)	22–26	Not reported	Not reported	16–22	23
Pco_2 (mm Hg)	38–42	Not reported	Not reported	25–33	23
Po_2 (mm Hg)	90–100	93–100	90–98	92–107	23, 67
pH	7.38–7.42 (arterial)	7.36–7.52 (venous)	7.40–7.52 (venous)	7.41–7.53 (venous) 7.39–7.45 (arterial)	23, 26

RENAL FUNCTION TESTS					
	Nonpregnant Adult[a]	1st Trimester	2nd Trimester	3rd Trimester	References
Effective renal plasma flow (mL/min)	492–696[d,e]	696–985	612–1170	595–945	19, 22
Glomerular filtration rate (GFR) (mL/min)	106–132[d]	131–166	135–170	117–182	19, 22, 50
Filtration fraction (%)	16.9–24.7[l]	14.7–21.6	14.3–21.9	17.1–25.1	19, 22, 50
Osmolarity, urine (mOsm/kg)	500–800	326–975	278–1066	238–1034	61
24–hr albumin excretion (mg/24 hr)	<30	5–15	4–18	3–22	27, 61
24–hr calcium excretion (mmol/24 hr)	<7.5[e]	1.6–5.2	0.3–6.9	0.8–4.2	66
24–hr creatinine clearance (mL/min)	91–130	69–140	55–136	50–166	22, 66
24–hr creatinine excretion (mmol/24 hr)	8.8–14[e]	10.6–11.6	10.3–11.5	10.2–11.4	61
24–hr potassium excretion (mmol/24 hr)	25–100[e]	17–33	10–38	11–35	66
24–hr protein excretion (mg/24 hr)	<150	19–141	47–186	46–185	27
24–hr sodium excretion (mmol/24 hr)	100–260[e]	53–215	34–213	37–149	17, 66

[a]Unless otherwise specified, all normal reference values are from the seventeenth edition of Harrison's Principles of Internal Medicine (37).

[b]Range includes references with and without iron supplementation.

[c]Reference values are from Laboratory Reference Handbook, Pathology Department, Parkland Hospital, 2005.

[d]Normal reference range is specific range for females.

[e]Reference values are from the 15th edition of Harrison's Principles of Internal Medicine (12).

[f]Range is for premenopausal females and varies by menstrual cycle phase.

[g]Reference values are from Cerneca et al: Coagulation and fibrinolysis changes in normal pregnancy increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis (15).

[h]Reference values are from Cerneca et al and Choi et al: Tissue plasminogen activator levels change with plasma f-ibrinogen concentrations during pregnancy (15, 16).

[i]Reference values are from Mannucci et al: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor (44A).

[j]Reference values are from Bacq et al: Liver function tests in normal pregnancy: a prospective study of 102 pregnant women and 102 matched controls (5).

[k]Reference values are from Leiserowitz et al: Creatine kinase and its MB isoenzyme in the third trimester and the -peripartum period (41).

[l]Reference values are from Dunlop: Serial changes in renal haemodynamics during normal human pregnancy (19).

Appendix courtesy of Dr. Mina Abbassi-Ghanavati and Dr. Laura G. Greer.

APPENDIX II: Maternal Echocardiographic Measurements

	Pregnancy			
Left Ventricle	**1st Trimester**	**2nd Trimester**	**3rd Trimester**	**Postpartum**
Geometry				
IVS_d (mm)	7.3 ± 1.0	7.4 ± 1.1	7.8 ± 1.2	7.1 ± 0.9
LVEDD (mm)	45–47.8	47–48.9	47–49.6	46–48.8
LVESD (mm)	28–30	29–30.1	30–30.8	28–30.6
PW_d	6.3 ± 0.7	6.6 ± 0.7	6.9 ± 1.0	6.1 ± 0.6
RWT	0.26–0.36	0.27–0.37	0.28–0.38	0.25–0.35
LV mass (g)	111–121	121–135	136–151	114–119
LV mass (g/m^2)	66 ± 13	70 ± 12	76 ± 16	67 ± 11
Systolic function				
FS (%)	37–38	76–78	80–85	67–69
SW thickening (%)	47 ± 17	53 ± 16	51 ± 15	54 ± 19
PW thickening (%)	66 ± 16	72 ± 16	74 ± 16	71 ± 14
VCFC (circ/sec)	1.15–0.3	1.18–0.16	1.18–0.12	1.18–0.12
ESS (g/cm^2)	59 ± 9	53 ± 11	52 ± 11	66 ± 12
Diastolic function				
Heart rate	75–76	76–78	80–85	67–69
Mitral E wave (m/sec)	0.85 ± 0.13	0.84 ± 0.16	0.77 ± 0.15	0.77 ± 0.11
Mitral A wave (m/sec)	0.5 ± 0.09	0.5 ± 0.1	0.55 ± 0.1	0.46 ± 0.1
Deceleration time (ms)	176 ± 44	188 ± 40	193 ± 33	201 ± 48

	Pregnancy			
Left Ventricle	**1st Trimester**	**2nd Trimester**	**3rd Trimester**	**Postpartum**
IVRT (ms)	90 ± 19	79 ± 18	72 ± 16	69 ± 10
E wave duration (ms)	263 ± 50	276 ± 43	282 ± 37	288 ± 48
E and A wave duration (ms)	454 ± 121	412 ± 79	375 ± 63	523 ± 88

Values are ranges or means ± SD.

Circ = circumference; d = diastolic; ESS = end-systolic wall stress; FS = fractional shortening; IVRT = isovolumic relaxation time; IVS_d = interventricular septum–diastole; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVESD = left ventricular end-systolic dimension; PW = posterior wall; RWT = relative wall thickening; SW = septal wall; VCFC = rate-adjusted mean velocity of circumferential fiber thickening.

Data from Savu (62A) and Vitarelli (71A).

APPENDIX III: Fetal Sonographic Measurements

TABLE III-1

Mean Gestational Sac Diameter and Crown-Rump Length and Corresponding Menstrual Age

Menstrual Age (day)	Menstrual Age (wk)	Gestational Sac Size (mm)	Crown-Rump Length (cm)
30	4.3		
32	4.6	3	
34	4.9	5	
36	5.1	6	
38	5.4	8	
40	5.7	10	0.2
42	6.0	12	0.35
44	6.3	14	0.5
46	6.6	16	0.7
48	6.9	18	0.9
50	7.1	20	1.0
52	7.4	22	1.2
54	7.7	24	1.4
56	8.0	26	1.6
58	8.3	27	1.8
60	8.6	29	2.0
62	8.9	31	2.2
64	9.1	33	2.4
66	9.4	35	2.6
68	9.7	37	2.9
70	10.0	39	3.1
72	10.3	41	3.4
74	10.6	43	3.7
76	10.9	45	4.0
78	11.1	47	4.2
80	11.4	49	4.6
82	11.7	51	5.0
84	12.0	53	5.4

Data from Nyberg, 1992; Hadlock, 1992; Robinson; 1975; Daya, 1991.

TABLE III-2

Mean Gestational Age Percentiles Corresponding to Crown-Rump Length (CRL) Measurements

CRL (mm)	Gestational Age (wk)			CRL (mm)	Gestational Age (wk)		
	Percentile				Percentile		
	5th	50th	95th		5th	50th	95th
10	6 + 5	7 + 3	8	30	9 + 5	10 + 2	11
11	6 + 6	7 + 4	8 + 2	31	9 + 5	10 + 3	11 + 1
12	7 + 1	7 + 5	8 + 3	32	9 + 6	10 + 4	11 + 2
13	7 + 2	8	8 + 4	33	10	10 + 5	11 + 2
14	7 + 3	8 + 4	8 + 6	34	10 + 1	10 + 6	11 + 3
15	7 + 4	8 + 2	9	35	10 + 2	10 + 6	11 + 4
16	7 + 5	8 + 3	9 + 1	36	10 + 2	11	11 + 5
17	8	8 + 4	9 + 2	37	10 + 3	11 + 1	11 + 6
18	8 + 1	8 + 5	9 + 3	38	10 + 4	11 + 2	11 + 6
19	8 + 2	8 + 6	9 + 4	39	10 + 5	11 + 2	12
20	8 + 3	9	9 + 5	40	10 + 5	11 + 3	12 + 1
21	8 + 4	9 + 1	9 + 6	41	10 + 6	11 + 4	12 + 1
22	8 + 5	9 + 2	10	42	11	11 + 4	12 + 2
23	8 + 6	9 + 3	10 + 1	43	11	11 + 5	12 + 3
24	8 + 6	9 + 4	10 + 2	44	11 + 1	11 + 6	12 + 3
25	9	9 + 5	10 + 3	45	11 + 2	11 + 6	12 + 4
26	9 + 1	9 + 6	10 + 4	46	11 + 2	12	12 + 5
27	9 + 2	10	10 + 5	47	11 + 3	12 + 1	12 + 5
28	9 + 3	10 + 1	10 + 5	48	11 + 4	12 + 1	12 + 6
29	9 + 4	10 + 2	10 + 6	49	11 + 4	11 + 2	13

TABLE III-3

Fetal Weight Percentiles According to Gestational Age

Gestational Age (wk)	Fetal Weight Percentiles (g)				
	3rd	10th	50th	90th	97th
10	26	29	35	41	44
11	34	37	45	53	56
12	43	48	58	68	73
13	54	61	73	85	92
14	69	77	93	109	117
15	87	97	117	137	147
16	109	121	146	171	183
17	135	150	181	212	227
18	166	185	223	261	280
19	204	227	273	319	342
20	247	275	331	387	415
21	298	331	399	467	500
22	357	397	478	559	599
23	424	472	568	664	712
24	500	556	670	784	840
25	586	652	785	918	984
26	681	758	913	1068	1145
27	787	876	1055	1234	1323
28	903	1005	1210	1415	1517
29	1029	1145	1379	1613	1729
30	1163	1294	1559	1824	1955
31	1306	1454	1751	2048	2196
32	1457	1621	1953	2285	2449
33	1613	1795	2162	2529	2711
34	1773	1973	2377	2781	2981
35	1936	2154	2595	3026	3254
36	2098	2335	2813	3291	3528
37	2259	2514	3028	3542	3797

Gestational Age (wk)	Fetal Weight Percentiles (g)				
	3rd	10th	50th	90th	97th
38	2414	2687	3236	3785	4058
39	2563	2852	3435	4018	4307
40	2700	3004	3619	4234	4538
41	2825	3144	3787	4430	4749
42	2935	3266	3934	4602	4933

Adapted with permission from Hadlock, 1991.

TABLE III-4

Smoothed Birth Weight Percentiles for Twins with Dichorionic Placentation

GA (wk)	Smoothed birth weight percentiles				
	5th	10th	50th	90th	95th
23	477	513	632	757	801
24	538	578	712	853	903
25	606	652	803	962	1018
26	684	735	906	1085	1148
27	771	829	1021	1223	1294
28	870	935	1152	1379	1459
29	980	1054	1298	1554	1645
30	1102	1186	1460	1748	1850
31	1235	1328	1635	1958	2072
32	1374	1477	1819	2179	2306
33	1515	1630	2007	2403	2543
34	1653	1778	2190	2622	2775
35	1781	1916	2359	2825	2989
36	1892	2035	2506	3001	3176
37	1989	2139	2634	3155	3339
38	2079	2236	2753	3297	3489
39	2167	2331	2870	3437	3637
40	2258	2428	2990	3581	3790
41	2352	2530	3115	3731	3948

GA = gestational age.

Reproduced with permission from Ananth, 1998.

TABLE III-5

Smoothed Birth Weight Percentiles for Twins with Monochorionic Placentation

GA (wk)	Smoothed birth weight percentiles				
	5th	10th	50th	90th	95th
23	392	431	533	648	683
24	456	501	620	753	794
25	530	582	720	875	922
26	615	676	836	1017	1072
27	713	784	970	1178	1242
28	823	904	1119	1360	1433
29	944	1037	1282	1559	1643
30	1072	1178	1457	1771	1867
31	1204	1323	1637	1990	2097
32	1335	1467	1814	2205	2325
33	1457	1601	1980	2407	2537
34	1562	1716	2123	2580	2720
35	1646	1808	2237	2719	2866
36	1728	1899	2349	2855	3009
37	1831	2012	2489	3025	3189
38	1957	2150	2660	3233	3408
39	2100	2307	2854	3469	3657
40	2255	2478	3065	3726	3927
41	2422	2661	3292	4001	4217

Reproduced with permission from Ananth, 1998.

TABLE III-6

Fetal Thoracic Circumference Measurements (cm) According to Gestational Age

Gestational age (wk)	Predictive percentiles									
	No.	2.5	5	10	25	50	75	90	95	97.5
16	6	5.9	6.4	7.0	8.0	9.1	10.3	11.3	11.9	12.4
17	22	6.8	7.3	7.9	8.9	10.0	11.2	12.2	12.8	13.3
18	31	7.7	8.2	8.8	9.8	11.0	12.1	13.1	13.7	14.2
19	21	8.6	9.1	9.7	10.7	11.9	13.0	14.0	14.6	15.1
20	20	9.6	10.0	10.6	11.7	12.8	13.9	15.0	15.5	16.0
21	30	10.4	11.0	11.6	12.6	13.7	14.8	15.8	16.4	16.9
22	18	11.3	11.9	12.5	13.5	14.6	15.7	16.7	17.3	17.8
23	21	12.2	12.8	13.4	14.4	15.5	16.6	17.6	18.2	18.8
24	27	13.2	13.7	14.3	15.3	16.4	17.5	18.5	19.1	19.7
25	20	14.1	14.6	15.2	16.2	17.3	18.4	19.4	20.0	20.6
26	25	15.0	15.5	16.1	17.1	18.2	19.3	20.3	21.0	21.5
27	24	15.9	16.4	17.0	18.0	19.1	20.2	21.3	21.9	22.4
28	24	16.8	17.3	17.9	18.9	20.0	21.2	22.2	22.8	23.3
29	24	17.7	18.2	18.8	19.8	21.0	22.1	23.1	23.7	24.2
30	27	18.6	19.1	19.7	20.7	21.9	23.0	24.0	24.6	25.1
31	24	19.5	20.0	20.6	21.6	22.8	23.9	24.9	25.5	26.0
32	28	20.4	20.9	21.5	22.6	23.7	24.8	25.8	26.4	26.9
33	27	21.3	21.8	22.5	23.5	24.6	25.7	26.7	27.3	27.8
34	25	22.2	22.8	23.4	24.4	25.5	26.6	27.6	28.2	28.7
35	20	23.1	23.7	24.3	25.3	26.4	27.5	28.5	29.1	29.6
36	23	24.0	24.6	25.2	26.2	27.3	28.4	29.4	30.0	30.6
37	22	24.8	25.5	26.1	27.1	28.2	29.3	30.3	30.9	31.5
38	21	25.9	26.4	27.0	28.0	29.1	30.2	31.2	31.9	32.4
39	7	26.8	27.3	27.9	28.9	30.0	31.1	32.2	32.8	33.3
40	6	27.7	28.2	28.8	29.8	30.9	32.1	33.1	33.7	34.2

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TABLE III-7

Length of Fetal Long Bones (mm) According to Gestational Age

Week	Humerus percentile			Ulna Percentile			Radius percentile			Femur percentile			Tibia percentile			Fibula percent	
	5	50	95	5	50	95	5	15	95	5	50	95	5	50	95	5	50
15	11	18	26	10	16	22	12	15	19	11	19	26	5	16	27	10	1
16	12	21	25	8	19	24	9	18	21	13	22	24	7	19	25	6	1
17	19	24	29	11	21	32	11	20	29	20	25	29	15	22	29	7	1
18	18	27	30	13	24	30	14	22	26	19	28	31	14	24	29	10	2
19	22	29	36	20	26	32	20	24	29	23	31	38	19	27	35	18	2
20	23	32	36	21	29	32	21	27	28	22	33	39	19	29	35	18	2
21	28	34	40	25	31	36	25	29	32	27	36	45	24	32	39	24	2
22	28	36	40	24	33	37	24	31	34	29	39	44	25	34	39	21	3
23	32	38	45	27	35	43	26	32	39	35	41	48	30	36	43	23	3
24	31	41	46	29	37	41	27	34	38	34	44	49	28	39	45	26	3
25	35	43	51	34	39	44	31	36	40	38	46	54	31	41	50	33	3
26	36	45	49	34	41	44	30	37	41	39	49	53	33	43	49	32	3
27	42	46	51	37	43	48	33	39	45	45	51	57	39	45	51	35	4
28	41	48	52	37	44	48	33	40	45	45	53	57	38	47	52	36	4
29	44	50	56	40	46	51	36	42	47	49	56	62	40	49	57	40	4
30	44	52	56	38	47	54	34	43	49	49	58	62	41	51	56	38	4
31	47	53	59	39	49	59	34	44	53	53	60	67	46	52	58	40	4
32	47	55	59	40	50	58	37	45	51	53	62	67	46	54	59	40	5
33	5	56	62	43	52	60	41	46	51	56	64	71	49	56	62	43	5
34	50	57	62	44	53	59	39	47	53	57	65	70	47	57	64	46	5
35	52	58	65	47	54	61	38	48	57	61	67	73	48	59	69	51	5
36	53	60	63	47	55	61	41	48	54	61	69	74	49	60	68	51	5
37	57	61	64	49	56	62	45	49	53	64	71	77	52	61	71	55	5
38	55	61	66	48	57	63	45	49	53	62	72	79	54	62	69	54	5
39	56	62	69	49	57	66	46	50	54	64	74	83	58	64	69	55	5
40	56	63	69	50	58	65	46	50	54	66	75	81	58	65	69	54	5

Reproduced with permission from Jeanty, 1983.

TABLE III-8

Ocular Parameters According to Gestational Age

Age (wk)	Binocular distance (mm)			Interocular distance (mm)			Ocular diameter (mm)		
	5th	50th	95th	5th	50th	95th	5th	50th	95th
15	15	22	30	6	10	14	4	6	9
16	17	25	32	6	10	15	5	7	9
17	19	27	34	6	11	15	5	8	10
18	22	29	37	7	11	16	6	9	11
19	24	31	39	7	12	16	7	9	12
20	26	33	41	8	12	17	8	10	13
21	28	35	43	8	13	17	8	11	13
22	30	37	44	9	13	18	9	12	14
23	31	39	46	9	14	18	10	12	15
24	33	41	48	10	14	19	10	13	15
25	35	42	50	10	15	19	11	13	16
26	36	44	51	11	15	20	12	14	16
27	38	45	53	11	16	20	12	14	17
28	39	47	54	12	16	21	13	15	17
29	41	48	56	12	17	21	13	15	18
30	42	50	57	13	17	22	14	16	18
31	43	51	58	13	18	22	14	16	19
32	45	52	60	14	18	23	14	17	19
33	46	53	61	14	19	23	15	17	19
34	47	54	62	15	19	24	15	17	20
35	48	55	63	15	20	24	15	18	20
36	49	56	64	16	20	25	16	18	20
37	50	57	65	16	21	25	1	18	21
38	50	58	65	17	21	26	16	18	21
39	51	59	66	17	22	26	16	19	21
40	52	59	67	18	22	26	16	19	21

Adapted with permission from Romero R, 1988.

TABLE III-9

Transverse Cerebellar Diameter Measurements According to Gestational Age

Gestational age (wk)	Cerebellum diameter (mm)				
	10	25	50	75	90
15	10	12	14	15	16
16	14	16	16	16	17
17	16	16	17	17	18
18	17	17	18	18	19
19	18	18	19	19	22
20	18	19	19	20	22
21	19	20	22	23	24
22	21	23	23	24	24
23	22	23	24	25	26
24	22	24	25	27	28
25	23	21.5	28	28	29
26	25	28	29	30	32
27	26	28.5	30	31	32
28	27	30	31	32	34
29	29	32	34	36	38
30	31	32	35	37	40
31	32	35	38	39	43
32	33	36	38	40	42
33	32	36	40	43	44
34	33	38	40	41	44
35	31	37	40.5	43	47
36	36	29	43	52	55
37	37	37	45	52	55
38	40	40	48.5	52	55
39	52	52	52	55	55

Adapted with permission from Goldstein, 1987.

TABLE III-10

Reference Values for Umbilical Artery Doppler Indices

GA (wk)	Percentiles					
	5th		50th		95th	
	Resistive Index	Systolic/Diastolic Ratio	Resistive Index	Systolic/Diastolic Ratio	Resistive Index	Systolic/Diastolic Ratio
16	0.70	3.39	0.80	5.12	0.90	10.50
17	0.69	3.27	0.79	4.86	0.89	9.46
18	0.68	3.16	0.78	4.63	0.88	8.61
19	0.67	3.06	0.77	4.41	0.87	7.90
20	0.66	2.97	0.76	4.22	0.86	7.30
21	0.65	2.88	0.75	4.04	0.85	6.78
22	0.64	2.79	0.74	3.88	0.84	6.33
23	0.63	2.71	0.73	3.73	0.83	5.94
24	0.62	2.64	0.72	3.59	0.82	5.59
25	0.61	2.57	0.71	3.46	0.81	5.28
26	0.60	2.50	0.70	3.34	0.80	5.01
27	0.59	2.44	0.69	3.22	0.79	4.76
28	0.58	2.38	0.68	3.12	0.78	4.53
29	0.57	2.32	0.67	3.02	0.77	4.33
30	0.56	2.26	0.66	2.93	0.76	4.14
31	0.55	2.21	0.65	2.84	0.75	3.97
32	0.54	2.16	0.64	2.76	0.74	3.81
33	0.53	2.11	0.63	2.68	0.73	3.66
34	0.52	2.07	0.62	2.61	0.72	3.53
35	0.51	2.03	0.61	2.54	0.71	3.40
36	0.50	1.98	0.60	2.47	0.70	3.29
37	0.49	1.94	0.59	2.41	0.69	3.18
38	0.47	1.90	0.57	2.35	0.67	3.08
39	0.46	1.87	0.56	2.30	0.66	2.98
40	0.45	1.83	0.55	2.24	0.65	2.89
41	0.44	1.80	0.54	2.19	0.64	2.81
42	0.43	1.76	0.53	2.14	0.63	2.73

GA = gestational age.

Adapted with permission from Kofnas AD, 1992.

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Figure and Table Gallery

FIGURE 2-20

The four parent pelvic types of the Caldwell-Moloy classification. A line passing through the widest transverse diameter divides the inlets into posterior (P) and anterior (A) segments.

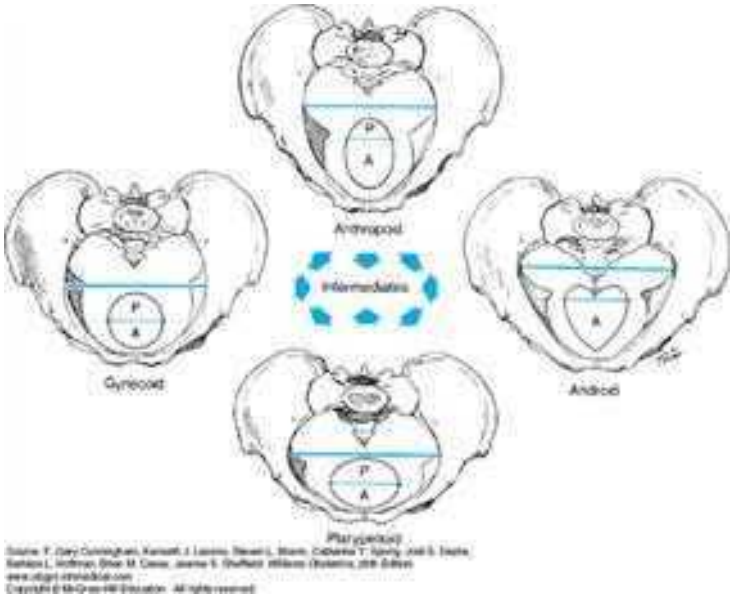

FIGURE 10-10

Alobar holoprosencephaly. **A.** Transverse cranial image of a 26-week fetus with alobar holoprosencephaly, depicting fused thalami (*Th*) encircled by a monoventricle (*V*). The midline falx is absent. **B.** In this profile view of the face and head, a soft tissue mass—a proboscis (*arrow*), protrudes from the region of the forehead.

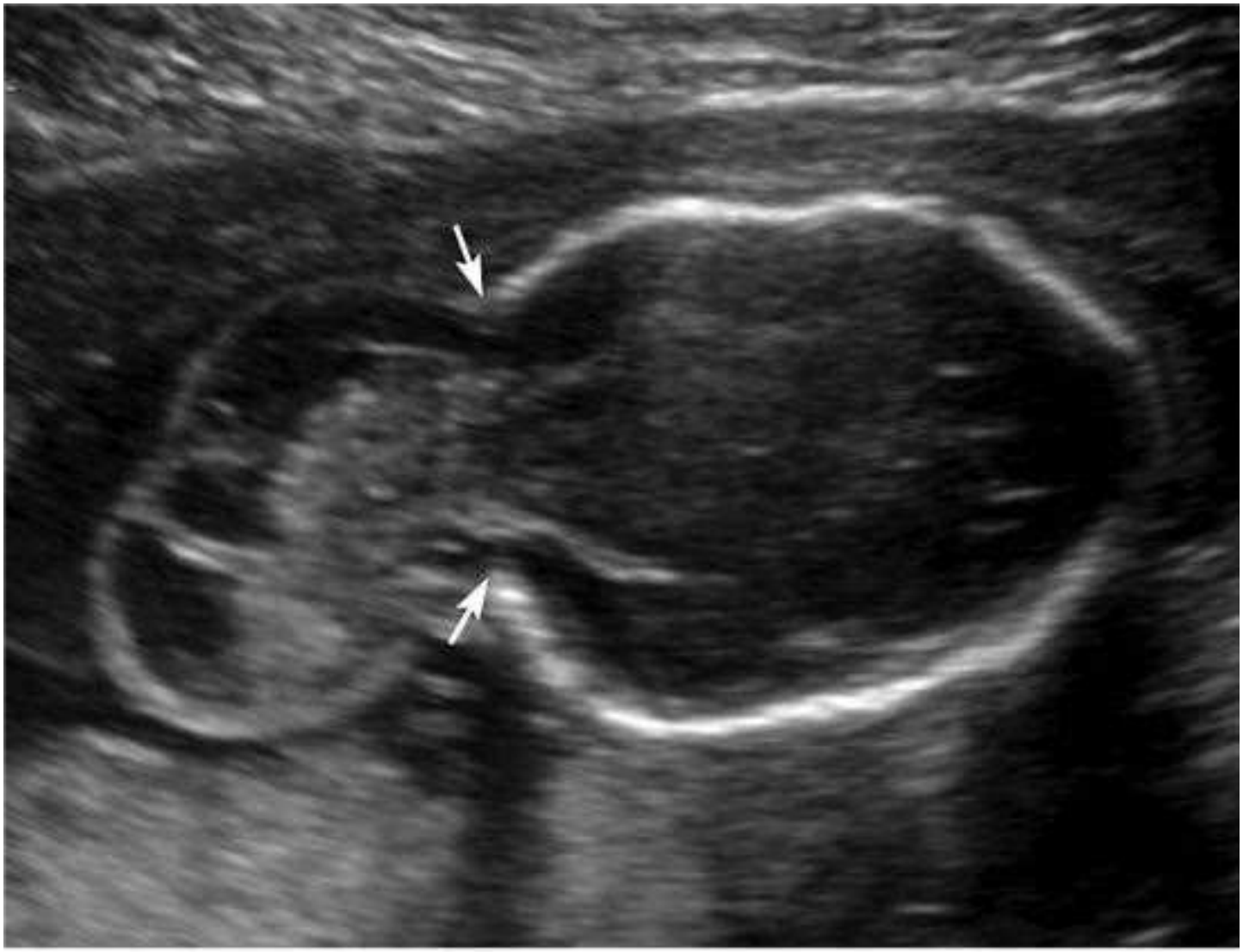

FIGURE 10-12

Sacrococcygeal teratoma. Sonographically, this tumor appears as a solid and/or cystic mass that arises from the anterior sacrum and tends to extend inferiorly and externally as it grows. In this image, a 7 × 6 cm inhomogeneous solid mass is visible below the normal-appearing sacrum. There is also an internal component to the tumor.

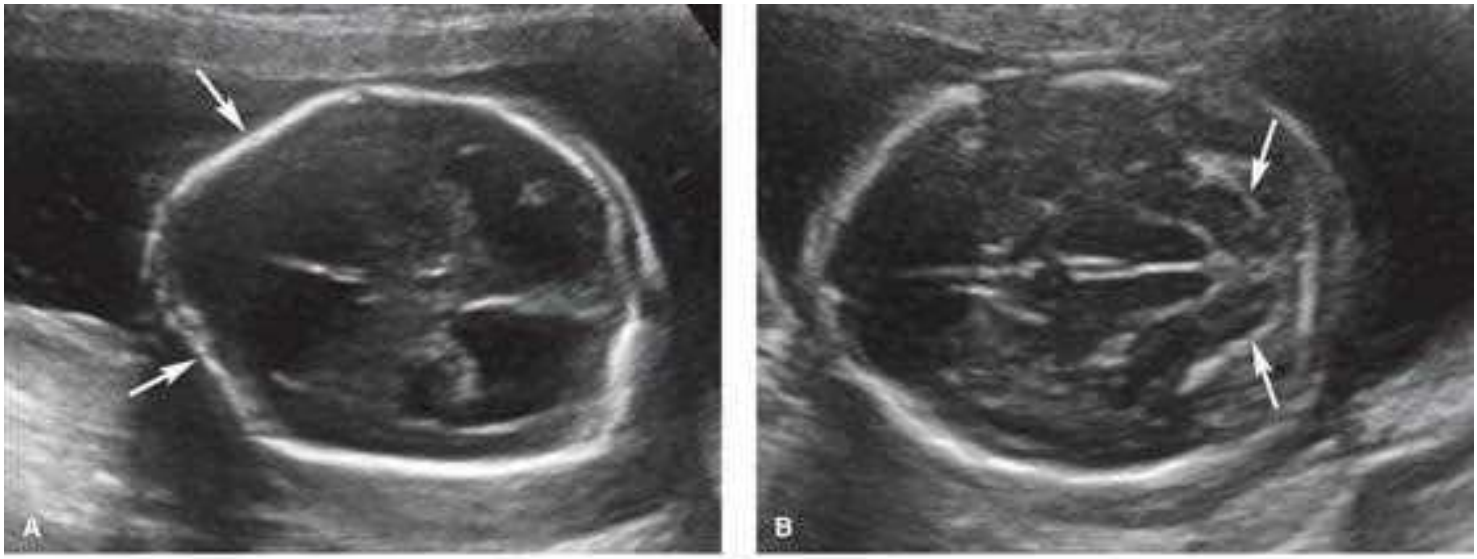

FIGURE 10-14

Fetal profile. **A.** This image depicts a normal fetal profile. **B.** This fetus has severe micrognathia, which creates a severely recessed chin.

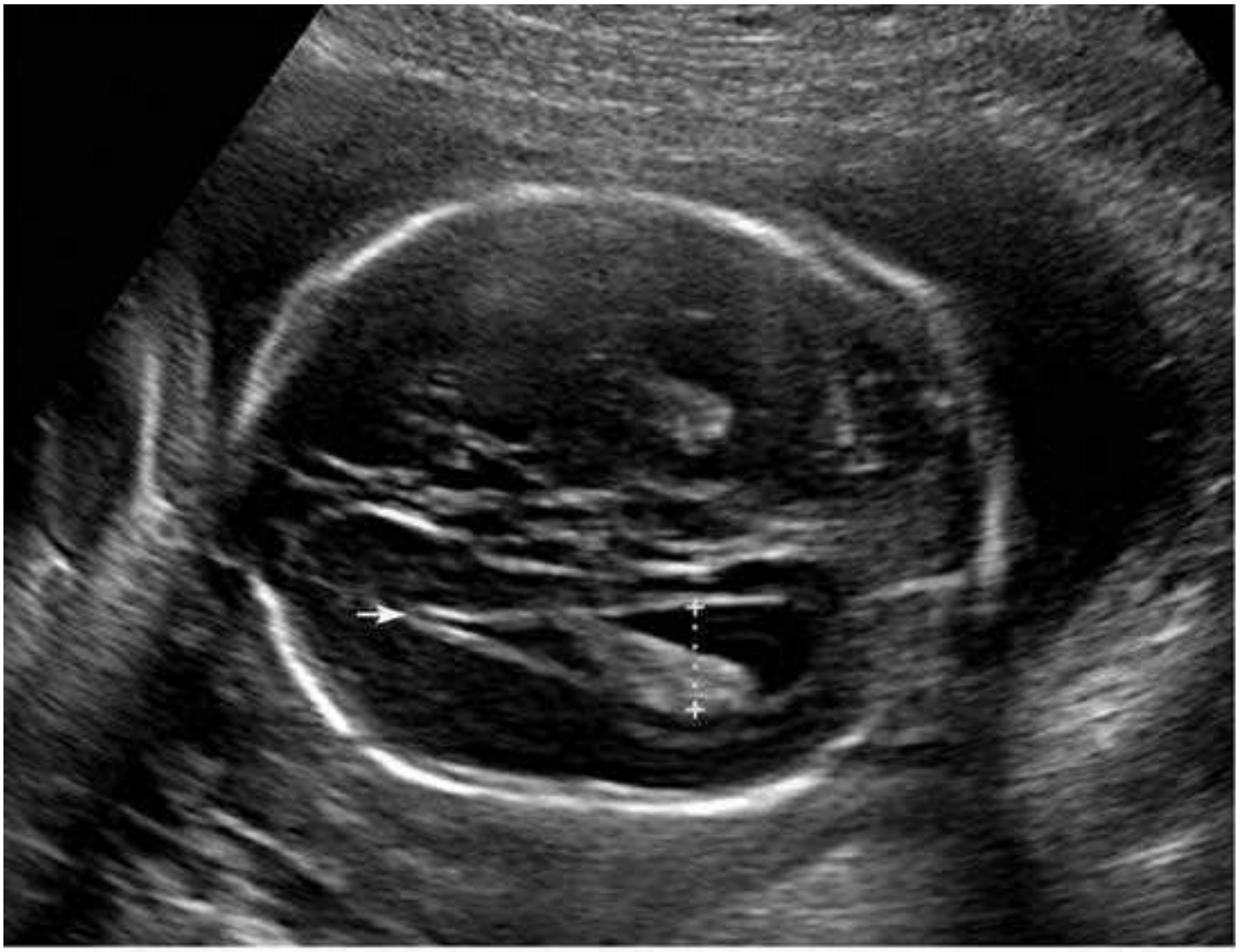

FIGURE 10-16

Cystic hygromas. **A.** This 9-week fetus with a cystic hygroma (*arrow*) was later found to have Noonan syndrome. **B.** Massive multiseptated hygromas (*arrowheads*) in the setting of hydrops fetalis at 15 weeks.

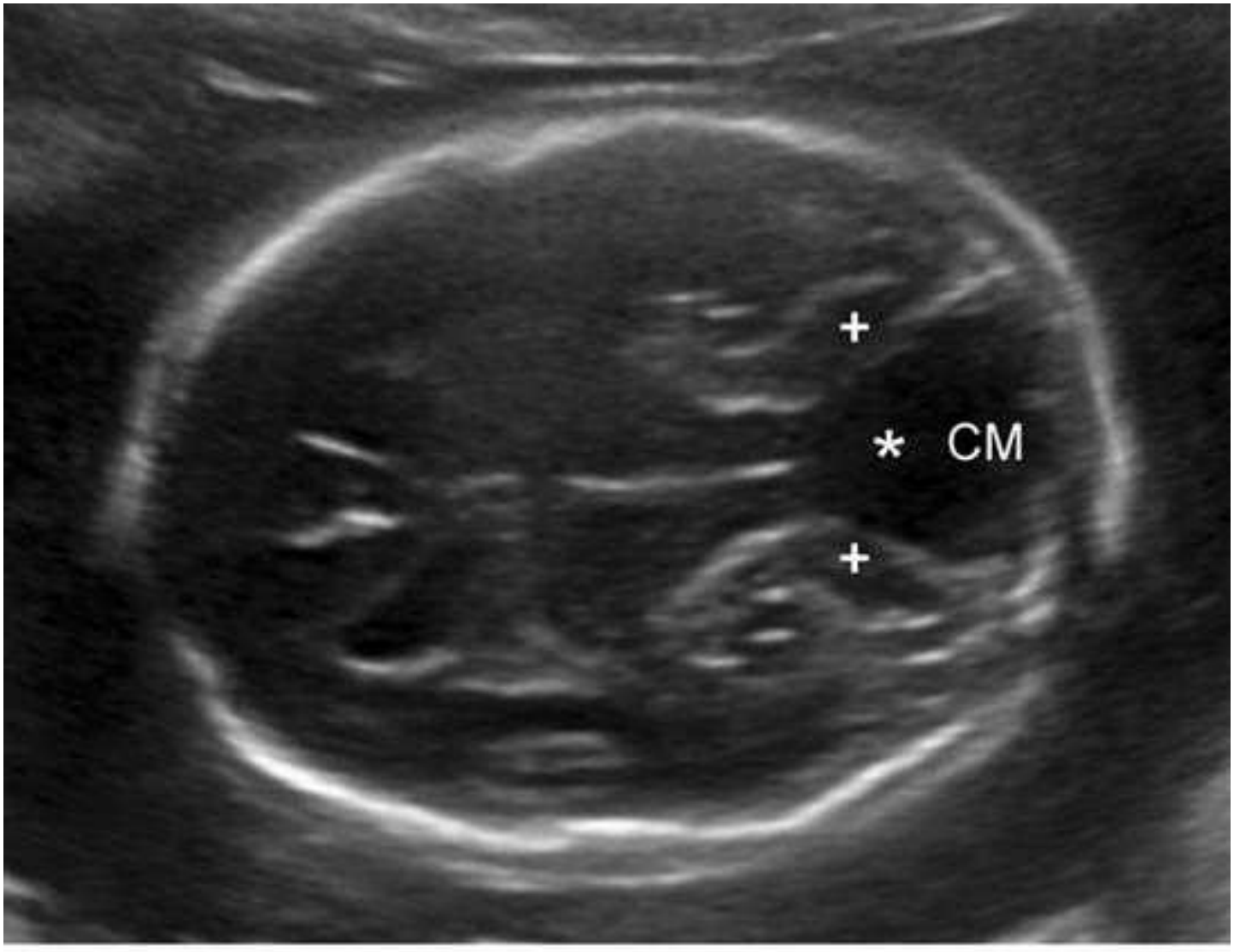

FIGURE 10-17

Congenital diaphragmatic hernia. In this transverse view of the thorax, the heart is shifted to the far right side of the chest by a left-sided diaphragmatic hernia containing stomach (S), liver (*L*), and bowel (*B*).

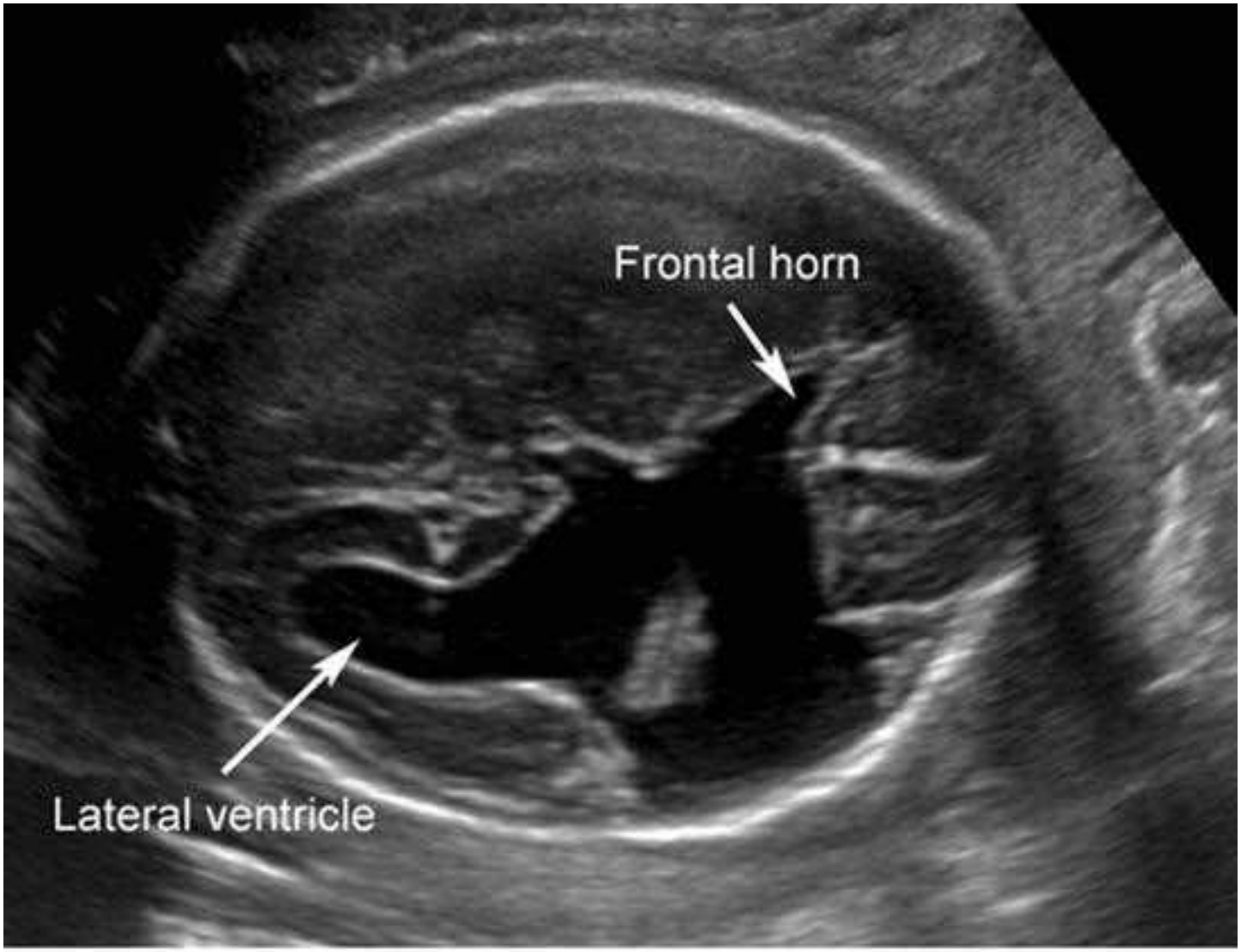

FIGURE 10-18

Transverse **(A)** and sagittal **(B)** images of a 26-week fetus with a very large left-sided microcystic congenital cystic adenomatoid malformation (CCAM). The mass (*C*) fills the thorax and has shifted the heart to the far right side of the chest, with development of ascites (*asterisks*). Fortunately, the mass did not continue to grow, the ascites resolved, and the infant was delivered at term and did well following resection.

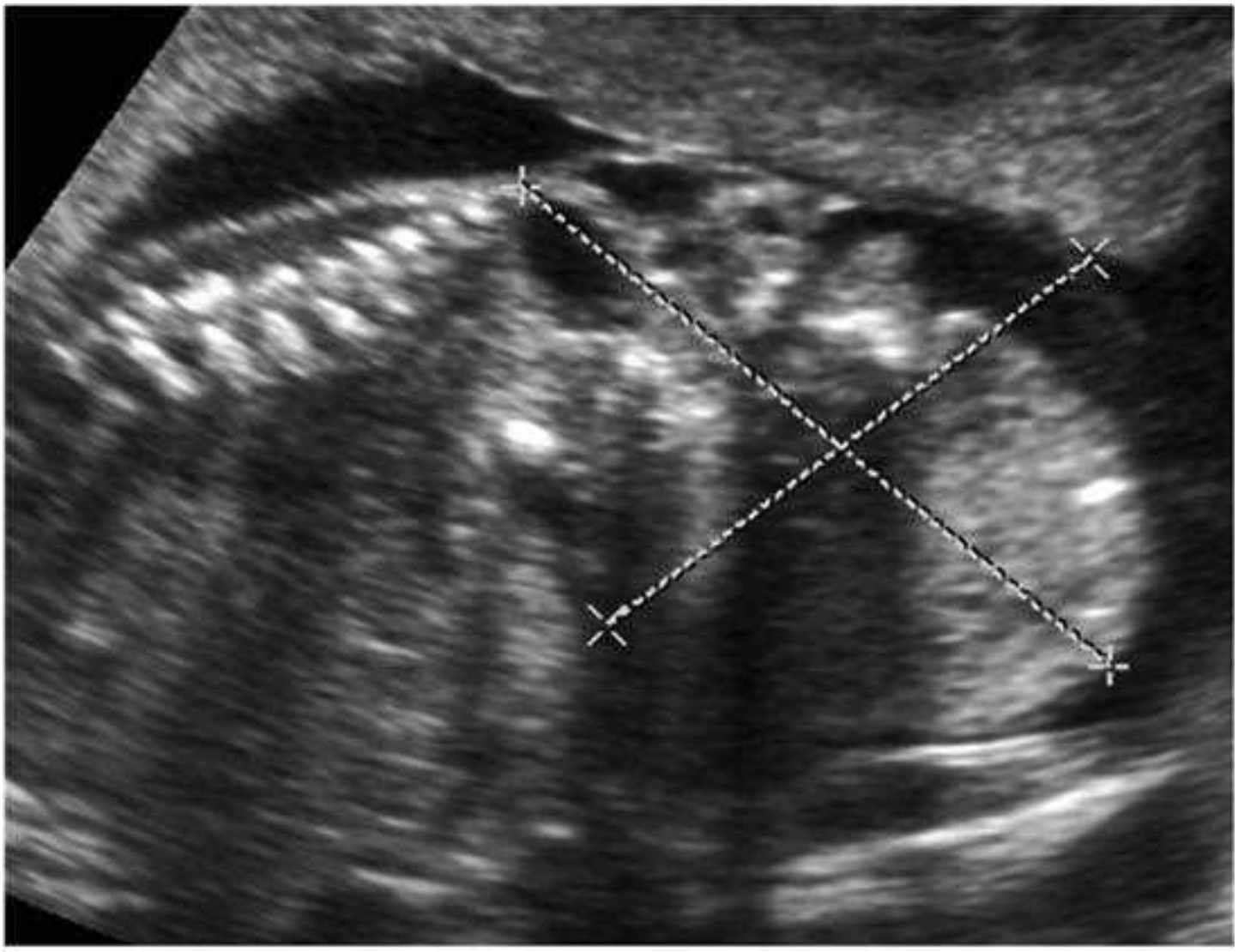

FIGURE 10-19

Congenital high airway obstruction sequence (CHAOS). The lungs appear brightly echogenic, and one is marked by an “L.” The bronchi, one of which is noted by an arrow, are dilated with fluid. Flattening and eversion of the diaphragm is common, as is ascites (*asterisks*).

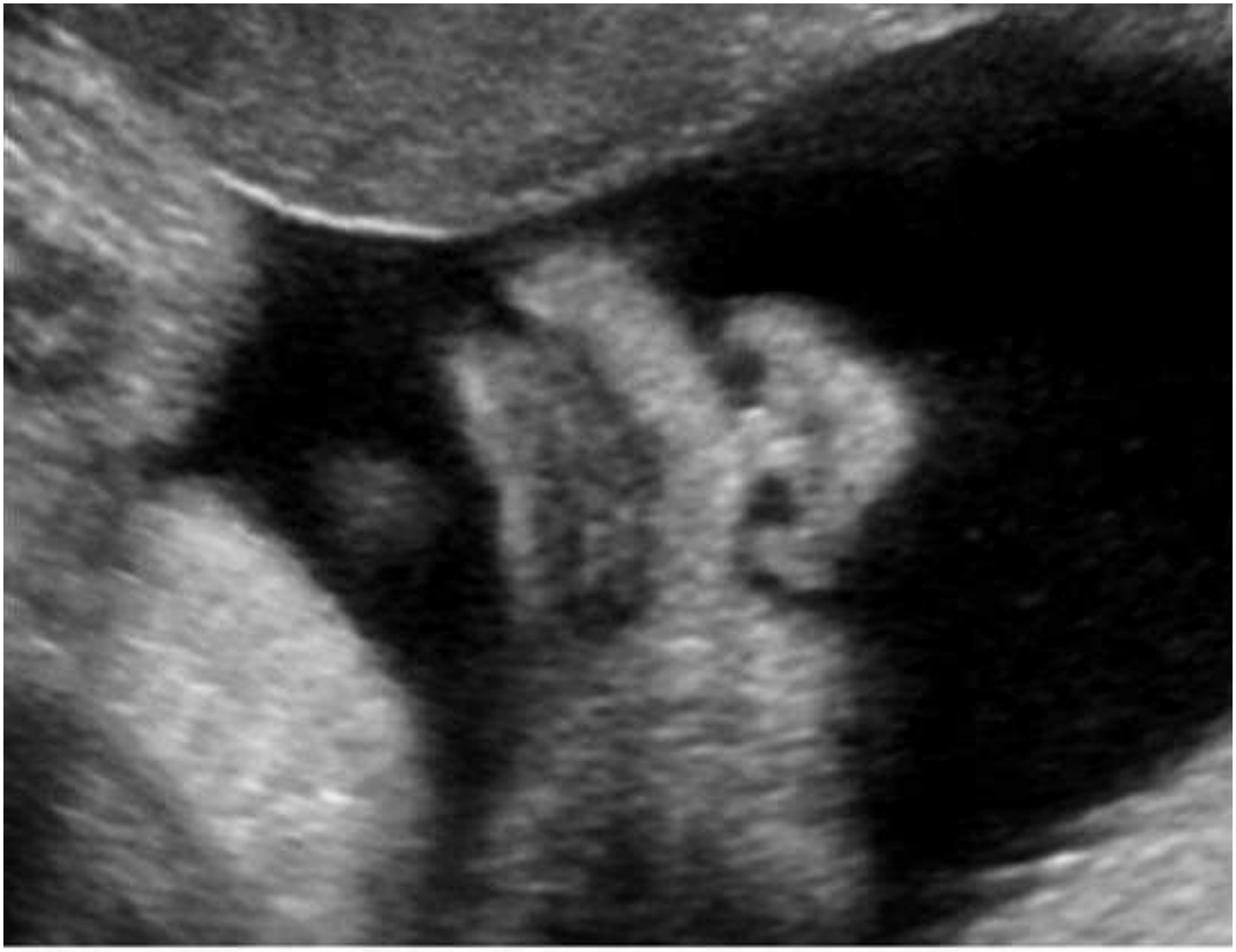

FIGURE 10-22

Ventricular septal defect. **A.** In this four-chamber view of a 22-week fetus, a defect (*arrow*) is noted in the superior (membranous) portion of the interventricular septum. **B.** The left-ventricular outflow tract view of the same fetus demonstrates a break (*arrow*) in continuity between the interventricular septum and the anterior wall of the aorta.

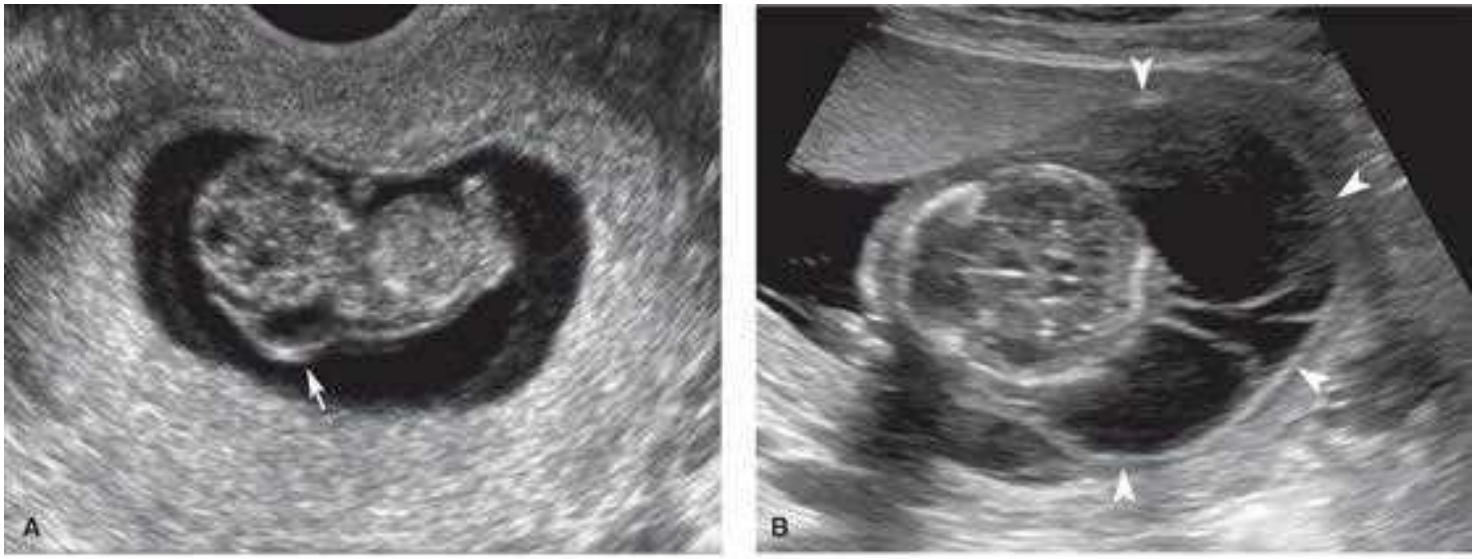

FIGURE 10-23

Endocardial cushion defect. **A.** During ventricular systole, the lateral leaflets of the mitral and triscuspid valves come together in the midline. But the atrioventricular valve plane is abnormal, a common atrium (*A*) is observed, and there is a visible defect (*arrow*) in the interventricular septum. **B.** During diastolic filling, opening of the atrioventricular valves more clearly demonstrates the absence of their medial leaflets.

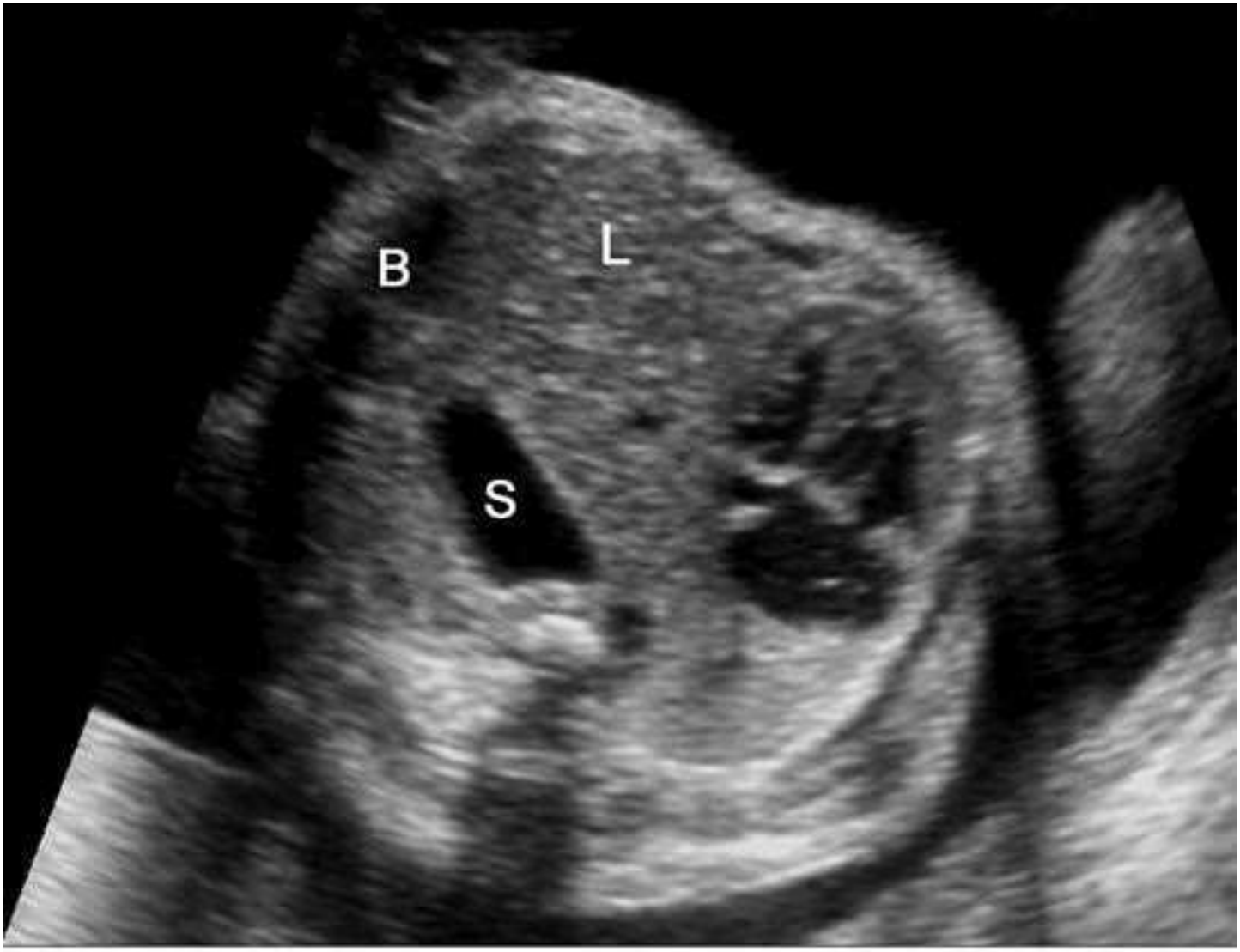

FIGURE 10-24

M-mode, or motion mode, is a linear display of the events of the cardiac cycle, with time on the x-axis and motion on the y-axis. M-mode is used commonly to measure the fetal heart rate. In this image, there is normal concordance between atrial (*A*) and ventricular contractions (*V*). Movement of the tricuspid valve (*T*) is also shown. There is also a premature atrial contraction (*arrow*) and a subsequent early ventricular contraction, followed by a compensatory pause.

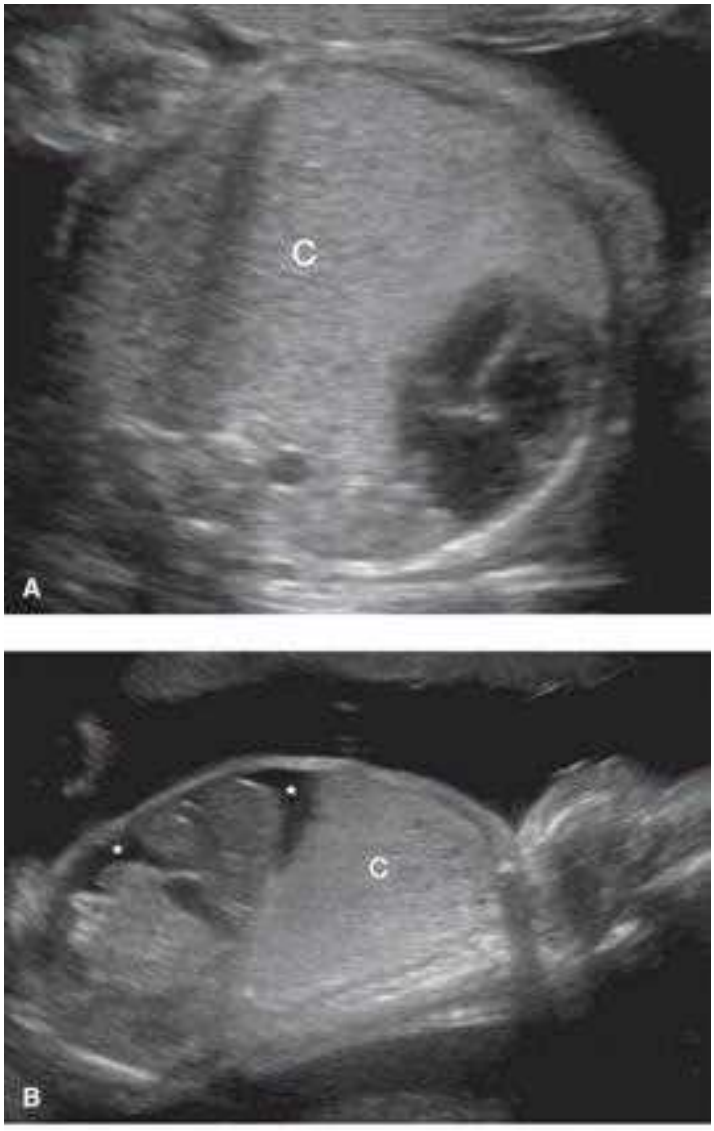

FIGURE 10-26

Gastroschisis. This 18-week fetus has a fullthickness ventral wall defect to the right of the cord insertion (*arrowhead*), through which multiple small bowel loops (*B*) have herniated into the amnionic cavity.

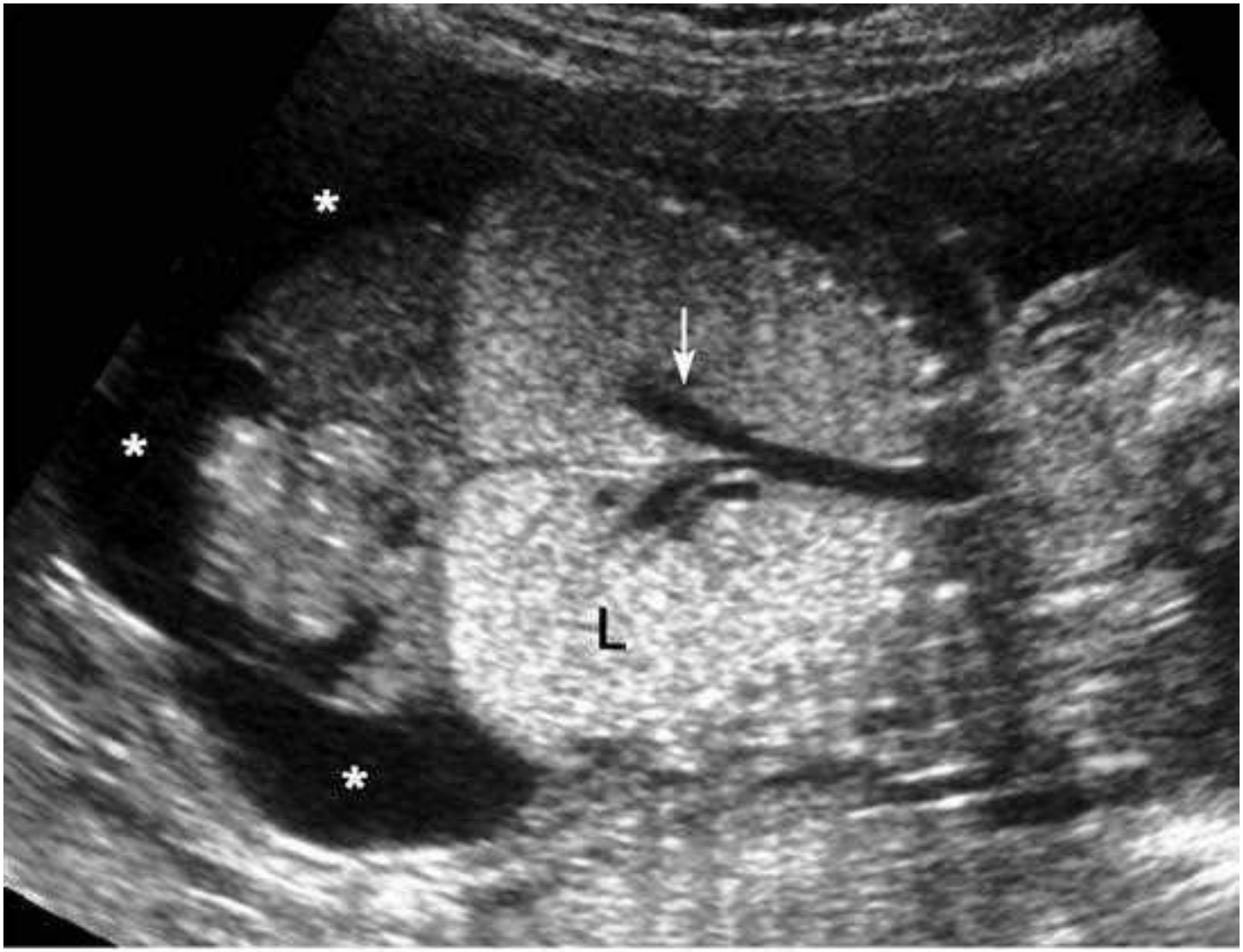

FIGURE 10-33

Posterior urethral valve. In this 19-week fetus with severe bladder outlet obstruction, the bladder is dilated and thick-walled, with dilatation of the proximal urethra that resembles a “keyhole.” Adjacent to the bladder is an enlarged kidney with evidence of cystic dysplasia, conferring a poor prognosis.

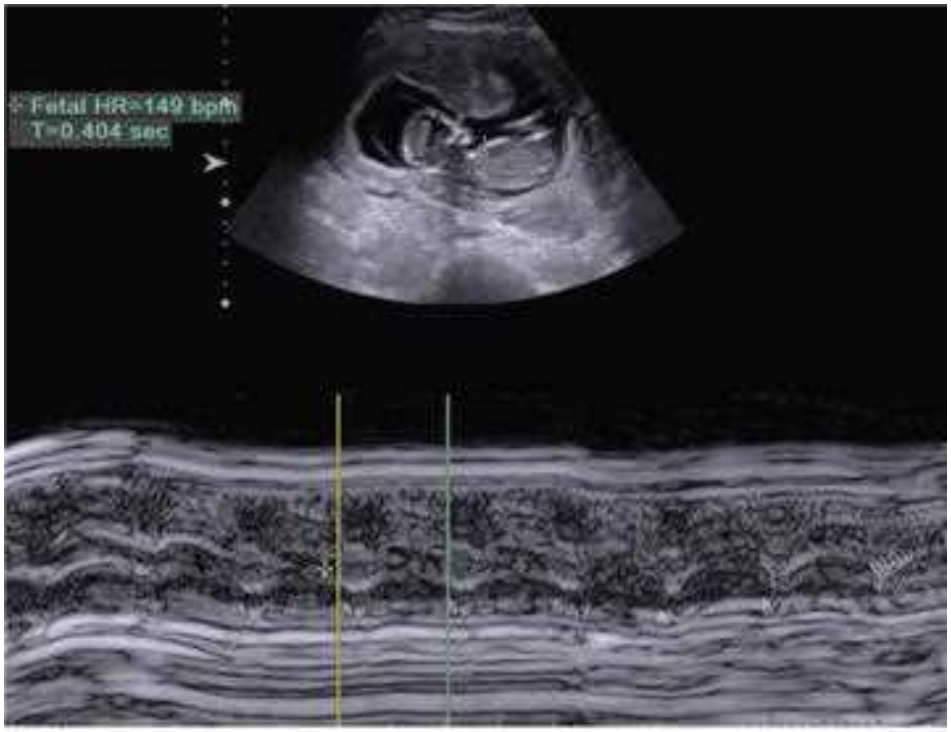

FIGURE 10-39

Umbilical artery Doppler waveforms. **A.** Normal diastolic flow. **B.** Absence of end-diastolic flow. **C.** Reversed enddiastolic flow.

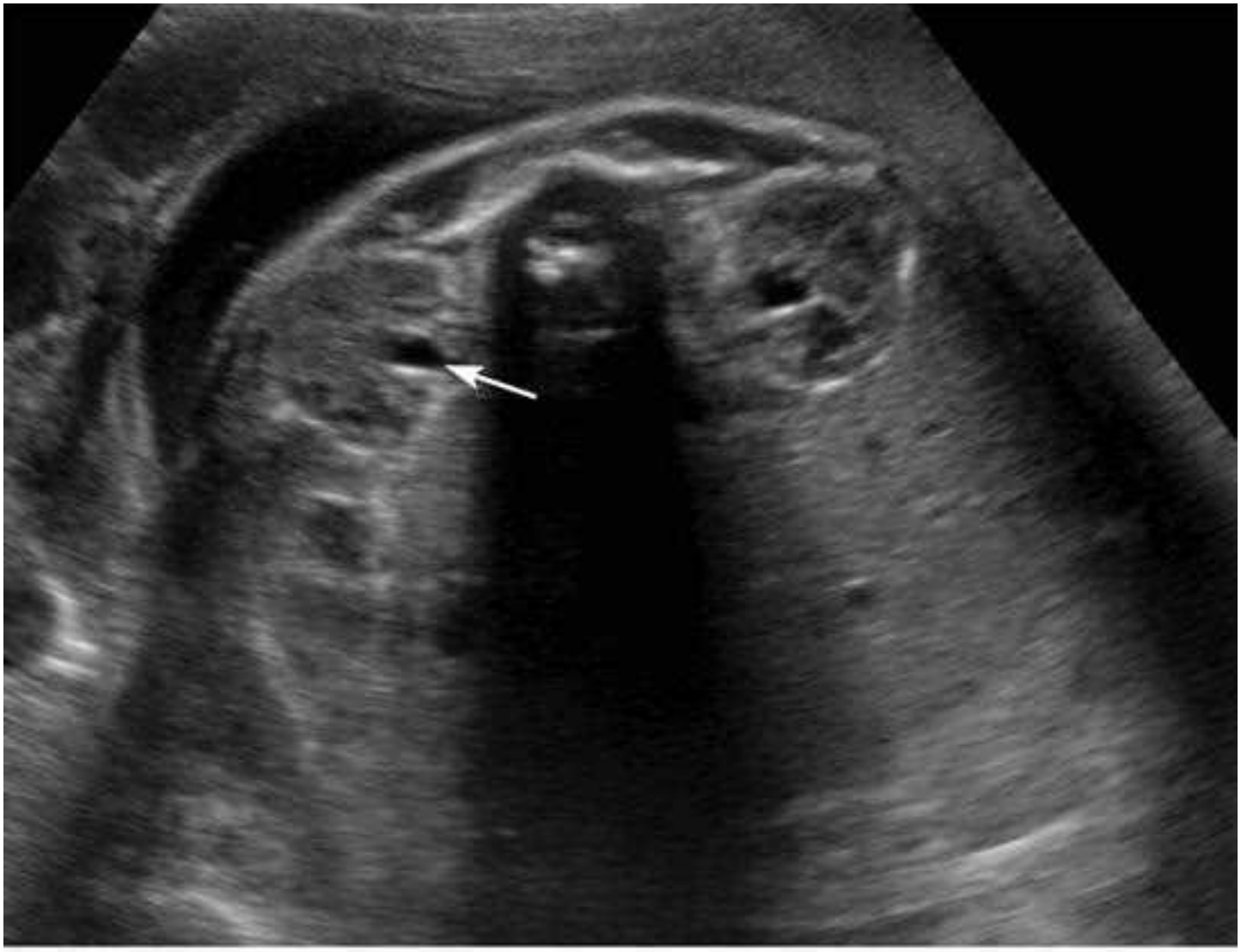

FIGURE 10-44

Congenital diaphragmatic hernia **A.** A HASTE image of a 26-week fetus with congenital diaphragmatic hernia involving the liver (*arrows*). **B.** Coronal STIR image through a 33-week fetal chest demonstrates multiple loops of bowel filling the left chest (*dashed lines*).

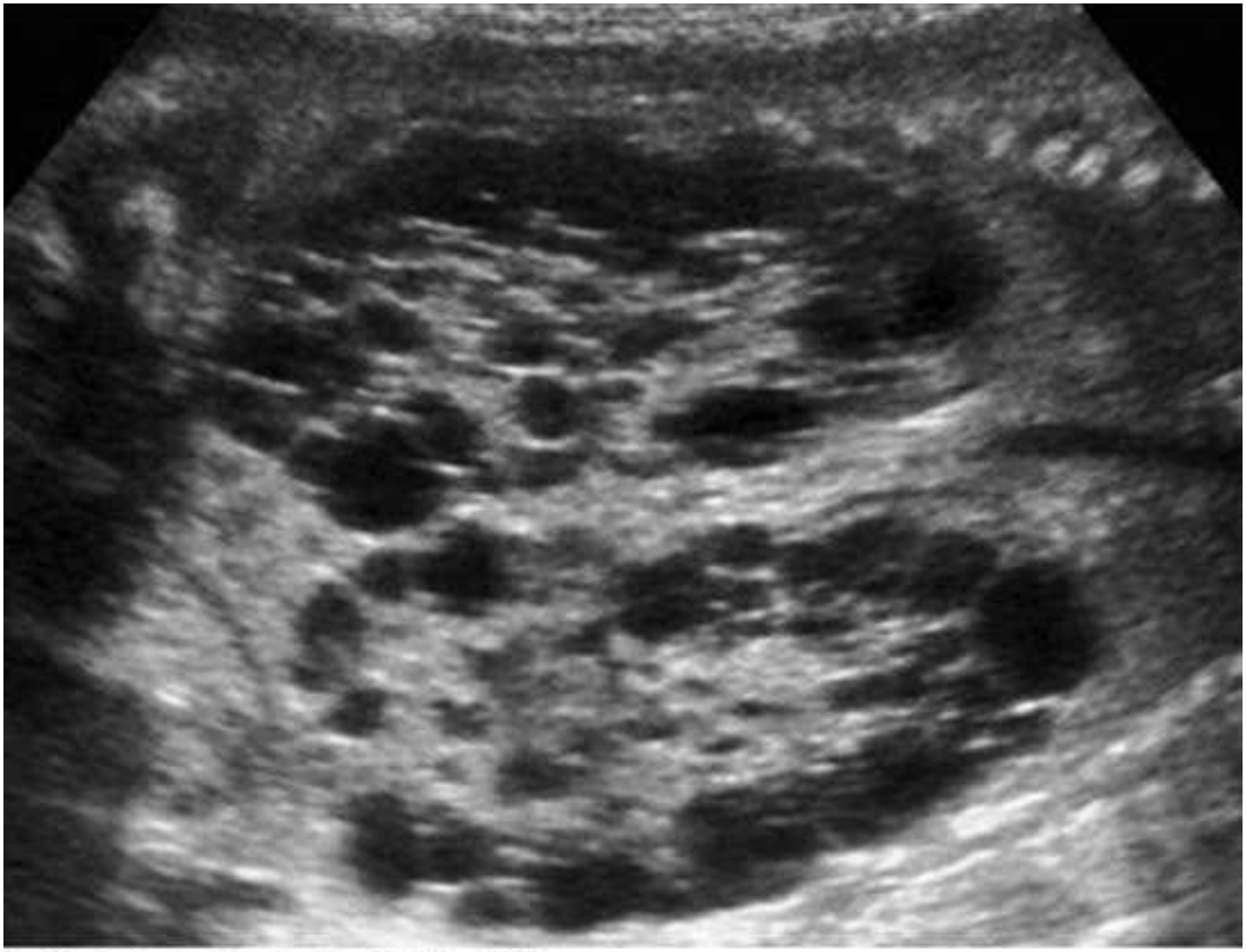

FIGURE 41-11

Schematic showing types of puerperal hematoma. **A.** Coronal view showing supralevator and anterior perineal triangle hematomas on the right. **B.** Perineal view shows anterior perineal triangle anatomy and an ischioanal fossa hematoma on the left.

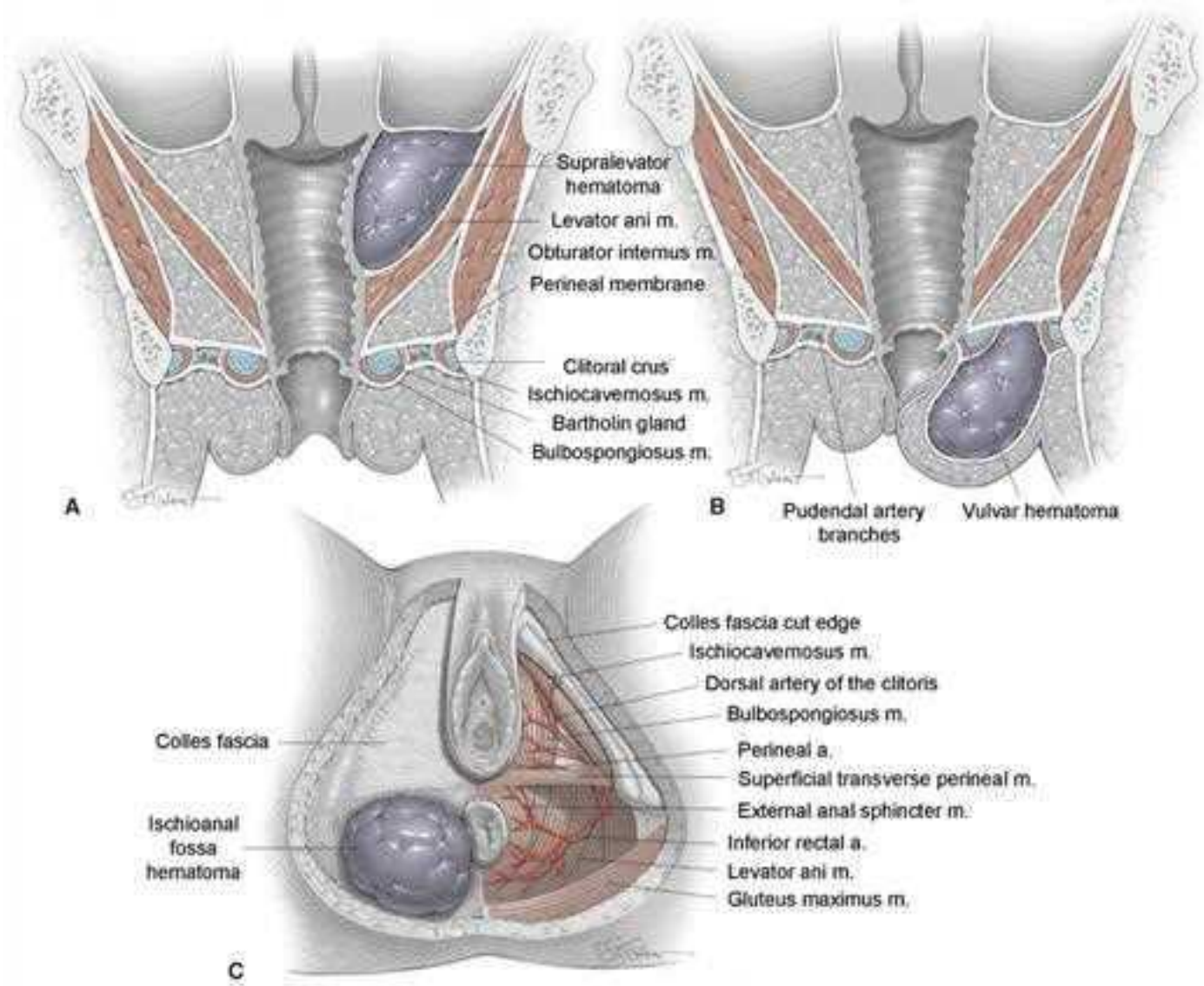

FIGURE 48-1

Chart for estimating body mass index (BMI). To find the BMI category for a particular subject, locate the point at which the height and weight intersect.

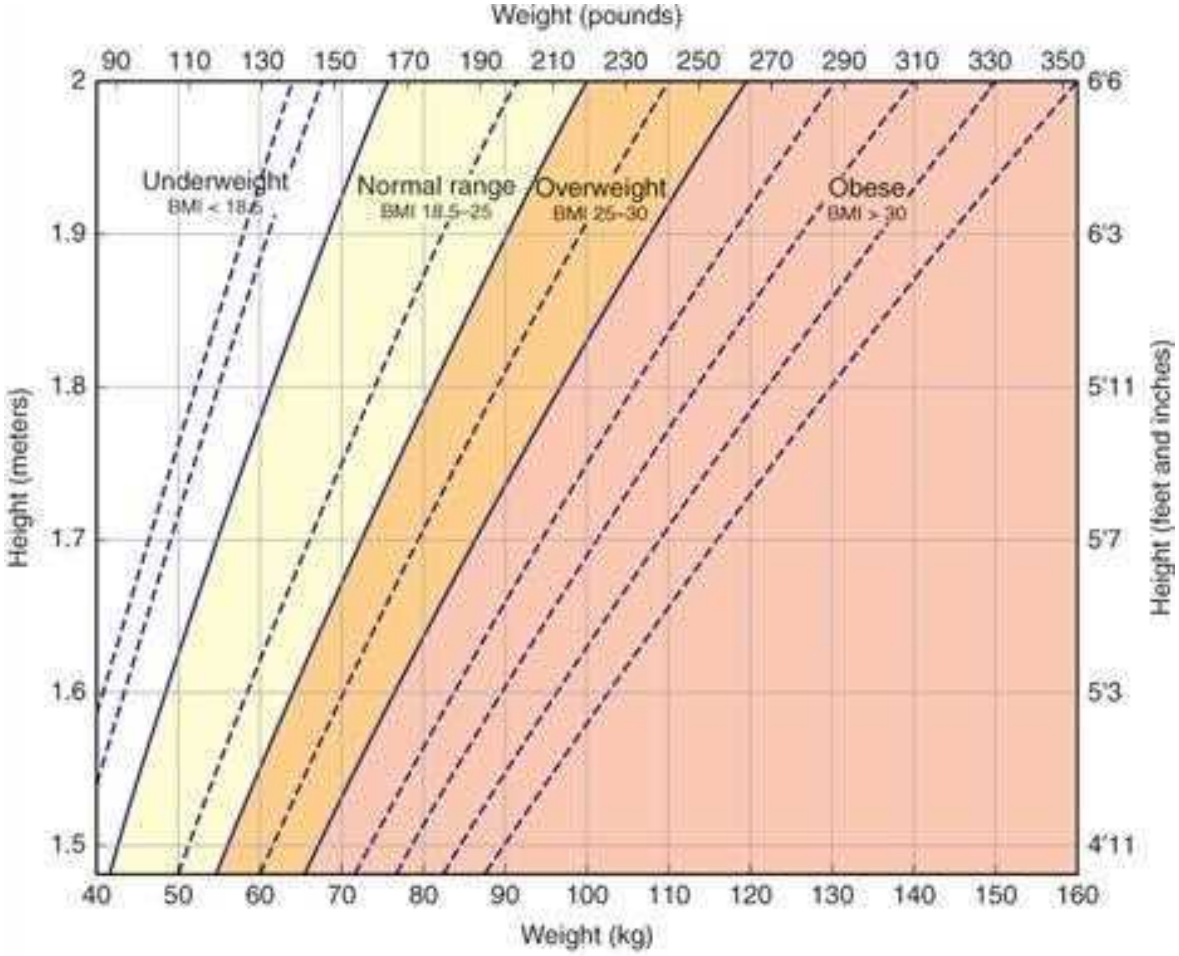

TABLE 9-9

Recommendations for Immunization During Pregnancy

Immunobiological Agent	Indications for Immunization During Pregnancy	Dose Schedule	Comments
Live Attenuated Virus Vaccines			
Measles	Contraindicated—see immune globulins	Single dose SC, preferably as MMR[a]	Vaccinate susceptible women postpartum. Breast feeding is not a contraindication
Mumps	Contraindicated	Single dose SC, preferably as MMR	Vaccinate susceptible women postpartum
Rubella	Contraindicated, but congenital rubella syndrome has never been described after vaccine	Single dose SC, preferably as MMR	Teratogenicity of vaccine is theoretical and not confirmed to date; vaccinate susceptible women postpartum
Poliomyelitis: Oral = live attenuated; injection = enhanced-potency inactivated virus	Not routinely recommended for women in the United States, except women at increased risk of exposure[a]	Primary: Two doses of enhanced-potency inactivated virus SC at 4–8 week intervals and a 3rd dose 6–12 months after 2nd dose Immediate protection: One dose oral polio vaccine (in outbreak setting)	Vaccine indicated for susceptible women traveling in endemic areas or in other high-risk situations
Yellow fever	Travel to high-risk areas	Single dose SC	Limited theoretical risk outweighed by risk of yellow fever
Varicella	Contraindicated, but no adverse outcomes reported in pregnancy	Two doses needed. 2nd dose given 4–8 weeks after 1st dose	Teratogenicity of vaccine is theoretical. Vaccination of susceptible women should be considered postpartum
Smallpox (vaccinia)	Contraindicated in pregnant women and in their household contacts	One dose SC, multiple pricks with lancet	Only vaccine known to cause fetal harm
Other			
Influenza	All pregnant women, regardless of trimester during flu season (October–May)	One dose IM every year	Inactivated virus vaccine
Rabies	Indications for prophylaxis not altered by pregnancy; each case considered individually	Public health authorities to be consulted for indications, dosage, and route of administration	Killed-virus vaccine
Human papillomavirus	Not recommended	Three-dose series IM at 0, 1, and 6 months	Quadrivalent or bivalent vaccines, both are inactivated virus. No teratogenic effects have been observed with either
Hepatitis A	Recommended not contraindicated	Three-dose series IM at 0, 1,	Used with hepatitis B vaccine

Hepatitis C	Preexposure and postexposure for women at risk of infection	Three dose schedule at 0, 1, and 6 months	Give with hepatitis B immune globulin for some exposures. Exposed newborn needs birth dose vaccination and immune globulin as soon as possible. All infants should receive birth dose of vaccine
Hepatitis A	Preexposure and postexposure if at risk (international travel)	Two dose schedule IM, 6 months apart	Inactivated virus
Inactivated Bacterial Vaccines			
Pneumococcus	Indications not altered by pregnancy. Recommended for women with asplenia, metabolic, renal, cardiac, or pulmonary diseases; immunosuppression; or smokers	In adults, one dose only; consider repeat dose in 5 years for high-risk women	Polyvalent polysaccharide vaccine; safety in the first trimester has not been evaluated
Meningococcus	Indications not altered by pregnancy; vaccination recommended in unusual outbreaks	One dose; tetravalent vaccine	Antimicrobial prophylaxis if significant exposure
Typhoid	Not recommended routinely except for close, continued exposure or travel to endemic areas	Killed Primary: 2 injections IM 4 weeks apart Booster: One dose, schedule not yet determined	Killed, injectable vaccine or live attenuated oral vaccine. Oral vaccine preferred
Anthrax	See text	Six-dose primary vaccination, then annual booster vaccination	Preparation from cell-free filtrate of *B anthracis*, No dead or live bacteria. Teratogenicity of vaccine theoretical
Toxoids			
Tetanus-diphtheria-acellular pertussis (Tdap)	Recommended in every pregnancy, preferably between 27 and 36 weeks to maximize passive antibody transfer	Primary: Two doses IM at 1-2 month interval with 3rd dose 6-12 months after the 2nd Booster: Single dose IM every 10 years, as a part of wound care if ≥ 5 years since last dose, or once per pregnancy	Combined tetanus-diphtheria toxoids with acellular pertussis (Tdap) preferred. Updating immune status should be part of antepartum care
Specific Immune Globulins			
Hepatitis B	Postexposure prophylaxis	Depends on exposure (Chap. 55, p. 1090)	Usually given with hepatitis B virus vaccine; exposed newborn needs immediate prophylaxis
Rabies	Postexposure prophylaxis	Half dose at injury site; full dose in deltoid	Used in conjunction with rabies killed virus vaccine
Tetanus	Postexposure prophylaxis	One dose IM	Used in conjunction with tetanus toxoid
Varicella	Should be considered for exposed pregnant women to protect against maternal, not congenital, infection	One dose IM within 96 hours of exposure	Indicated also for newborns or women who developed varicella within 4 days before delivery or 2 days following delivery
Standard Immune Globulins			
Hepatitis A Hepatitis A virus vaccine should be used with hepatitis A immune globulin	Postexposure prophylaxis and those at high risk	0.02 mL/kg IM in one dose	Immune globulin should be given as soon as possible and within 2 weeks of exposure; infants born to women who are incubating the virus or are acutely ill at delivery should receive one dose of 0.5 mL as soon as possible after birth

*Two doses necessary for students entering institutions of higher education, newly hired medical personnel, and travel abroad.
†Inactivated polio vaccine recommended for nonimmunized adults at increased risk.
ID = intradermally; IM = intramuscularly; MMR = measles, mumps, rubella; PO = orally; SC = subcutaneously
Adapted from the Centers for Disease Control and Prevention, 2013a,b,c.

TABLE 10-3

Guidelines for Nuchal Translucency (NT) Measurement

The margins of NT edges must be clear enough for proper caliper placement
The fetus must be in the midsagittal plane
The image must be magnified so that it is filled by the fetal head, neck, and upper thorax
The fetal neck must be in a neutral position, not flexed and not hyperextended
The amnion must be seen as separate from the NT line
Electronic calipers must be used to perform the measurement
The + calipers must be placed on the inner borders of the nuchal space with none of the horizontal crossbar itself protruding into the space
The calipers must be placed perpendicular to the long axis of the fetus
The measurement must be obtained at the widest space of the NT

From the American Institute of Ultrasound in Medicine, 2013a, with permission.

TABLE 49-4

Risks for Fetal Heart Lesions Related to Affected Family Members

	Congenital Heart Disease in Fetus (%)		
Cardiac Lesion	Previous Sibling Affected	Father Affected	Mother Affected
Marfan syndrome	NS	50	50
Aortic stenosis	2	3	15–18
Pulmonary stenosis	2	2	6–7
Ventricular septal defect	3	2	10–16
Atrial septal defect	2.5	1.5	5–11
Patent ductus arteriosus	3	2.5	4
Coarctation of the aorta	NS	NS	14
Fallot tetralogy	2.5	1.5	2–3

NS = not stated.
Data from Lupton, 2002.

TABLE 52-8

Some Recommendations for Thromboprophylaxis during Pregnancy

	Pregnancy		Postpartum	
Clinical Scenario	ACOG[a]	ACCP[b]	ACOG[a]	ACCP[b]
Prior single VTE				
Risk factor no longer present	Surveillance only	Surveillance only	Postpartum anticoagulation[c] "Surveillance only acknowledged by some experts."	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Pregnancy- or estrogen-related or no known association (idiopathic) **and** not receiving long-term therapy	Prophylactic UFH or LMWH **or** "Surveillance only acknowledged by some experts"	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks

Receiving long-term warfarin	NSS	Adjusted-dose LMWH **or** 75% of a therapeutic dose of LMWH	NSS	Resume long-term anticoagulation
Associated with a high-risk thrombophilia[a] **and** not receiving long-term anticoagulation or an affected first-degree relative	Prophylactic, intermediate-, or adjusted-dose LMWH or UFH	NSS	Postpartum anticoagulation[c] **or** intermediate- or adjusted-dose LMWH or UFH × 6 weeks[c]	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Associated with a low-risk thrombophilia[b] and not receiving treatment	Prophylactic or intermediate-dose LMWH or UFH **or** surveillance only	NSS	Postpartum anticoagulation[c] **or** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Two or more prior VTEs with or without thrombophilia				
Not receiving long-term therapy	Prophylactic or therapeutic-dose UFH or LMWH	NSS	Postpartum anticoagulation[c] **or** therapeutic-dose LMWH or UFH × 6 weeks	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Receiving long-term anticoagulation	Therapeutic-dose LMWH or UFH	Adjusted-dose LMWH **or** 75% of a therapeutic dose of LMWH	Resumption of long-term anticoagulation	Resumption of long-term anticoagulation
No prior VTE				
High-risk thrombophilia[a]	Surveillance only **or** prophylactic or intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH	Postpartum anticoagulation[c]	Intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE **and** homozygous factor V Leiden or prothrombin 20210A mutation	NSS	Prophylactic or intermediate-dose LMWH	NSS	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Negative family history VTE and homozygous factor V Leiden or prothrombin 20210A mutation	Surveillance only **or** prophylactic LMWH or UFH	Surveillance only	Postpartum anticoagulation[c]	Prophylactic or intermediate-dose LMWH **or** warfarin target INR 2.0–3.0 × 6 weeks
Positive family history VTE and low-risk thrombophilias[b]	Surveillance only	Surveillance only	Postpartum anticoagulation[c] **or** intermediate-dose LMWH or UFH	Prophylactic or intermediate-dose LMWH **or** in women not protein C or S deficient, warfarin target INR 2.0–3.0
Low-risk thrombophilia[b]	Surveillance only	Surveillance only if no family history	Surveillance only; postpartum anticoagulation with additional risk factors[c]	Surveillance only if no family history
Antiphospholipid antibodies				
History of VTE	Prophylactic anticoagulation with UFH or LMWH (?plus low-dose aspirin)	NSS	Prophylactic anticoagulation[c]; referral to specialist[d]	NSS
No prior VTE	Surveillance only **or** prophylactic LMWH or UFH **or** prophylactic LMWH or UFH plus low-dose aspirin if prior recurrent pregnancy loss or stillbirth	Prophylactic- or intermediate-dose UFH **or** prophylactic-dose LMWH, both given with 75–100 mg/day aspirin[e]	Prophylactic heparin plus low-dose aspirin × 6 weeks if prior recurrent pregnancy loss or stillbirth[f]	NSS

[a]American College of Obstetricians and Gynecologists, 2012, 2013.
[b]American College of Chest Physicians (Bates, 2012).
[c]Postpartum treatment levels should be ≥ antepartum treatment.
[d]Antithrombin deficiency, doubly heterozygous or homozygous for prothrombin 20210A and factor V Leiden.
[e]Heterozygous factor V Leiden or prothrombin 20210A, protein S or C deficiency.
[f]First-degree relative with VTE at < 50 years; other major thrombotic risk factors, e.g., obesity, prolonged immobility.
[g]Women with antiphospholipid syndrome should not use estrogen-containing contraceptives.
[h]Treatment is recommended if the diagnosis of antiphospholipid syndrome is based on three or more prior pregnancy losses.
LMWH = low molecular weight heparin; NSS = not specifically stated; UFH = unfractionated heparin; VTE = venous thromboembolism.

Prophylactic, intermediate-, and adjusted-dose regimens are listed in Table 52-5 (p. 1037).